Risk of stroke subsequent to infective endocarditis: A nationwide study

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Background The aim of the study was to investigate the associated risk of stroke after discharge of infective endocarditis (IE) in patients with stroke during IE admission compared with patients without stroke during IE admission.

Methods Using Danish nationwide registries, we identified nonsurgically treated patients with IE discharged alive in the period from 1996 to 2016. The study population was grouped into (1) patients with stroke during IE admission and (2) patients without stroke during IE admission. Multivariable adjusted Cox proportional-hazard analysis was used to compare the associated risk of stroke between groups.

Results We identified 4,284 patients with IE, of whom 239 (5.6%) had a stroke during IE admission. We identified differentials in the associated risk of stroke during follow-up between groups ($P = .006$ for interaction with time). The associated risk of stroke was higher in patients with stroke during IE admission with a 1-year follow-up, HR = 3.21 (95% CI 1.66-6.20), compared with patients without stroke during IE admission. From 1 to 5 years of follow-up, we identified no difference in the associated risk of stroke between groups, HR = 0.91 (95% CI 0.33-2.50).

Conclusions Patients with nonsurgically treated IE with a stroke during IE admission were at significant higher associated risk of subsequent stroke within the first year of follow-up as compared with patients without a stroke during IE admission. This risk difference was not evident beyond 1 year of discharge. These findings underline the need for identification of causes and mechanisms of recurrent strokes after IE to develop preventive means. (Am Heart J 2019;212:144-51.)

Stroke is a common and disabling complication in patients with infective endocarditis (IE) and contributes to the high mortality.[1-5] Much attention has been focused on the risk and prevention of stroke in the initial phase of IE.[5-8] Thus, little data are available on the long-term risk of recurrent stroke in patients having a cerebral embolic event during IE admission.[9-11] An American population-based study with a case crossover design observed an increased risk of stroke up to 5 months after the diagnosis of IE.[12] Furthermore, a Taiwanese population-based study identified that patients surviving IE were at a higher associated risk of stroke compared with controls from the background population.[13] However, no study has yet assessed the associated risk of stroke in patients with and without stroke during IE admission treated with medical therapy only. Such data should address the potential magnitude of differences in risk between subgroups of patients with IE and may help guide clinical follow-up of medically treated IE patients. Furthermore, these data may be of importance for the development of future strategies for preventive regimens, which previously has been shown to be difficult.[14] The objective of this study was to investigate the long-term associated risk and timing of stroke in patients with and without stroke during IE admission.

Methods

Data sources

Every Danish citizen is provided with a unique identifier making it possible to crosslink different nationwide administrative registries. We used the Danish National Patient Registry, the Danish Prescription Registry, and the Cause of Death Registry.

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The Danish National Patient Registry was initiated in 1977 and provides information on every patient admitted to a Danish Hospital based in the discharge paper filled by the discharging physician. Diagnoses codes are stated in the discharge paper based on the *International Classification of Diseases, 10th Revision* (*ICD-10*) from 1994 and the *ICD, Eighth Revision* before 1994. Furthermore, surgical procedures were added to the National Patient Registry from 1996 and medical examinations from 2000 where the coding is based upon the Nordic Medico-Statistical Committee Classification of Surgical Procedures. The National Patient Registry was used to identify the study population, the main outcome, and baseline characteristics.

The Danish Prescription Registry holds information on every prescription filled from a Danish pharmacy from 1994 based upon the Anatomical Therapeutic Chemical Classification System (ATC codes). The registry provides information on type of drug prescribed, strength of drug, package size, and date of filling.

