



LJMU Research Online

Buckley, BJR, Harrison, SL, Hill, A, Underhill, P, Lane, DA and Lip, GYH

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

<http://researchonline.ljmu.ac.uk/id/eprint/16817/>

Article

Citation (please note it is advisable to refer to the publisher's version if you intend to cite from this work)

Buckley, BJR, Harrison, SL, Hill, A, Underhill, P, Lane, DA and Lip, GYH (2022) Stroke-Heart Syndrome: Incidence and Clinical Outcomes of Cardiac Complications Following Stroke. Stroke, 53 (5). pp. 1759-1763. ISSN 0039-2499

LJMU has developed [LJMU Research Online](#) for users to access the research output of the University more effectively. Copyright © and Moral Rights for the papers on this site are retained by the individual authors and/or other copyright owners. Users may download and/or print one copy of any article(s) in LJMU Research Online to facilitate their private study or for non-commercial research. You may not engage in further distribution of the material or use it for any profit-making activities or any commercial gain.

The version presented here may differ from the published version or from the version of the record. Please see the repository URL above for details on accessing the published version and note that access may require a subscription.

For more information please contact researchonline@ljmu.ac.uk

<http://researchonline.ljmu.ac.uk/>

1 **Brief Report**

2
3
4 **Stroke-Heart Syndrome: Incidence and clinical outcomes of cardiac complications following stroke**

5 Benjamin J.R. Buckley, PhD^{1,2*}, Stephanie L. Harrison, PhD^{1,2}, Andrew Hill, MBChB³, Paula Underhill⁴,
6 Deirdre A. Lane, PhD^{1,2,5}, Gregory Y.H. Lip, MD^{1,2,5}

7
8
9
10 ¹Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest
11 Hospital, Liverpool, United Kingdom

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

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

16 ⁴TriNetX LLC., London, United Kingdom

17 ⁵Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

18
19 **Date** January, 2022

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

21
22 ***Corresponding author**

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

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

26 Phone: +44 (0)151 794 2000

27
28 **Funding**

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

31
32 **Disclosures**

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

39 **Abstract**

40 **Background and purpose**

41 Following a stroke, individuals have an increased risk of new-onset cardiovascular
42 complications. However, the incidence and long-term clinical consequence of newly
43 diagnosed cardiovascular complications following a stroke is unclear. The aim of the present
44 study was to investigate the incidence and long-term clinical outcomes of newly diagnosed
45 cardiovascular complications following incident ischaemic stroke.

46

47 **Methods**

48 A retrospective cohort study was conducted using anonymised electronic medical records
49 from 53 participating healthcare organizations. Patients with incident ischaemic stroke aged
50 ≥ 18 years with 5-years of follow-up were included. Patients who were diagnosed with new-
51 onset cardiovascular complications within 4-weeks (exposure) of incident ischaemic stroke
52 were 1:1 propensity score-matched (age, sex, ethnicity, comorbidities, cardiovascular care)
53 with ischaemic stroke patients who were not diagnosed with a new-onset cardiovascular
54 complication (control). Logistic regression models produced odds ratios (OR) with 95%
55 confidence intervals (CIs) for 5-year incidence of major adverse cardiovascular events (MACE;
56 acute coronary syndrome, atrial fibrillation/flutter, heart failure, ventricular
57 fibrillation/flutter, and Takotsubo syndrome).

