Brief Report

Stroke-Heart Syndrome: Incidence and clinical outcomes of cardiac complications following stroke

Benjamin J.R. Buckley, PhD[1,2*], Stephanie L. Harrison, PhD[1,2], Andrew Hill, MBChB[3], Paula Underhill[4], Deirdre A. Lane, PhD[1,2,5], Gregory Y.H. Lip, MD[1,2,5]

[1]Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom

[2]Department of Cardiovascular and Metabolic Medicine, Institute of Life Course and Medical Sciences, University of Liverpool, Liverpool, United Kingdom

[3]Department of Medicine for Older People, Whiston Hospital, St Helens & Knowsley Teaching Hospitals NHS Trust, Prescot, United Kingdom

[4]TriNetX LLC., London, United Kingdom

[5]Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

Date January, 2022

Manuscript wordcount 1,918 (including title page, abstract and references)

***Corresponding author**

Benjamin Buckley PhD, Liverpool Centre for Cardiovascular Science, University of Liverpool, William Henry Duncan Building, Liverpool, L7 8TX United Kingdom

Email: Benjamin.Buckley@liverpool.ac.uk.

Phone: +44 (0)151 794 2000

Funding

There was no specific funding received for this study. TriNetX LLC funded the acquisition of the data used through use of the network database.

Disclosures

Benjamin JR Buckley has received funding from Bristol-Myers Squibb (BMS)/Pfizer. Stephanie L Harrison has received funding from BMS. Paula Underhill is an employee of TriNetX LLC. Deirdre A Lane has received investigator-initiated educational grants from BMS, has been a speaker for Boehringer Ingeheim, Bayer, and BMS/Pfizer and has consulted for BMS, Boehringer Ingelheim, and Daiichi-Sankyo. Gregory YH Lip: consultant and speaker for BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. No fees are directly received personally.

Abstract

Background and purpose

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 ischaemic stroke.

Methods

A retrospective cohort study was conducted using anonymised electronic medical records from 53 participating healthcare organizations. Patients with incident ischaemic stroke aged ≥18 years with 5-years of follow-up were included. Patients who were diagnosed with new-onset cardiovascular complications within 4-weeks (exposure) of incident ischaemic stroke were 1:1 propensity score-matched (age, sex, ethnicity, comorbidities, cardiovascular care) with ischaemic stroke patients who were not diagnosed with a new-onset cardiovascular complication (control). Logistic regression models produced odds ratios (OR) with 95% confidence intervals (CIs) for 5-year incidence of major adverse cardiovascular events (MACE; acute coronary syndrome, atrial fibrillation/flutter, heart failure, ventricular fibrillation/flutter, and Takotsubo syndrome).

Results

Of 365,383 stroke patients with 5-year follow-up: 11.1% developed acute coronary syndrome (ACS); 8.8% atrial fibrillation/flutter; 6.4% heart failure; 1.2% severe ventricular arrythmias; and 0.1% Takotsubo syndrome within 4-weeks of incident ischaemic stroke. Following propensity score matching, odds of 5-year all-cause mortality were significantly higher in stroke patients with ACS (OR 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 to matched controls. Odds of 5-year rehospitalisation and acute myocardial infarction were also significantly higher for stroke patients diagnosed with new-onset cardiovascular complications. Takotsubo syndrome was associated with significantly higher odds of 5-year composite MACE (1.89, 1.29-2.77). Atrial fibrillation/flutter was the only new-onset cardiac complication associated with significantly higher odds of recurrent ischaemic stroke at 5-years (1.10, 1.07-1.14).

Conclusions

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

Background

New-onset cardiovascular complications are a major medical challenge following ischaemic stroke.[1 2] One randomised controlled trial reported up to 20% of ischaemic stroke patients 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 ischaemic 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 post-stroke cardiovascular complications known as the stroke-heart syndrome, sudden cardiac death, and Takotsubo syndrome, among other neurocardiogenic syndromes. An official neuro-cardiology 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 unfavourable 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 ischaemic stroke.

Methods

This retrospective observational study utilised complete case, anonymised data within TriNetX, a global federated health research network with access to electronic medical records (EMRs) from participating academic medical centres, 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 de-identified datasets were analysed that included data from 2002-2021 with at least 5-years of follow-up (i.e. index event (incident ischaemic stroke) occurred at least five years ago). This study is reported as per the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (eTable 1). More detailed information regarding the online database and methods used can be found within Supplement 2 of the supplementary file.

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.