The Danish Prescription Registry was used to identify concomitant pharmacotherapy at baseline defined as filled prescription 6 months prior to IE admission. The Cause of Death Registry provides information on date of death and cause of death based on *ICD-10* codes.[15]

The Danish registries are of high quality and have been described in detail previously.[16,17]

Study population, outcome, and follow-up

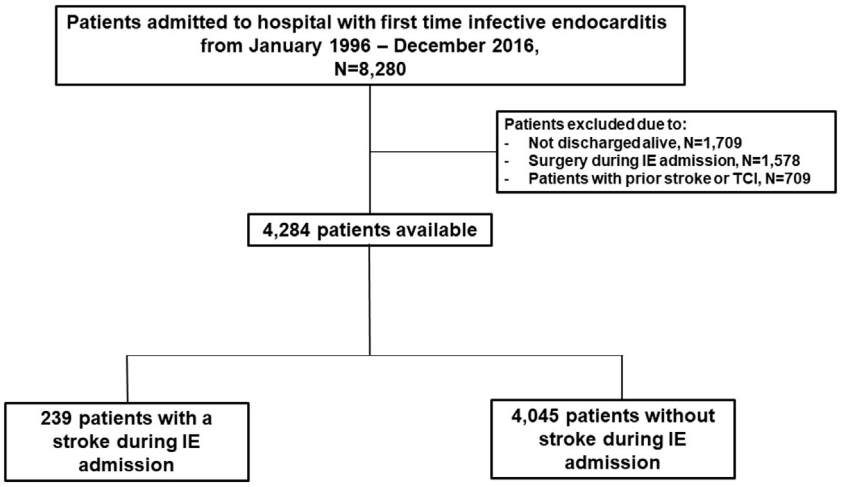
The study population was derived from the Danish National Patient Registry and included patients with first-time hospitalization due to IE according to the following *ICD-10* codes I33, I38, and I39.8 in the period from 1996 to 2016 using primary and secondary diagnosis codes. Patients with these codes and a length of hospital stay ≥14 days have been validated with a positive predictive value of 90% in the National Patient Registry. Patients coded as IE with a length of hospital stay <14 days were excluded.[18,19] Furthermore, patients undergoing cardiac surgical treatment during IE admission were excluded because of the risk of stroke subsequent and during surgery for heart valve replacement.[20] Patients not discharged alive were excluded. Patients with a stroke or transient cerebral ischemia (TCI) any time prior to IE admission were excluded. The study population was grouped into (1) patients with stroke during IE admission and (2) patients without stroke during IE- admission. Hospital admission for IE was identified as the combined hospitalization in which a diagnosis of IE was given. In that way, we accounted for transfers between departments and hospitals during the course of IE. If a primary or secondary diagnosis code of stroke (*ICD-10* codes DI61-DI64) was given during this hospitalization, the patient was categorized as "stroke during IE admission." Figure 1 shows a flowchart of the patient selection process. The primary outcome was defined as an inpatient primary diagnosis of stroke, including ischemic, intracerebral hemorrhage and nonclassified stroke (see Supplemental Table I for specific codes). The codes of the primary outcome have been validated in the Danish National Patient Registry with a positive predictive value between 74% and 97%.[21] Diagnosis codes of unspecified stroke from the Danish National Patient Registry have been identified, in a validation study, to account for ischemic stroke in 57.1%-63.8% of the cases. Our secondary outcome was all-cause mortality. The patients were followed from date of discharge after IE until hospital admission for stroke, death, emigration, end of study period (December 31, 2016), or a maximum of 5 years of follow-up.

Statistics

Baseline characteristics were shown by study groups (patients with and without stroke during IE admission). Categorical variables were shown in the counts and percentages, whereas continuous variables were shown with a median and 25th and 75th percentiles. The χ^2 test was used to assess differences in baseline characteristics between groups for categorical variables, and the Kruskal-Wallis test was used for continuous variables. Crude incidence rates of stroke were presented for the 2 groups per 1,000 person-years (PY) and with a 95% CI. Cumulative incidence curves for time to stroke were plotted for the 2 study populations using the Aalen-Johansen estimator accounting for death as competing risk. Gray test was used to identify difference between curves. Mortality rate for the 2 groups were plotted using Kaplan-Meier estimates and the log-rank test for difference between curves.