58

59 **Results**

60 Of 365,383 stroke patients with 5-year follow-up: 11.1% developed acute coronary syndrome
61 (ACS); 8.8% atrial fibrillation/flutter; 6.4% heart failure; 1.2% severe ventricular arrhythmias;
62 and 0.1% Takotsubo syndrome within 4-weeks of incident ischaemic stroke. Following
63 propensity score matching, odds of 5-year all-cause mortality were significantly higher in
64 stroke patients with ACS (OR 1.49, 95% CI 1.44-1.54), atrial fibrillation/flutter (1.45, 1.40-
65 1.50), heart failure (1.83, 1.76-1.91), and severe ventricular arrhythmias (2.08, 1.90-2.29),
66 compared to matched controls. Odds of 5-year rehospitalisation and acute myocardial
67 infarction were also significantly higher for stroke patients diagnosed with new-onset
68 cardiovascular complications. Takotsubo syndrome was associated with significantly higher
69 odds of 5-year composite MACE (1.89, 1.29-2.77). Atrial fibrillation/flutter was the only new-
70 onset cardiac complication associated with significantly higher odds of recurrent ischaemic
71 stroke at 5-years (1.10, 1.07-1.14).

72

73 **Conclusions**

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

78

79 **Background**

80 New-onset cardiovascular complications are a major medical challenge following ischaemic
81 stroke.^{1,2} One randomised controlled trial reported up to 20% of ischaemic stroke patients
82 are diagnosed with new-onset major adverse cardiovascular events (MACE) including acute
83 coronary syndrome (ACS), heart failure, and arrhythmias within the acute stroke phase.³
84 Importantly, these new-onset cardiovascular complications following an ischaemic stroke are
85 associated with poor functional prognosis and increased mortality in the weeks following the
86 cerebral event.³

87

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

97

98 Although some studies have demonstrated that the stroke-heart syndrome associates with
99 unfavourable short-term (acute) prognosis, long-term consequences, including secondary
100 cardiac events and mortality, have not been previously described. Therefore, the aim of the
101 present study was to investigate the incidence and long-term clinical outcomes of new-onset
102 cardiovascular complications diagnosed following incident ischaemic stroke.

103

104

105 **Methods**

106 This retrospective observational study utilised complete case, anonymised data within
107 TriNetX, a global federated health research network with access to electronic medical records
108 (EMRs) from participating academic medical centres, specialty physician practices, and
109 community hospitals, predominantly in the United States. As a federated network, research
110 studies using TriNetX do not require ethical approval or patient informed consent as no

111 identifiable information is received. The TriNetX network was searched on August 1, 2021 and
112 de-identified datasets were analysed that included data from 2002-2021 with at least 5-years
113 of follow-up (i.e. index event (incident ischaemic stroke) occurred at least five years ago). This
114 study is reported as per the Strengthening the Reporting of Observational Studies in
115 Epidemiology (STROBE) guidelines (eTable 1). More detailed information regarding the online
116 database and methods used can be found within Supplement 2 of the supplementary file.

117

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

121

122 Patients with an incident acute ischaemic stroke, aged ≥ 18 years with at least 5-years follow-
123 up were identified from the first instance of an International Classification of Diseases, Tenth
124 Revision, Clinical Modification (ICD-10-CM) code I63 (Cerebral infarction). The complete
125 dataset including index event and all outcomes spanned 2002 to 2021. The ischaemic stroke
126 cohort was stratified by newly diagnosed, post-stroke cardiovascular complications. Newly
127 diagnosed cardiovascular complications (within 4-weeks of ischaemic stroke) were identified
128 via ICD-10-CM codes: I20-I25 (Ischaemic heart diseases) [i.e., ACS], I48 (Atrial
129 fibrillation/flutter), I50 (Heart failure), I49.0 (Ventricular fibrillation/flutter) and I47.2
130 (ventricular tachycardia) [i.e., severe ventricular arrhythmias], and I51.81 (Takotsubo
131 syndrome). For propensity score matching, these cardiovascular complications were excluded
132 in the controls. At the time of the search, 53 (primarily US-based) participating healthcare
133 organisations had data available for patients who met the study inclusion criteria.