Patients with an incident acute ischaemic stroke, aged ≥18 years with at least 5-years 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 dataset including index event and all outcomes spanned 2002 to 2021. The ischaemic stroke cohort was stratified by newly diagnosed, post-stroke cardiovascular complications. Newly diagnosed cardiovascular complications (within 4-weeks of ischaemic stroke) were identified via ICD-10-CM codes: I20-I25 (Ischaemic heart diseases) [i.e., ACS], I48 (Atrial fibrillation/flutter), I50 (Heart failure), I49.0 (Ventricular fibrillation/flutter) and I47.2 (ventricular tachycardia) [i.e., 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 healthcare organisations had data available for patients who met the study inclusion criteria.

Baseline characteristics were compared using chi-squared 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 ischaemic stroke were 1:1 propensity score-matched to patients without a new-onset cardiovascular complication post-stroke for age, sex, ethnicity, hypertensive diseases, ischaemic heart diseases (except for ACS cohort), cerebrovascular diseases (e.g., haemorrhage, transient ischaemic attack, sequelae of cerebrovascular disease), heart failure (except for heart failure cohort), pulmonary heart

disease/disease of the pulmonary circulation, diabetes mellitus, cardiovascular procedures (including electrocardiography, echocardiography, catheterization, cardiac devices, and electrophysiological procedures), and cardiovascular medications (including beta-blockers, antiarrhythmics, diuretics, antilipemic agents, antianginals, calcium channel blockers, and ACE inhibitors). These variables were chosen because they may impact clinical outcomes. Following propensity score matching, logistic regression produced odds ratios (OR) with 95% confidence intervals (CIs) for 5-year incidence of MACE (all-cause mortality, rehospitalisation, 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 post-stroke 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 ischaemic stroke were identified from 53 (primarily US) healthcare organisations 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 1). Following propensity score matching, there were *n*=80,988 patients in ACS, 32,012 in atrial fibrillation/flutter, 46,990 in heart failure, 8,918 in severe ventricular arrhythmia, and 676 in Takotsubo syndrome cohort comparisons. The cohorts were overall well-matched for age, sex, ethnicity, included comorbidities, and cardiovascular care (eTables 2-6).

Using the propensity score matched cohorts, 5-year mortality was significantly higher with stroke patients 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 to propensity score matched stroke patients who did not develop new-onset cardiovascular complications (Table 1).

The 5-year rehospitalisation rate was significantly higher among those with any new-onset cardiovascular condition post-stroke, compared to 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 to matched post-stroke controls.

Only atrial fibrillation/flutter was associated with significantly higher odds of recurrent ischaemic stroke at 5-years (1.10, 1.07-1.14), compared to post-stroke patients without atrial fibrillation/flutter. Takotsubo syndrome was associated with significantly higher odds of a composite outcome of MACE (mortality, rehospitalisation, recurrent stroke, and acute myocardial infarction), compared to matched post-stroke controls without Takotsubo syndrome (1.89, 1.29-2.77). Please refer to **Table 1** for full presentation of results.

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

Limitations

The Centre for Stroke Research Berlin has proposed criteria for stroke-heart syndrome including a broad range of clinical presentations such as repolarisation changes, cardiac arrhythmia, exacerbation of heart failure, Takotsubo syndrome, and acute myocardial infarction (to name a few).[2] Elevations in cardiac biomarkers (i.e., cardiac troponin and brain natriuretic peptide) are among the most studied manifestations of stroke–heart syndrome yet are not included in the present paper. Instead, we focussed on more substantial cardiovascular complications, newly diagnosed within 4-weeks of an incident ischaemic stroke. The characterisation of stroke and cardiovascular complications were based on ICD codes from EMRs and reporting of conditions with ICD codes may vary by healthcare organisation.[6] Although we used the first instance of an electronic medical record of ischaemic stroke, it is possible that if a stroke occurred outside of the TriNetX network it may not be captured. We used a complete case analyses and were unable to access incomplete cases. The 5-year MACE rate may at first seem relatively high compared to previous work. For example, it has been previously shown that post-stroke acute myocardial infarction has a ~2% incidence (at 1-year), which is substantially lower than the 5-year incidence seen in our paper (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 focussing 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 ischaemic stroke, were caused by stroke, or contributed to the stroke is unclear. Indeed, prospective research is needed to infer causation, albeit a challenging endeavour in a stroke population.

Conclusion

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 post-stroke; and develop and test specific, personalised therapeutic interventions for patients with stroke-heart syndrome.

Table 1. Incidence of post-stroke cardiovascular complications and associated 5-year MACE, comparing patients with/without presentation of acute cardiovascular complications following incident stroke.

