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*Original Article*

# In-hospital outcomes of acute ischaemic stroke patients with atrial septal defect. A national inpatient sample study

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**Abstract:** Background and Aims: Atrial septal defects (ASD) are a well-recognised risk factor for acute ischaemic stroke (AIS). We aimed to delineate the relationship between ASD and in-hospital AIS outcomes (mortality, severe stroke (National Institutes of Health Stroke Scale (NIHSS) > 15), prolonged hospitalisation > 4 days and routine home discharge) in contemporary practice using data from the United States National Inpatient Sample. Methods: NIS admissions with a primary diagnosis of AIS between 2016-2018 were extracted. The NIHSS variable had 75% missing data, which were imputed using multiple imputations by chained equations. The relationship between ASD and the main outcomes was modelled using multivariable logistic regressions, adjusting for age, sex, comorbidities, stroke severity and revascularisation therapies. Results: 245,859 records representative of 1,229,295 AIS admissions were included, 35,840 (2.91%) of whom had ASD. ASD patients were younger (median age 63 years versus 72 years) and less likely to have traditional cardiovascular risk factors than their counterparts without ASD. ASD was independently associated with 58% lower odds of in-hospital mortality (hazard ratio (95% confidence interval) = 0.42 (0.33-0.54)), 18% lower odds of severe stroke (0.82 (0.71-0.94)), 20% higher odds of routine home discharge (1.20 (1.14-1.28)) and 28% higher odds of prolonged hospitalisation (1.28 (1.21-1.35)). Conclusions: ASD was associated with better in-hospital outcomes, which were likely driven by younger age, lower prevalence of traditional cardiovascular risk factors, and lower stroke severity. Further research is warranted to clarify the ASD anatomical characteristics which are most strongly associated with these associations.

**Keywords:** Atrial septal defect, patent foramen ovale, acute ischaemic stroke, mortality, severe stroke

## Introduction

Atrial septal defects (ASD) and patent foramen ovale (PFO) are well-recognised risk factors for ischaemic stroke, with possible underlying pathophysiological mechanisms including higher risk of paradoxical venous embolisms through the inter-atrial shunt [1], in-situ thrombosis, particularly in the presence of an atrial septal aneurysm (ASA) [2], as well as higher burden of other AIS risk factors, such as atrial fibrillation and heart failure amongst this patient group [3]. A previous meta-analysis estimated that PFO patients younger than 55 years have a 3-fold increase in the odds of first incident stroke (AIS) [4], while patients with both PFO and ASA had 15-fold increased risk [4]. However, it is also important to note that PFOs have a ~25% prevalence in the general population [5], and may not necessarily be implicated in the pathogenesis of AIS in some patients [6], especially in older patients with a high burden of traditional AIS risk factors [1]. Based on the results of several large multi-centre randomised controlled trials [7-12], a recent European Society of Cardiology Position Paper recommended PFO closure as secondary preventative therapy after AIS in patients aged 18-65 years who have a high estimated probability of a causal role of the PFO in the AIS pathogenesis [13].

Despite the wide interest in the association between PFO and ASD and incident AIS, the association between these inter-atrial shunts and patient outcomes after AIS remains only partially characterised. A recent Swedish nationwide case-control study including ~20,000 patients with ASDs, ~1800 of whom had an incident ischaemic stroke over a 25-year follow-up, has established that while ASD was associated with a 6-fold increase in the risk of incident AIS compared to age- and sex-matched controls, ASD patients were 30% less likely to suffer a recurrent event and over 50% less likely to die over the study follow-up period [3]. Possible explanations for these results include different underlying stroke aetiologies between patients with and without congenital heart defects (CHD) as well as different patient demographics, with CHD patients being younger and less likely to have traditional risk factors such as hypertension or diabetes [3]. However, PFOs are associated with increased risk of recurrent AIS, with an increasing risk amongst older patients [14] and those with large shunt sizes [15]. The relationship between PFOs and post-stroke mortality remains largely uncharacterised.

We therefore aimed to evaluate the association between ASD/PFO and in-hospital outcomes (mortality, length of stay, discharge destination and stroke severity) amongst patients admitted with AIS using data from the United States National Inpatient Sample in order to delineate this important relationship in contemporary US clinical practice.