Multivariable adjusted Cox proportional-hazard analysis was used to examine the associated risk of stroke between the 2 groups and to identify factors at baseline and their associated risk of stroke. The following covariates were included in the model: stroke during IE admission, sex, age, calendar year, heart failure before IE admission, chronic obstructive lung disorder, pacemaker before IE admission, aortic valve disease, mitral valve disease, renal disease and dialysis before IE admission, heart valve surgery, antihypertensive drugs, corticosteroid treatment, atrial fibrillation, anticoagulant therapy (vitamin K antagonist, dabigatran, rivaroxaban, or apixaban), glucose-lowering treatment, and antiplatelet therapy (clopidogrel and aspirin). The proportional-hazard assumption was tested for the primary outcome (stroke) and death, and we identified a *P* value of .006 and .006 for interaction with follow-up time for the primary outcome and all-cause mortality, respectively. Therefore, follow-up time was split at 1 year of follow-up. We tested whether there was an interaction with sex and age on the primary outcome. Furthermore, linearity for age and hospital duration was tested. Results were presented with a hazard ratio (HR) and a 95% CI. A *P* value less than .05 was considered statistically significant. We performed a sensitivity analysis including patients with a TCI or stroke during IE admission or in a period of 6 months prior to IE admission in the group defined as "stroke during IE admission." Furthermore, we

Figure 1



Patient selection. The figure shows a flowchart of the patient selection.

conducted 5 additional sensitivity analyses: (1) we included patients undergoing heart valve surgery during IE admission; (2) we split follow-up time at 0-90 days of follow-up, and 90 days and up to 5 years of follow-up; (3) we investigated the associated risk of stroke in patients with stroke during IE admission compared with patients without stroke during IE admission with a mechanical prosthetic heart valve and without a mechanical prosthetic heart valve; (4) we investigated the associated risk of stroke in patients with prior myocardial infarction and treated with aspirin; and (5) we investigated the risk of stroke in patients treated with antithrombotic and/or anticoagulant therapy compared with patients with stroke during IE admission.

All statistical analyses were performed using the SAS statistical software, version 9.4 (SAS Institute, Inc, Cary, NC).

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Results

We included a total of 4,284 patients with IE: 239 (5.6%) patients with stroke and 4,045 (94.4%) patients without stroke during IE admission. For patients with stroke during IE admission, 140 (58.6%) had an ischemic lesion, 23 (9.8%) had a hemorrhagic lesion, and 76 (33.0%) were categorized as having a stroke without further specifications. Furthermore, for patients with stroke during IE admission, 136 (56.9%) were admitted with IE at the same date as admission for stroke, whereas 103 patients (43.1%) had a diagnosis of stroke within hospitalization for IE. Table I presents characteristics for the 2 study populations. Patients with stroke during IE admission were older, were more often female, and had a longer length of stay in hospital. We identified no difference in anticoagulant therapy or antiplatelet therapy 6 months prior to IE admission between groups; see Table I.

Incidence of stroke subsequent to IE discharge

For patients with stroke during IE admission, 15 patients were hospitalized with stroke during follow-up: 3 patients (20.0%) with hemorrhagic stroke, 6 patients (40.0%) with ischemic stroke, and 6 patients (40.0%) with unspecified stroke; see Supplemental Table II. The median time from hospital discharge to event was 74 days (25th and 75th percentiles 21-581 days). For patients without stroke during IE admission, 145 patients were hospitalized with stroke during follow-up: 30 patients (20.7%) with hemorrhagic stroke, 74 (51.0%) with ischemic stroke, and 41 (28.3%) with unspecified stroke.