134

135 Baseline characteristics were compared using chi-squared tests or independent-sample t-
136 tests. Propensity score matching was used to control for differences in the comparison
137 cohorts. Using logistic regression, patients diagnosed with a new-onset cardiovascular
138 complication within 4-weeks of an incident ischaemic stroke were 1:1 propensity score-
139 matched to patients without a new-onset cardiovascular complication post-stroke for age,
140 sex, ethnicity, hypertensive diseases, ischaemic heart diseases (except for ACS cohort),
141 cerebrovascular diseases (e.g., haemorrhage, transient ischaemic attack, sequelae of
142 cerebrovascular disease), heart failure (except for heart failure cohort), pulmonary heart

143 disease/disease of the pulmonary circulation, diabetes mellitus, cardiovascular procedures
144 (including electrocardiography, echocardiography, catheterization, cardiac devices, and
145 electrophysiological procedures), and cardiovascular medications (including beta-blockers,
146 antiarrhythmics, diuretics, antilipemic agents, antianginals, calcium channel blockers, and
147 ACE inhibitors). These variables were chosen because they may impact clinical outcomes.
148 Following propensity score matching, logistic regression produced odds ratios (OR) with 95%
149 confidence intervals (CIs) for 5-year incidence of MACE (all-cause mortality, rehospitalisation,
150 incident acute myocardial infarction, recurrent stroke, and incident atrial fibrillation/flutter),
151 comparing stroke patients with new-onset cardiovascular complications with propensity
152 matched controls (without new-onset post-stroke cardiovascular complications). For the
153 Takotsubo syndrome cohort comparisons, a composite of 5-year MACE was used due to a
154 relatively small sample size. Statistical significance was set at $P < 0.05$.

155

156 **Results**

157 In total, 365,383 patients with incident ischaemic stroke were identified from 53 (primarily
158 US) healthcare organisations with 5-year follow-up. Of which, 11.1% developed ACS, 8.8%
159 atrial fibrillation/flutter, 6.4% heart failure, 1.2% severe ventricular arrhythmia, and 0.1%
160 Takotsubo syndrome within 4-weeks following stroke (Table 1). Following propensity score
161 matching, there were $n=80,988$ patients in ACS, 32,012 in atrial fibrillation/flutter, 46,990 in
162 heart failure, 8,918 in severe ventricular arrhythmia, and 676 in Takotsubo syndrome cohort
163 comparisons. The cohorts were overall well-matched for age, sex, ethnicity, included
164 comorbidities, and cardiovascular care (eTables 2-6).

165

166 Using the propensity score matched cohorts, 5-year mortality was significantly higher with
167 stroke patients who developed ACS (OR 1.49, 95%CI 1.44-1.54), atrial fibrillation/flutter (OR
168 1.45, 95%CI 1.40-1.50), heart failure (OR 1.83, 95%CI 1.76-1.91), severe ventricular arrhythmia
169 (OR 2.08, 95%CI 1.90-2.29), and Takotsubo syndrome (OR 1.89, 95%CI 1.29-2.77), compared
170 to propensity score matched stroke patients who did not develop new-onset cardiovascular
171 complications (Table 1).

172

173 The 5-year rehospitalisation rate was significantly higher among those with any new-onset
174 cardiovascular condition post-stroke, compared to those without. Atrial fibrillation/flutter,

175 heart failure, and severe ventricular arrhythmia were associated with significantly higher odds
176 of an acute myocardial infarction at 5-years compared to matched post-stroke controls.