## Methods

### *Data source*

This retrospective cohort study used data from the United States National Inpatient Sample, the largest US all-payer inpatient claims registry which represents a 20% stratified sample of all community hospital admissions [16]. Each record sampled in the NIS is assigned a sampling weight (a measure inversely related to the probability of each hospital discharge being selected into the sample) [17]. Using the provided sampling weight and information regarding the NIS strata, this dataset can provide national estimates for the sampling population, representative of 95% of the US population [16]. The authors completed the online Healthcare Cost and Utilization project Training Tool and read and signed the Data Use Agreement. The NIS is an anonymised, publicly available database. Ethical approval was not required. Using admission data files between 2016 and 2018, records with a primary diagnosis of ischemic stroke (International Classification of Diseases, Tenth revision [ICD-10] codes I63.0-I63.9) were extracted.

### *Outcomes, exposures and confounders*

The following primary outcomes were analysed: (1) in-hospital mortality, (2) prolonged hospitalisation > 4 days, (3) routine discharge and (4) moderate/severe stroke, defined as National Institutes of Health Stroke Scale (NIHSS) > 15. Vital status at discharge (dead/alive) and the length of hospital stay (LOS) serve as standard variables in the NIS [18, 19]. Prolonged hospitalisation was defined as LOS > 4 days [20]. Discharge status was coded using the provided discharge destinations [21]. Discharge destination was dichotomized into routine discharges and other discharges ("home health care", "short term-hospital", "other facilities including intermediate care and skilled nursing homes", "died in hospital", "discharged against medical advice", "discharged to an unknown population"). The NIHSS was determined using ICD-10-CM codes R297.00 (NIHSS = 0) to R297.42 (NIHSS = 42).

The main exposure of interest was the presence of an atrial septal defect or patent foramen ovale coded during the respective stroke admission (ICD-10 code Q21.1). As ICD-10 coding does not allow differentiation between PFO and ASD, in the absence of adjunctive echocardiographic information to differentiate between the two entities, these were analysed together and were described collectively as ASD in this study. Adjusting covariates was based on clinical judgement and literature [3, 20]. Elixhauser comorbidities (congestive heart failure, valvular disease, pulmonary circulation disease, peripheral vascular disease, paralysis, other neurological disorders, chronic pulmonary disease, diabetes mellitus, hypothyroidism, renal failure, liver disease, peptic ulcer disease, acquired immune deficiency syndrome, lymphoma, metastatic cancer, solid tumour without metasta-

sis, rheumatoid arthritis/collagen vascular disease, coagulopathy, obesity, weight loss, fluid and electrolyte disorders, anaemia, alcohol abuse, drug abuse, psychosis, depression and hypertension) were determined using the Healthcare Cost and Utilization Project Elixhauser comorbidity software [22]. Other comorbidities were determined using the corresponding ICD-10 codes specified in Supplementary Table 1. The administration of intravenous thrombolysis (IVT) and endovascular thrombectomy (EVT) was identified using ICD-10-PCS codes (Supplementary Table 1).

*Statistical analyses*

All analyses were performed with Stata MP 14.1, using provided discharge weights as probability weights and using survey data analysis techniques stratifying by NIS stratum and admission year [23] to account for patient clustering within hospitals [24]. A 5% statistical significance threshold was used ($P < 0.05$).

*Descriptive statistics*

Patient characteristics were compared between patients with and without ASD on admission. Non-normally distributed continuous variables were described as median (interquartile range), while categorical variables were described as number (percentage). The Mann-Whitney U and Pearson's Chi-squared tests were employed to compare characteristics for non-normally distributed continuous and categorical variables, respectively.

*Missing data*

The NIHSS had ~75% missing values (**Table 1**). Admissions with missing NIHSS data were significantly older, more likely to be women, and had a higher prevalence of comorbidities. More recent admissions and those to urban teaching centres had less NIHSS data missing (Supplementary Table 2). Data missingness was likely dependent only on observed, but not unobserved data and subsequently deemed likely missing-at-random [25]. A multiple imputation by chained equation algorithm with 20 iterations was employed to impute missing NIHSS values using an ordinal logistic regression with the predictors outlined in Supplementary Table 2.