The crude incidence rate of stroke within 1 year of follow-up was 62.2 cases/1,000 PY (95% CI 34.4-112.3) and 17.2 cases/1,000 PY (95% CI 13.3-22.2) for patients with and without stroke during IE admission, respectively. From 1 year after discharge and up to 5 years after discharge, the incidence rate of stroke was 7.0 cases of stroke/1,000 PY (95% CI 2.6-18.6) and 7.3/1,000 PY (95% CI 5.9-9.1) for patients with and without stroke during IE admission, respectively. Figure 2, *A* and *B* shows the cumulative incidence of stroke for the 2 study groups with 1 year of follow-up ($P < .0001$ for difference between curves) and from 1 to 5 years of follow-up ($P = .86$ for difference between curves). Within the first 6 months after IE discharge, we observed that 21.0% and 24.3% filled a prescription for an anticoagulant drug ($P = .24$ for difference between groups), 32.6% and 29.2% filled a prescription for aspirin ($P = .25$), and 16.7% and 4.1% filled

Table I. Baseline patient characteristics

	Stroke during IE admission	No stroke during IE admission	*P* value
Demographics			
Number	239	4045	
Male, n (%)	139 (58.2)	2622 (64.8)	.04
Age (y), median (IQR)	71.9 (61.1-81.0)	69.7 (56.1-78.8)	.01
Duration of hospital admission (d), median (IQR)	54.0 (42.0-79.0)	42.0 (31.0-51.0)	<.0001
Medical history during IE admission			
Heart failure, (%)	28 (11.7)	472 (11.7)	.98
Cardiac implantable electronic device, n (%)	9 (3.8)	281 (7.0)	.06
Renal disease, n (%)	25 (10.5)	382 (9.4)	.60
Renal dialysis, n (%)	21 (8.8)	273 (6.8)	.23
Comorbidity, medical history prior to IE admission			
Heart failure, n (%)	39 (16.3)	820 (20.3)	.14
Atrial flutter/fibrillation, n (%)	41 (17.2)	861 (21.3)	.13
COLD, n (%)	20 (8.4)	447 (11.1)	.20
Cardiac implantable electronic device, n (%)	12 (5.0)	506 (12.5)	.001
Aortic valve disease, n (%)	60 (25.1)	882 (21.8)	.23
Aortic stenosis, n (%)	36 (15.1)	577 (14.3)	
Aortic regurgitation, n (%)	9 (3.8)	147 (3.6)	
Other or nonclassified aortic valve disease, n (%)	15 (6.3)	158 (3.9)	
Mitral valve disease, n (%)	20 (8.4)	337 (8.3)	.98
Mitral regurgitation, n (%)	8 (3.4)	209 (5.2)	
Mitral prolapse, n (%)	0	35 (0.9)	
Mitral stenosis, n (%)	0	25 (0.6)	
Other or nonclassified mitral valve disease, n (%)	12 (5.0)	68 (1.7)	
Renal disease, n (%)	14 (5.9)	398 (9.8)	.04
Renal dialysis, n (%)	9 (3.8)	226 (5.6)	.23
Cancer, n (%)	37 (15.5)	630 (15.6)	.97
Prosthetic heart valve, n (%)	23 (9.6)	513 (12.7)	.16
Prehospital medication			
Aspirin, n (%)	65 (27.2)	1140 (28.2)	.74
Clopidogrel, n (%)	4 (1.7)	145 (3.6)	.12
Anticoagulant therapy, n (%)	51 (21.3)	882 (21.8)	.87
Glucose-lowering medication, n (%)	31 (13.0)	541 (13.4)	.86
Corticosteroids, n (%)	21 (8.8)	440 (10.9)	.31
Lipid-lowering medication, n (%)	55 (23.0)	1025 (25.3)	.42
Antihypertensives,* n (%)	91 (38.1)	1431 (35.4)	.40

COLD, chronic obstructive lung disease.
*Defined as at least 2 drugs of antihypertensive medication (see Supplemental Table I)

a prescription for clopidogrel ($P < .0001$) for patients with and without a stroke during IE, respectively. Among patients with stroke during IE admission, 18 patients (7.5%) underwent valve surgery during follow-up with a median time to surgery from IE discharge of 257 days (25th and 75th percentiles: 89-824 days). Among patients without stroke during IE admission, 395 patients (9.8%) underwent valve surgery during follow-up with a median time to surgery from IE discharge of 313 days (25th and 75th percentiles: 90-1,310 days).

