Stroke

BRIEF REPORT

Stroke-Heart Syndrome: Incidence and Clinical Outcomes of Cardiac Complications Following Stroke

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BACKGROUND: The risk of major adverse cardiovascular events is substantially increased following a stroke. Although exercise-based cardiac rehabilitation has been shown to improve prognosis following cardiac events, it is not part of routine care for people following a stroke. We, therefore, investigated the association between cardiac rehabilitation and major adverse cardiovascular events for people following a stroke. Following a stroke, individuals have an increased risk of new-onset cardiovascular complications. However, the incidence and long-term clinical consequence of newly diagnosed cardiovascular complications following a stroke is unclear. The aim of the present study was to investigate the incidence and long-term clinical outcomes of newly diagnosed cardiovascular complications following incident ischemic stroke.

METHODS: A retrospective cohort study was conducted using anonymized electronic medical records from 53 participating health care organizations. Patients with incident ischemic stroke aged ≥18 years with 5 years of follow-up were included. Patients who were diagnosed with new-onset cardiovascular complications (heart failure, severe ventricular arrhythmia, atrial fibrillation, ischemic heart disease, Takotsubo syndrome) within 4-weeks (exposure) of incident ischemic stroke were 1:1 propensity score-matched (age, sex, ethnicity, comorbidities, cardiovascular care) with ischemic stroke patients who were not diagnosed with a new-onset cardiovascular complication (control). Logistic regression models produced odds ratios (OR) with 95% CIs for 5-year incidence of all-cause mortality, recurrent stroke, hospitalization, and acute myocardial infarction.

RESULTS: Of 365 383 patients with stroke with 5-year follow-up: 11.1% developed acute coronary syndrome; 8.8% atrial fibrillation/flutter; 6.4% heart failure; 1.2% severe ventricular arrythmias; and 0.1% Takotsubo syndrome within 4 weeks of incident ischemic stroke. Following propensity score matching, odds of 5-year all-cause mortality were significantly higher in stroke patients with acute coronary syndrome (odds ratio, 1.49 [95% CI, 1.44–1.54]), atrial fibrillation/flutter (1.45 [1.40–1.50]), heart failure (1.83 [1.76–1.91]), and severe ventricular arrhythmias (2.08 [1.90–2.29]), compared with matched controls. Odds of 5-year rehospitalization and acute myocardial infarction were also significantly higher for patients with stroke diagnosed with new-onset cardiovascular complications. Takotsubo syndrome was associated with significantly higher odds of 5-year composite major adverse cardiovascular events (1.89 [1.29–2.77]). Atrial fibrillation/flutter was the only new-onset cardiac complication associated with significantly higher odds of recurrent ischemic stroke at 5 years (1.10 [1.07–1.14]).

CONCLUSIONS: New-onset cardiovascular complications diagnosed following an ischemic stroke are very common and associate with significantly worse 5-year prognosis in terms of major adverse cardiovascular events. People with stroke and newly diagnosed cardiovascular complications had >50% prevalence of recurrent stroke at 5 years.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: acute coronary syndrome ■ arrythmias ■ atrial fibrillation ■ cerebrovascular disorders ■ heart failure ■ ischemic stroke ■ secondary prevention

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Nonstandard Abbreviations and Acronyms

ACS	acute coronary syndrome
ICD-10-CM	*International Classification of Diseases, Tenth Revision, Clinical Modification*
MACE	major adverse cardiovascular events
OR	odds ratio

New-onset cardiovascular complications are a major medical challenge following ischemic stroke.[1,2] One randomized controlled trial reported up to 20% of patients with ischemic stroke are diagnosed with new-onset major adverse cardiovascular events (MACE), including acute coronary syndrome (ACS), heart failure, and arrhythmias within the acute stroke phase.[3] Importantly, these new-onset cardiovascular complications following an ischemic stroke are associated with poor functional prognosis and increased mortality in the weeks following the cerebral event.[3]

An increasing body of evidence suggests that the varying new-onset cardiovascular complications which present following a stroke likely share the same underlying mechanisms, that is, autonomic and inflammatory mechanisms mediated by damage to the brain-heart axis.[4] The brain-heart axis is, therefore, implicated in poststroke cardiovascular complications known as the stroke-heart syndrome, sudden cardiac death, and Takotsubo syndrome, among other neurocardiogenic syndromes. An official neurocardiology working group (World Stroke Organization Brain & Heart Task Force) was recently established, which highlights the need and commitment for multidisciplinary clinical and research collaborations to improve care and outcomes for conditions, such as the stroke-heart syndrome.[5]

Although some studies have demonstrated that the stroke-heart syndrome associates with unfavorable short-term (acute) prognosis, long-term consequences, including secondary cardiac events and mortality, have not been previously described. Therefore, the aim of the present study was to investigate the incidence and long-term clinical outcomes of new-onset cardiovascular complications diagnosed following incident ischemic stroke. It is hoped that by understanding the incidence and impact of stroke-heart syndrome, more targeted preventive and rehabilitation strategies can be developed for people following stroke.[6]

METHODS

To gain access to TriNetX data, a request can be made (https://live.trinetx.com), but costs may be incurred, a data sharing agreement would be necessary, and no patient identifiable information can be obtained.