*Main analyses*

Multivariable logistic regressions were used to analyse the relationship between ASD and the outcomes of interest. In order to ascertain any possible treatment effect by revascularisation therapies on these relationships, further models including interaction terms between ASD and IVT/ET were constructed. All models were adjusted for age, sex, year of admission, hospital location/teaching status, hospital region, primary payer, Elixhauser comorbidities, other comorbidities (cancer, anaemia, dyslipidaemia, dementia, smoking, Parkinson disease, infective endocarditis, atrial fibrillation, previous transient ischaemic attack, pneumonia (including aspiration), rheumatic heart disease, coronary heart disease, all-cause bleeding, shock, previous stroke, thrombolysis, thrombectomy and the NIHSS score).

## Results

*Descriptive statistics*

All ischemic stroke records (identified as admissions with a primary diagnosis ICD10 code I63, n = 266,996) from the National Inpatient Sample between 2016-2018 were extracted. After the exclusion of elective admissions (n = 8776) as well as those with missing data on key variables (age, vital status at discharge, sex, length of stay, primary payer, race, quartile of estimated median household and discharge destination, n = 12,361), a total of 245,859 records were included in the analyses. Having applied the sampling weights and excluded strata with single sampling units, included records were used to provide estimates for the population from which they were sampled: 1,229,295 admissions with the primary diagnosis of acute ischaemic stroke (**Figure 1**).

**Table 1** details the descriptive statistics of the included cohort. There were 35,840 (2.91%) admissions with co-existing ASD. These were significantly younger, more likely to be male, more likely to be white and more likely to be drawn from a later admission year, compared to AIS patients without ASD. ASD patients were more likely to have pre-existing valvular disease, pulmonary circulation disease and peripheral vascular disease compared to their counterparts without ASD. Conversely, ASD