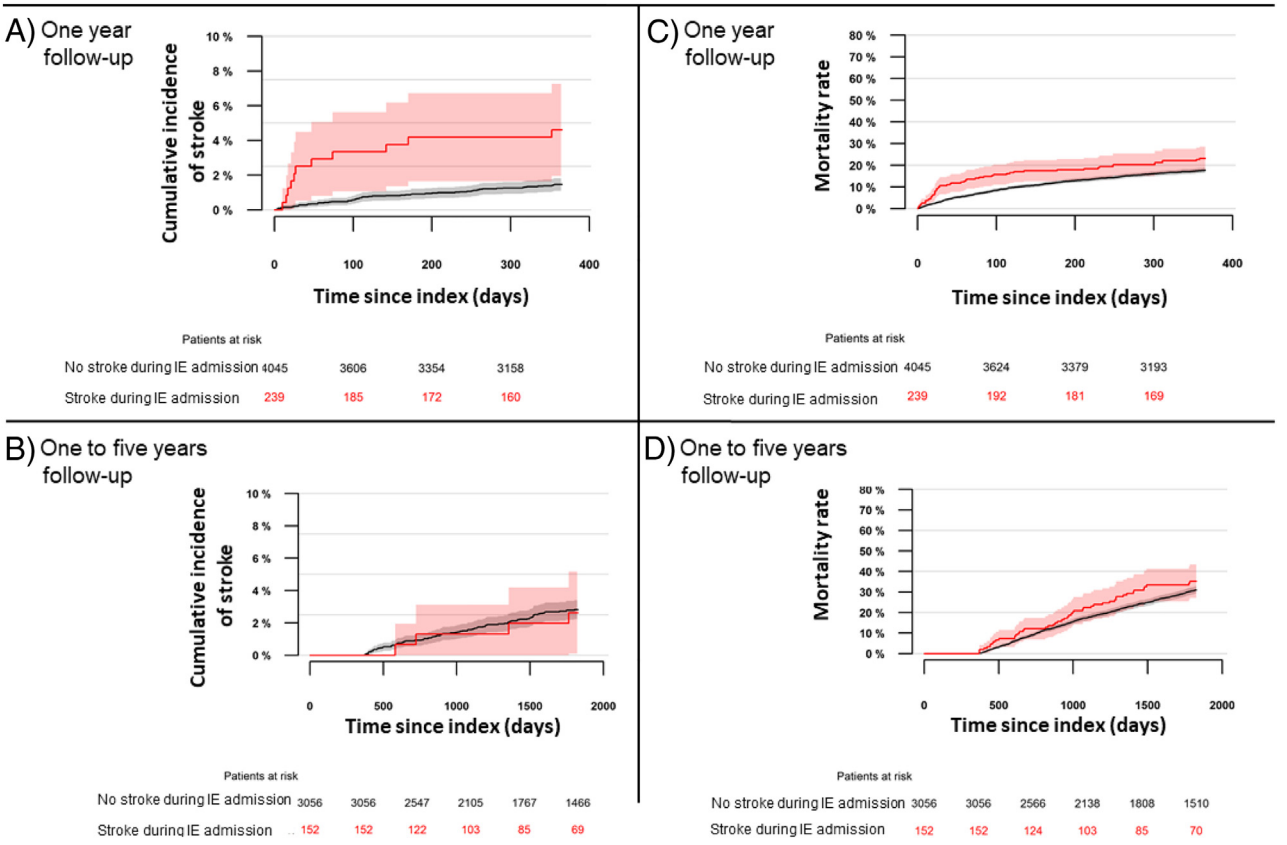
Associated risk of stroke between study groups

In a multivariable adjusted analysis, at 1 year of follow-up, we identified a higher associated risk of subsequent stroke in patients with stroke during IE admission compared with patients without a stroke, HR = 3.21 (95% CI 1.66-6.20). With 1 to 5 years of follow-up, we found no significant difference in the associated risk of stroke in patients with stroke during IE admission compared with patients without a stroke, HR = 0.91 (95% CI 0.33-2.50) in a multivariable adjusted analysis. Age or sex did not modify the associated risk of stroke. Figure 3 shows factors associated with stroke with up to 1 year of follow-up and 1 to 5 years of follow-up, *A* and *B*, respectively. With up to 1 year of follow-up, no other factors than stroke during IE admission were associated with an increased risk of subsequent stroke. With 1 to 5 years of follow-up, we identified that age was associated with an increased risk of stroke subsequent to IE discharge.