Acute cardiovascular complications[1]	*n*= acute cardiovascular complications vs without[1]	Odds Ratio	95% CI	*P*-value
MACE[2]	**% Events (MACE)[2]**			
ACS[1] (11.1%)	(40,497 vs 324,886)			
All-cause mortality[2]	25.3 vs 18.5	1.49	1.44, 1.54	<0.0001
Hospitalisation[2]	41.6 vs 38.3	1.15	1.12, 1.18	<0.0001
Recurrent stroke[2]	55.7 vs 56.5	0.97	0.95, 1.00	0.04
AF/flutter[1] (8.8%)	(32,012 vs 333,371)			
All-cause mortality[2]	29.7 vs 22.6	1.45	1.40, 1.50	<0.0001
Hospitalisation[2]	44.2 vs 37.9	1.30	1.26, 1.34	<0.0001
Recurrent stroke[2]	57.2 vs 54.8	1.10	1.07, 1.14	<0.0001
AMI[2]	4.9 vs 5.1	0.97	0.91, 1.05	0.49
Heart failure[1] (6.4%)	(23,498 vs 341,884)			
All-cause mortality[2]	31.2 vs 19.9	1.83	1.76, 1.91	<0.0001
Hospitalisation[2]	49.0 vs 40.1	1.44	1.39, 1.49	<0.0001
Recurrent stroke[2]	56.7 vs 57.2	0.98	0.94, 1.01	0.21
AMI[2]	15.2 vs 7.1	2.35	2.21, 2.50	<0.0001
HFrEF[1] (2.2%)	(8,637)			
All-cause mortality[2]	33.7 vs 19.8	2.06	1.92, 2.06	<0.0001
Hospitalisation[2]	47.6 vs 38.3	1.46	1.38, 1.55	<0.0001
Recurrent stroke[2]	57.09 vs 56.8	1.01	0.95, 1.07	0.74
AMI[2]	21.1 vs 8.9	2.73	2.50, 2.99	<0.0001
HFpEF[1] (1.8%)	(7,083)			
All-cause mortality[2]	31.8 vs 22.7	1.59	1.48, 1.72	<0.0001
Hospitalisation[2]	51.7 vs 40.9	1.54	1.45, 1.65	<0.0001
Recurrent stroke[2]	60.8 vs 57.5	1.15	1.07, 1.23	<0.0001
AMI[2]	13.5 vs 9.4	1.51	1.36, 1.67	<0.0001
VT/VF[1] (1.2%)	(4,459 vs 360,923)			
All-cause mortality[2]	35.9 vs 21.2	2.08	1.90, 2.29	<0.0001
Hospitalisation[2]	48.4 vs 43.7	1.21	1.11, 1.31	<0.0001
Recurrent stroke[2]	53.2 vs 57.7	0.84	0.77, 0.91	<0.0001
AMI[2]	8.8 vs 6.3	1.42	1.19, 1.70	<0.0001
Takotsubo syndrome[1] (0.1%)	(338 vs 364,494)			
MACE[3]	84.3 vs 74.0	1.89	1.29, 2.77	<0.001

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

[2]Associated MACE 5-years following incident stroke comparing 1:1 propensity score matched populations with/without acute cardiovascular complications following incident stroke.

[3]Composite outcome presented (MACE; all-cause mortality, hospitalisation, recurrent stroke, and AMI) due to relatively small sample size.

MACE; major adverse cardiovascular event (mortality, hospitalisation, stroke, AMI), 95% CI; 95% confidence interval, HFrEF; heart failure with reduced ejection fraction, HFpEF; heart failure with preserved ejection fraction, AMI; acute myocardial infarction, ACS; acute coronary syndrome, VT/VF; Ventricular tachycardia/ventricular fibrillation, AF/flutter; atrial fibrillation/atrial flutter.

224

225

References

1. Kumar S, Selim MH, Caplan LR. Medical complications after stroke. *The Lancet Neurology* 2010;9(1):105-18. doi: https://doi.org/10.1016/S1474-4422(09)70266-2
2. Scheitz JF, Nolte CH, Doehner W, et al. Stroke–heart syndrome: clinical presentation and underlying mechanisms. *The Lancet Neurology* 2018;17(12):1109-20. doi: https://doi.org/10.1016/S1474-4422(18)30336-3
3. Prosser J, MacGregor L, Lees KR, et al. Predictors of early cardiac morbidity and mortality after ischemic stroke. *Stroke* 2007;38(8):2295-302. doi: 10.1161/strokeaha.106.471813 [published Online First: 2007/06/16]
4. Sposato Luciano A, Hilz Max J, Aspberg S, et al. Post-Stroke Cardiovascular Complications and Neurogenic Cardiac Injury. *Journal of the American College of Cardiology* 2020;76(23):2768-85. doi: 10.1016/j.jacc.2020.10.009
5. Sposato LA, Aspberg S, Scheitz JF, et al. The World Stroke Organization Brain & Heart Task Force: collaborations between stroke physicians and cardiologists. *European Heart Journal* 2021 doi: 10.1093/eurheartj/ehab198
6. 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;11:105-05. doi: 10.1186/1472-6963-11-105