This retrospective observational study used complete case, anonymized data within TriNetX, a global federated health research network with access to electronic medical records from participating academic medical centers, specialty physician practices, and community hospitals, predominantly in the United States. As a federated network, research studies using TriNetX do not require ethical approval or patient informed consent as no identifiable information is received. The TriNetX network was searched on August 1, 2021, and deidentified datasets were analyzed that included data from 2002 to 2021 with at least 5-year of follow-up (ie, index event [incident ischemic stroke] occurred at least 5 years ago). This study is reported as per the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (Table S1). More detailed information about the online database and methods used can be found within Supplemental Material 2.

Patients with an incident acute ischemic stroke, aged ≥18 years with at least 5-year follow-up were identified from the first instance of an *International Classification of Diseases, Tenth Revision, Clinical Modification* (*ICD-10-CM*) code I63 (Cerebral infarction). The complete data set including index event and all outcomes spanned 2002 to 2021. The ischemic stroke cohort was stratified by newly diagnosed, poststroke cardiovascular complications. Newly diagnosed cardiovascular complications (within 4 weeks of ischemic stroke) were identified via *ICD-10-CM* codes: I20-I25 (ischemic heart diseases; ie, ACS), I48 (atrial fibrillation/flutter), I50 (heart failure), I49.0 (ventricular fibrillation/flutter), and I47.2 (ventricular tachycardia; ie, severe ventricular arrhythmias), and I51.81 (Takotsubo syndrome). For propensity score matching, these cardiovascular complications were excluded in the controls. At the time of the search, 53 (primarily US-based) participating health care organizations had data available for patients who met the study inclusion criteria.

Baseline characteristics were compared using χ^2 tests or independent-sample *t* tests. Propensity score matching was used to control for differences in the comparison cohorts. Using logistic regression, patients diagnosed with a new-onset cardiovascular complication within 4 weeks of an incident ischemic stroke were 1:1 propensity score matched to patients without a new-onset cardiovascular complication poststroke for age, sex, ethnicity, hypertensive diseases, ischemic heart diseases (except for ACS cohort), cerebrovascular diseases (eg, hemorrhage, transient ischemic attack, and sequelae of cerebrovascular disease), heart failure (except for heart failure cohort), pulmonary heart disease/disease of the pulmonary circulation, diabetes, cardiovascular procedures (including electrocardiography, echocardiography, catheterization, cardiac devices, and electrophysiological procedures), and cardiovascular medications (including β-blockers, antiarrhythmics, diuretics, antilipemic agents, antianginals, calcium channel blockers, and angiotensin-converting-enzyme inhibitors). These variables were chosen because they may impact clinical outcomes. Following propensity score matching, logistic regression produced odds ratios (OR) with 95% CIs for 5-year incidence of MACE (all-cause mortality, rehospitalization, incident acute myocardial infarction, recurrent stroke, and incident atrial fibrillation/flutter), comparing stroke patients with new-onset cardiovascular complications with propensity matched controls (without new-onset poststroke cardiovascular complications). For the Takotsubo syndrome cohort comparisons, a composite of 5-year MACE was used due to a relatively small sample size. Statistical significance was set at $P<0.05$.

RESULTS

In total, 365 383 patients with incident ischemic stroke were identified from 53 (primarily United States) health care organizations with 5-year follow-up. Of which, 11.1% developed ACS, 8.8% atrial fibrillation/flutter, 6.4% heart failure, 1.2% severe ventricular arrythmia, and 0.1% Takotsubo syndrome within 4 weeks following stroke (Table). Following propensity score matching, there were n=80 988 patients in ACS, 32 012 in atrial fibrillation/flutter, 46 990 in heart failure, 8918 in severe ventricular arrhythmia, and 676 in Takotsubo syndrome

Table. Incidence of Poststroke Cardiovascular Complications and Associated 5-Year MACE, Comparing Patients With/Without Presentation of Acute Cardiovascular Complications Following Incident Stroke