Mortality

The all-cause mortality rate for the 2 study groups are shown in Figure 2, *C* and *D*. One-year mortality rate was 23.1% and 17.7% ($P = .01$ for difference between curves) for patients with and without a stroke during IE admission, respectively. In an adjusted analysis, the mortality rate remained statistically significant higher in patients with a stroke during IE admission compared with patients without

Figure 2



Cumulative incidence of stroke and mortality rate. The figure shows the cumulative incidence of stroke at 0-1 year of follow-up (**A**) and 1-5 years of follow-up (**B**) for patients with and without stroke during endocarditis admission. Furthermore, the mortality rate for patients with and without stroke during endocarditis admission is seen with 0-1 year of follow-up (**C**) and 1-5 years of follow-up (**D**).

a stroke during IE admission, HR = 1.37 (95% CI 1.03-1.82). With 1 to 5 years of follow-up, the mortality rate was 35.2% and 31.0% (P = .18 for difference between curves) for patients with and without a stroke during IE admission, respectively. In an adjusted analysis, the difference in the mortality rate remained statistically nonsignificant between groups, HR = 1.26 (95% CI 0.94-1.69).

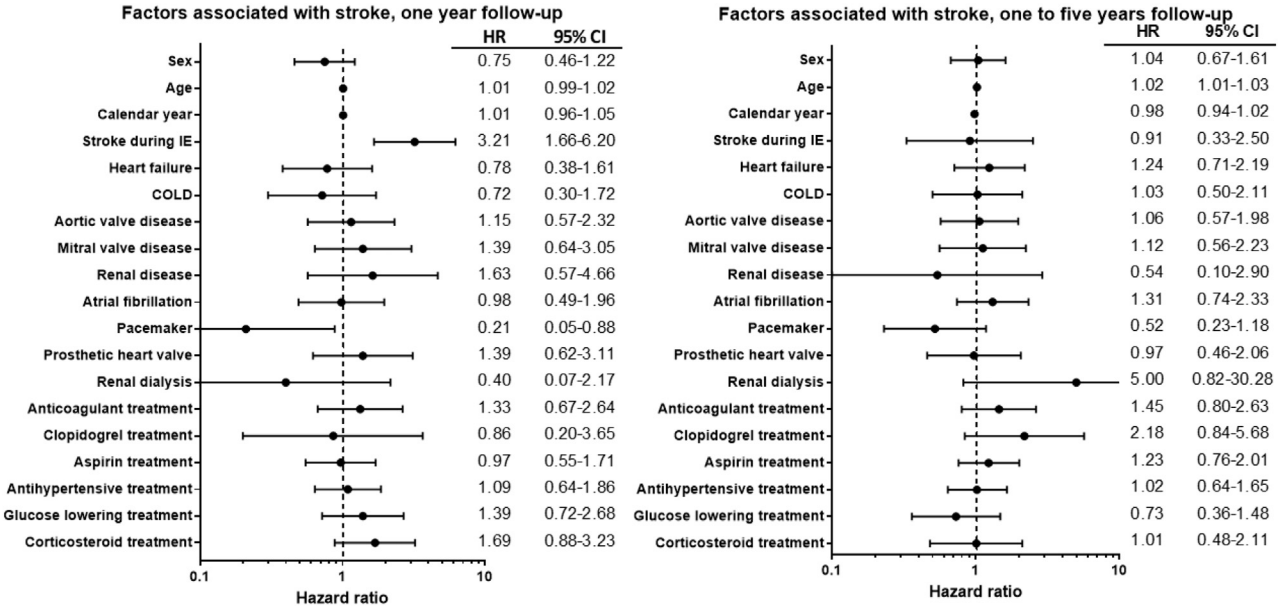
Sensitivity analyses

We found no major differences from our primary findings when stroke 6 months prior to IE admission was included and TCI also was included as an exposure: 250 patients were classified as patients with stroke during IE admission, and 4,034 patients were classified without stroke during IE admission. The 1-year incidence of stroke was 58.6/1,000 PY (95% CI 32.5-105.8) for patients with a stroke or TCI during IE admission and 17.2/1,000 PY (95% CI 13.4-22.2) for patients without a stroke or TCI during IE admission.