177

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

184

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

187

188 **Limitations**

189 The Centre for Stroke Research Berlin has proposed criteria for stroke-heart syndrome
190 including a broad range of clinical presentations such as repolarisation changes, cardiac
191 arrhythmia, exacerbation of heart failure, Takotsubo syndrome, and acute myocardial
192 infarction (to name a few).² Elevations in cardiac biomarkers (i.e., cardiac troponin and brain
193 natriuretic peptide) are among the most studied manifestations of stroke–heart syndrome
194 yet are not included in the present paper. Instead, we focussed on more substantial
195 cardiovascular complications, newly diagnosed within 4-weeks of an incident ischaemic
196 stroke. The characterisation of stroke and cardiovascular complications were based on ICD
197 codes from EMRs and reporting of conditions with ICD codes may vary by healthcare
198 organisation.⁶ Although we used the first instance of an electronic medical record of
199 ischaemic stroke, it is possible that if a stroke occurred outside of the TriNetX network it may
200 not be captured. We used a complete case analyses and were unable to access incomplete
201 cases. The 5-year MACE rate may at first seem relatively high compared to previous work. For
202 example, it has been previously shown that post-stroke acute myocardial infarction has a ~2%
203 incidence (at 1-year), which is substantially lower than the 5-year incidence seen in our paper
204 (up to ~15% in people with stroke and newly diagnosed heart failure within 4-weeks of
205 stroke). However, it is important to highlight that we investigated 5-year outcomes in people
206 with stroke and 4-week cardiovascular complications, thereby focussing on a higher risk

207 subgroup of stroke survivors. The incidence of acute myocardial infarction in the entire stroke
208 cohort was 5%. Importantly, we were not able to determine the severity/location of stroke
209 and any impact this had on outcomes. Perhaps most notably, distinguishing stroke–heart
210 syndrome from (otherwise unknown) concomitant or preceding cardiovascular complications
211 is challenging, and reverse causation may have impacted the results of this study. For
212 example, whether the new-onset cardiovascular complications, *diagnosed* after ischaemic
213 stroke, were caused by stroke, or contributed to the stroke is unclear. Indeed, prospective
214 research is needed to infer causation, albeit a challenging endeavour in a stroke population.

215

216 **Conclusion**

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

223

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 complications¹	n= acute cardiovascular complications vs without¹	Odds Ratio	95% CI	P-value
MACE²	% Events (MACE)²			
ACS¹ (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/flutter¹ (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 failure¹ (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
HFrEF¹ (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
HFpEF¹ (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/VF¹ (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 syndrome¹ (0.1%)	(338 vs 364,494)			
MACE ³	84.3 vs 74.0	1.89	1.29, 2.77	<0.001

¹Incidence 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.

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

³Composite 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.

226 **References**

227

228 1. Kumar S, Selim MH, Caplan LR. Medical complications after stroke. *The Lancet Neurology*
229 2010;9(1):105-18. doi: [https://doi.org/10.1016/S1474-4422\(09\)70266-2](https://doi.org/10.1016/S1474-4422(09)70266-2)

230 2. Scheitz JF, Nolte CH, Doehner W, et al. Stroke–heart syndrome: clinical presentation and
231 underlying mechanisms. *The Lancet Neurology* 2018;17(12):1109-20. doi:
232 [https://doi.org/10.1016/S1474-4422\(18\)30336-3](https://doi.org/10.1016/S1474-4422(18)30336-3)

233 3. Prosser J, MacGregor L, Lees KR, et al. Predictors of early cardiac morbidity and mortality
234 after ischemic stroke. *Stroke* 2007;38(8):2295-302. doi:
235 10.1161/strokeaha.106.471813 [published Online First: 2007/06/16]

236 4. Sposato Luciano A, Hilz Max J, Aspberg S, et al. Post-Stroke Cardiovascular Complications
237 and Neurogenic Cardiac Injury. *Journal of the American College of Cardiology*
238 2020;76(23):2768-85. doi: 10.1016/j.jacc.2020.10.009

239 5. Sposato LA, Aspberg S, Scheitz JF, et al. The World Stroke Organization Brain & Heart
240 Task Force: collaborations between stroke physicians and cardiologists. *European*
241 *Heart Journal* 2021 doi: 10.1093/eurheartj/ehab198

242 6. Chong WF, Ding YY, Heng BH. A comparison of comorbidities obtained from hospital
243 administrative data and medical charts in older patients with pneumonia. *BMC*
244 *Health Serv Res* 2011;11:105-05. doi: 10.1186/1472-6963-11-105

245

246