Acute cardiovascular complications*	n=acute cardiovascular complications vs without*			
MACE†	% Events (MACE)†	Odds ratio	95% CI	*P* value
ACS* (11.1%)	(40 497 vs 324 886)			
All-cause mortality†	25.3 vs 18.5	1.49	1.44–1.54	<0.0001
Hospitalization†	41.6 vs 38.3	1.15	1.12–1.18	<0.0001
Recurrent stroke†	55.7 vs 56.5	0.97	0.95–1.00	0.04
AF/flutter* (8.8%)	(32 012 vs 333 371)			
All-cause mortality†	29.7 vs 22.6	1.45	1.40–1.50	<0.0001
Hospitalization†	44.2 vs 37.9	1.30	1.26–1.34	<0.0001
Recurrent stroke†	57.2 vs 54.8	1.10	1.07–1.14	<0.0001
AMI†	4.9 vs 5.1	0.97	0.91–1.05	0.49
Heart failure* (6.4%)	(23 498 vs 341 884)			
All-cause mortality†	31.2 vs 19.9	1.83	1.76–1.91	<0.0001
Hospitalization†	49.0 vs 40.1	1.44	1.39–1.49	<0.0001
Recurrent stroke†	56.7 vs 57.2	0.98	0.94–1.01	0.21
AMI†	15.2 vs 7.1	2.35	2.21–2.50	<0.0001
HFrEF* (2.2%)	(8637)			
All-cause mortality†	33.7 vs 19.8	2.06	1.92–2.06	<0.0001
Hospitalization†	47.6 vs 38.3	1.46	1.38–1.55	<0.0001
Recurrent stroke†	57.09 vs 56.8	1.01	0.95–1.07	0.74
AMI†	21.1 vs 8.9	2.73	2.50–2.99	<0.0001
HFpEF* (1.8%)	(7083)			
All-cause mortality†	31.8 vs 22.7	1.59	1.48–1.72	<0.0001
Hospitalization†	51.7 vs 40.9	1.54	1.45–1.65	<0.0001
Recurrent stroke†	60.8 vs 57.5	1.15	1.07–1.23	<0.0001
AMI†	13.5 vs 9.4	1.51	1.36–1.67	<0.0001
VT/VF* (1.2%)	(4459 vs 360 923)			
All-cause mortality†	35.9 vs 21.2	2.08	1.90–2.29	<0.0001
Hospitalization†	48.4 vs 43.7	1.21	1.11–1.31	<0.0001
Recurrent stroke†	53.2 vs 57.7	0.84	0.77–0.91	<0.0001
AMI†	8.8 vs 6.3	1.42	1.19–1.70	<0.0001
Takotsubo syndrome* (0.1%)	(338 vs 364 494)			
MACE‡	84.3 vs 74.0	1.89	1.29–2.77	<0.001

ACS indicates acute coronary syndrome; AF/flutter, atrial fibrillation/atrial flutter; AMI, acute myocardial infarction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MACE, major adverse cardiovascular event (mortality, hospitalization, stroke, AMI); and VT/VF, ventricular tachycardia/ventricular fibrillation.

*Incidence of first occurrence of cardiovascular complications within 4 wk of incident stroke presented as % of total population (n=with vs n=without cardiovascular complication). Sample sizes for prepost propensity score matched cohorts are presented in baseline characteristics tables.

†Associated MACE 5 y following incident stroke comparing 1:1 propensity score matched populations with/without acute cardiovascular complications following incident stroke.

‡Composite outcome presented (MACE; all-cause mortality, hospitalization, recurrent stroke, and AMI) due to relatively small sample size.

cohort comparisons. The cohorts were overall well-matched for age, sex, ethnicity, included comorbidities, and cardiovascular care (Tables S2–S6).

Using the propensity score matched cohorts, 5-year mortality was significantly higher with patients with stroke who developed ACS (OR, 1.49 [95% CI, 1.44–1.54]), atrial fibrillation/flutter (OR, 1.45 [95% CI, 1.40–1.50]), heart failure (OR, 1.83 [95% CI, 1.76–1.91]), severe ventricular arrythmia (OR, 2.08 [95% CI, 1.90–2.29]), and Takotsubo syndrome (OR, 1.89 [95% CI, 1.29–2.77]), compared with propensity score matched patients with stroke who did not develop new-onset cardiovascular complications (Table).

The 5-year rehospitalization rate was significantly higher among those with any new-onset cardiovascular condition poststroke, compared with those without. Atrial fibrillation/flutter, heart failure, and severe ventricular arrythmia were associated with significantly higher odds of an acute myocardial infarction at 5 years compared with matched poststroke controls.

Only atrial fibrillation/flutter was associated with significantly higher odds of recurrent ischemic stroke at 5 years (1.10 [1.07–1.14]), compared with poststroke patients without atrial fibrillation/flutter. Takotsubo syndrome was associated with significantly higher odds of a composite outcome of MACE (mortality, rehospitalization, recurrent stroke, and acute myocardial infarction), compared with matched poststroke controls without Takotsubo syndrome (1.89 [1.29–2.77]). Please refer to the Table for full presentation of results.