When including patients undergoing heart valve surgery during IE admission (total study population, n = 5,735) with up to 1 year of follow-up, we found an incidence rate of 59.2 strokes/1,000 PY (95% CI 37.3-94.0) and 16.5/1,000 PY (95% CI 13.2-20.6) for patients with and without stroke during IE admission, respectively. With 1 to 5 years of follow-up, we found an incidence rate of 7.7/1,000 PY (95% CI 3.8-15.3) and 7.5/1,000 PY (95% CI 6.3-8.9) for patients with and without stroke during IE admission, respectively.

Follow-up period was changed to 0-90 days of follow-up and from 90 days of follow-up and up to 5 years. No overall change was seen in the main results (Supplemental Figure 1). We found that patients without stroke with a prosthetic mechanical heart valve were at similar associated risk of stroke compared with patients with stroke during IE admission (Supplemental Figure 2). Patients with stroke during IE admission were at increased associated risk of stroke compared with patients without stroke during IE admission who also had prior myocardial infarction treated with aspirin (Supplemental Figure 3). Finally, patients with stroke during IE admission were at increased associated risk of stroke compared with patients without stroke during IE

Figure 3



Factors associated with stroke. The figure shows factors included in the multivariable adjusted regression analysis and the associated risk of stroke subsequent to discharge for infective endocarditis for 0-1 year of follow-up (**left panel**) and 1-5 years of follow-up (**right panel**).

admission treated with antithrombotic and/or anticoagulant therapy prior to IE admission (Supplemental Figure 4).

Discussion

We investigated the long-term risk of stroke in patients discharged alive after IE treatment with medical therapy only. Our study yielded 3 major findings: (1) the associated risk of stroke within the first year after IE discharge was 3 times higher for patients with a stroke during IE admission compared with patients without a stroke during IE admission; (2) after 1 year of follow-up, the associated risk of stroke was similar between groups; and (3) the mortality rate was significantly higher among patients with stroke during IE admission compared with patients without stroke within the first year after IE discharge; however, after 1 year of follow-up, mortality rates were no longer significantly different.

It is well known from randomized controlled trials that a previous stroke or TCI is a risk factor for subsequent stroke[22,23]; however, whether a stroke during IE admission is a risk factor for stroke on the long term is not clear. Our data suggest that patients with a stroke during IE admission are at a considerably higher risk within the first year post discharge compared with patients without a stroke during IE admission. Residual vegetation, vulnerable valve tissue, postinfection alterations in coagulation or thrombocyte function, other comorbidities, or general patient frailty may explain this increased risk.

The long-term risk of stroke in patients surviving IE has previously been investigated.[12,13] A nationwide, population-based study from Taiwan compared IE survivors (n = 10,116) with controls from the background population (n = 17,926) and identified a significantly higher risk of ischemic and hemorrhagic stroke, HR = 1.59 (95% CI 1.40-1.80) and HR = 2.37 (95% CI 1.90-2.96), respectively.[13] This study included IE patients treated surgically, and the risk of stroke may be related to the postsurgical risk of stroke. Our data only included nonsurgically treated IE patients. We chose this approach to examine the relationship as homogenously as possible, as patients with a valve prothesis have many other competing factors for stroke and also anticoagulation therapy. However, in a sensitivity analysis, including patients treated surgically during IE admission did not alter our main findings. The proportion of patients undergoing surgical treatment during IE admission and the proportion of patients with a prosthetic heart valve diagnosed with IE identified from our cohort are in line with previous population-based studies from Spain and the United States.[24,25] Furthermore, an American population-based study identified an increased risk of stroke not only around the time of IE diagnosis but also 4 months prior to and 5 months after IE in a case crossover design.[12] Our

study adds valuable knowledge to current data showing an increased associated risk of subsequent stroke after IE discharge in patients with a stroke during IE admission compared with patients without a stroke during IE admission for the first year only. Compared with previous literature, our data suggest that all IE patients carry a higher risk of stroke compared with patients without stroke risk factors.[23] We present data that are unique because we were able to follow an unselected cohort with long-term follow-up.

Whereas no prior studies have assessed the risk of stroke subsequent to IE in patients with and without stroke during IE admission, some studies have investigated the mortality rate among IE survivors. A study by Thuny et al showed an excess mortality in patients surviving IE compared with expected survival.[26] Furthermore, a population-based Swedish study found an increased standardized mortality ratio in patients surviving IE, which remained increased with up to 5 years of follow-up.[27] High clinical awareness of stroke is needed especially in the first year after discharge where the occurrence of stroke is substantially higher in patients with stroke during IE admission compared with patients without a stroke during IE admission. However, beyond 1 year after discharge, mortality and stroke rates become similar between groups according to our data.

Several studies have investigated factors at IE admission and the associated risk of stroke during IE admission. Size and mobility of the vegetation, *Staphylococcus aureus* etiology, and mitral valve IE are factors considered to be associated with an increased risk of stroke during IE admission[3,28-31]; however, these studies have not been able to identify factors associated with long-term stroke risk. With follow-up from 1 to 5 years, we identified that age was associated with an increased risk of stroke after IE discharge.

The use of anticoagulant in patients with IE is an area of much debate,[32] and the recommendations on anticoagulant or antiplatelet therapy in patients with IE from the European Society of Cardiology and the American Heart Association are based on few studies.[10,11] The initiation of aspirin in patients with IE is not recommended.[14] For patients already treated with anticoagulant therapy before the onset of IE, data from observational studies are conflicting. Snygg-Martin et al showed that warfarin treatment on IE admission was associated with a decreased risk of cerebrovascular complications and with no increase in hemorrhagic lesions.[33] In patients with *S aureus* IE, a study by Tornos et al identified an increased risk of death due to neurologic complications in patients on anticoagulant therapy; however, Rasmussen et al identified no increased risk of cerebral hemorrhage in patients with *S aureus* IE treated with anticoagulant therapy.[34] The aim of our study was not to determine safety and effectiveness of anticoagulant therapy during IE admission. Future studies are needed on this subject to guide clinical decision on this area.

Limitations

Our study has several limitations which need to be addressed. First, we identified 239 patients (5.6%) with a stroke during IE admission. This number is low in comparison with previous studies on this area[3,35]; however, these studies have been conducted on cohorts from referral centers which may differ from a large unselected cohort as ours. Furthermore, our study population consisted of patients surviving IE and patients only receiving antibacterial therapy as IE treatment (ie, surgically treated patients were excluded). In addition, differences on the awareness of cerebral lesions on magnetic resonance imaging may have led to differences between study populations.[36] Our study did not have information on magnetic resonance imaging, which could have described the cerebral lesion in more detail. Second, we had no data on vegetation size, affected valve, or microbiological etiology. This could have helped characterize whether differences were seen on the risk of stroke by residual vegetation, affected valve, or type of microbiological agent. Furthermore, data on intravenous drug users and blood pressure readings were not accessible from the registries used. Third, our outcome of stroke is based on diagnosis codes, and no clinical data have been available to confirm a new case of stroke. To account for this limitation, we only included in-hospital codes with a primary diagnosis code of stroke.

Conclusion

Patients with a stroke during IE admission were at a significantly higher risk of subsequent stroke within 1 year of follow-up compared with patients without stroke during IE admission. This risk difference was not evident beyond 1 year of discharge. These findings underline the need for identification of causes and mechanisms of recurrent strokes after IE to develop preventive means.

Appendix. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2019.03.010.

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