Of note, all cohorts with a newly diagnosed cardiovascular complication within 4 weeks of an ischemic stroke presented with >50% prevalence of recurrent stroke at 5-year follow-up.

Limitations

The Center for Stroke Research Berlin has proposed criteria for stroke-heart syndrome including a broad range of clinical presentations, such as repolarization changes, cardiac arrhythmia, exacerbation of heart failure, Takotsubo syndrome, and acute myocardial infarction (to name a few).[2] Elevations in cardiac biomarkers (ie, cardiac troponin and brain natriuretic peptide) are among the most studied manifestations of stroke-heart syndrome yet are not included in the present article. Instead, we focused on more substantial cardiovascular complications, newly diagnosed within 4 weeks of an incident ischemic stroke. The characterization of stroke and cardiovascular complications were based on *ICD* codes from electronic medical records and reporting of conditions with *ICD* codes may vary by health care organization.[7] Although we used the first instance of an electronic medical record of ischemic stroke, it is possible that if a stroke occurred outside of the TriNetX network it may not be captured. We used a complete-case analysis and were unable to access incomplete cases. The 5-year MACE rate may at first seem relatively high compared with previous work. For example, it has been previously shown that poststroke acute myocardial infarction has a ≈2% incidence (at 1 year), which is substantially lower than the 5-year incidence seen in our article (up to ≈15% in people with stroke and newly diagnosed heart failure within 4 weeks of stroke). However, it is important to highlight that we investigated 5-year outcomes in people with stroke and 4-week cardiovascular complications, thereby focusing on a higher risk subgroup of stroke survivors. The incidence of acute myocardial infarction in the entire stroke cohort was 5%. Importantly, we were not able to determine the severity/location of stroke and any impact this had on outcomes. Perhaps most notably, distinguishing stroke-heart syndrome from (otherwise unknown) concomitant or preceding cardiovascular complications is challenging, and reverse causation may have impacted the results of this study. For example, whether the new-onset cardiovascular complications, diagnosed after ischemic stroke, were caused by stroke, or contributed to the stroke is unclear. Indeed, prospective research is needed to infer causation, albeit a challenging endeavor in a stroke population.

Conclusions

New-onset cardiovascular complications diagnosed following a stroke are very common and are associated with significantly worse long-term prognosis in terms of 5-year MACE. Further multidisciplinary research is needed to: improve causal inferences within stroke-heart syndrome research; create and validate a risk prediction score for developing new-onset cardiovascular complications poststroke; and develop and test specific, personalized therapeutic interventions for patients with stroke-heart syndrome.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S6
STROBE Statement

REFERENCES

1. Kumar S, Selim MH, Caplan LR. Medical complications after stroke. *Lancet Neurol.* 2010;9:105–118. doi: 10.1016/S1474-4422(09)70266-2
2. Scheitz JF, Nolte CH, Doehner W, Hachinski V, Endres M. Stroke-heart syndrome: clinical presentation and underlying mechanisms. *Lancet Neurol.* 2018;17:1109–1120. doi: 10.1016/S1474-4422(18)30336-3
3. Prosser J, MacGregor L, Lees KR, Diener HC, Hacke W, Davis S; VISTA Investigators. Predictors of early cardiac morbidity and mortality after ischemic stroke. *Stroke.* 2007;38:2295–2302. doi: 10.1161/STROKEAHA.106.471813
4. Sposato Luciano A, Hilz Max J, Aspberg S, Murthy Santosh B, Bahit MC, Hsieh C-Y, Sheppard MN, Scheitz JF. Post-stroke cardiovascular complications and neurogenic cardiac injury. *J Am Coll Cardiol.* 2020;76:2768–2785. doi: 10.1016/j.jacc.2020.10.009
5. Sposato LA, Gurol ME. Advances in neurocardiology: focus on atrial fibrillation. *Stroke.* 2021;52:3696–3699. doi: 10.1161/STROKEAHA.121.033970
6. Buckley BJR, Harrison SL, Fazio-Eynullayeva E, Underhill P, Lane DA, Thijssen DHJ, Lip GYH. Exercise-based cardiac rehabilitation associates with lower major adverse cardiovascular events in people with stroke. *Cerebrovasc Dis.* 2021:1–5. doi: 10.1159/000521025
7. Chong WF, Ding YY, Heng BH. A comparison of comorbidities obtained from hospital administrative data and medical charts in older patients with pneumonia. *BMC Health Serv Res.* 2011;11:105. doi: 10.1186/1472-6963-11-105