**Table 1.** Descriptive statistics of the included cohort, stratified by the presence of an atrial septal defect

| | Total | No ASD | ASD | *P* value |
|---|---|---|---|---|
| N | 1229295 | 1193455 | 35840 | |
| Age, y | | | | |
| median (IQR) | 72.00 (61.00-82.00) | 72.00 (61.00-82.00) | 63.00 (52.00-74.50) | < 0.001 |
| Sex | | | | |
| Women n (%) | 621605 (50.57) | 605080 (50.70) | 16525 (46.11) | < 0.001 |
| Length of stay, d | | | | |
| median (IQR) | 3.00 (2.00-6.00) | 3.00 (2.00-6.00) | 4.00 (2.00-6.00) | < 0.001 |
| NIHSS | | | | |
| Median (IQR) | 4.00 (2.00-9.00) | 4.00 (2.00-9.00) | 3.00 (1.00-8.00) | < 0.001 |
| *missing, n (%)* | *929430 (75.61)* | *904135 (75.76)* | *25295 (70.58)* | *< 0.001* |
| Race/Ethnicity n (%) | | | | < 0.001 |
| White | 853450 (69.43) | 827220 (69.31) | 26230 (73.19) | |
| Black | 220270 (17.92) | 214700 (17.99) | 5570 (15.54) | |
| Hispanic | 87950 (7.15) | 85510 (7.16) | 2440 (6.81) | |
| Asian/Pacific Islander | 32390 (2.63) | 31660 (2.65) | 730 (2.04) | |
| Native American | 4890 (0.40) | 4730 (0.40) | 160 (0.45) | |
| Other | 30345 (2.47) | 29635 (2.48) | 710 (1.98) | |
| Year of admission, n (%) | | | | < 0.001 |
| 2016 | 439515 (35.75) | 427665 (35.83) | 11850 (33.06) | |
| 2017 | 461665 (37.56) | 448480 (37.58) | 13185 (36.79) | |
| 2018 | 328115 (26.69) | 317310 (26.59) | 10805 (30.15) | |
| Comorbidities n (%) | | | | |
| Valvular Disease | 124410 (10.12) | 120335 (10.08) | 4075 (11.37) | 0.001 |
| Pulmonary circulation disease | 9405 (0.77) | 8355 (0.70) | 1050 (2.93) | < 0.001 |
| Peripheral vascular disease | 119155 (9.69) | 115410 (9.67) | 3745 (10.45) | 0.035 |
| Paralysis | 127880 (10.40) | 122875 (10.30) | 5005 (13.96) | < 0.001 |
| Other neurological disorders | 6580 (0.54) | 6265 (0.52) | 315 (0.88) | < 0.001 |
| Chronic pulmonary disease | 196070 (15.95) | 190425 (15.96) | 5645 (15.75) | 0.637 |
| Diabetes mellitus (without chronic complications) | 222090 (18.07) | 217325 (18.21) | 4765 (13.30) | < 0.001 |
| Diabetes mellitus (with chronic complications) | 256110 (20.83) | 250715 (21.01) | 5395 (15.05) | < 0.001 |
| Hypothyroidism | 177380 (14.43) | 172965 (14.49) | 4415 (12.32) | < 0.001 |
| Renal failure | 206730 (16.82) | 202725 (16.99) | 4005 (11.17) | < 0.001 |
| Liver disease | 20890 (1.70) | 20320 (1.70) | 570 (1.59) | 0.459 |
| Peptic ulcer disease | 8185 (0.67) | 7920 (0.66) | 265 (0.74) | 0.440 |
| AIDS | 2680 (0.22) | 2610 (0.22) | 70 (0.20) | 0.674 |
| Lymphoma | 6265 (0.51) | 6110 (0.51) | 155 (0.43) | 0.348 |
| Metastatic cancer | 19920 (1.62) | 19255 (1.61) | 665 (1.86) | 0.119 |
| Solid tumour without metastasis | 22300 (1.81) | 21815 (1.83) | 485 (1.35) | 0.003 |
| Rheumatoid arthritis/collagen vascular disease | 33870 (2.76) | 32855 (2.75) | 1015 (2.83) | 0.687 |
| Coagulopathy | 45225 (3.68) | 43830 (3.67) | 1395 (3.89) | 0.338 |
| Obesity | 169955 (13.83) | 165080 (13.83) | 4875 (13.60) | 0.582 |
| Weight loss | 50540 (4.11) | 49405 (4.14) | 1135 (3.17) | < 0.001 |
| Fluid and electrolyte disorders | 275845 (22.44) | 269100 (22.55) | 6745 (18.82) | < 0.001 |
| Anaemia (deficiency) | 148365 (12.07) | 144360 (12.10) | 4005 (11.17) | 0.018 |
| Alcohol abuse | 53925 (4.39) | 52310 (4.38) | 1615 (4.51) | 0.614 |
| Drug abuse | 31655 (2.58) | 30425 (2.55) | 1230 (3.43) | < 0.001 |
| Psychoses | 30035 (2.44) | 29120 (2.44) | 915 (2.55) | 0.546 |
| Depression | 141370 (11.50) | 136955 (11.48) | 4415 (12.32) | 0.026 |
| Hypertension | 1056115 (85.91) | 1030050 (86.31) | 26065 (72.73) | < 0.001 |
| Congestive Heart Failure | 196000 (15.94) | 192445 (16.13) | 3555 (9.92) | < 0.001 |
| Transient Ischaemic Attack | 9695 (0.79) | 9440 (0.79) | 255 (0.71) | 0.456 |
| Smoking | 231380 (18.82) | 223645 (18.74) | 7735 (21.58) | < 0.001 |
| Dyslipidaemia | 725100 (58.99) | 704950 (59.07) | 20150 (56.22) | < 0.001 |

| | | | | |
|---|---|---|---|---|
| Dementia | 147135 (11.97) | 144975 (12.15) | 2160 (6.03) | < 0.001 |
| Pneumonia | 31940 (2.60) | 31120 (2.61) | 820 (2.29) | 0.103 |
| Atrial fibrillation | 310530 (25.26) | 305365 (25.59) | 5165 (14.41) | < 0.001 |
| Coronary heart disease | 349855 (28.46) | 340935 (28.57) | 8920 (24.89) | < 0.001 |
| Parkinson's disease | 18015 (1.47) | 17655 (1.48) | 360 (1.00) | 0.001 |
| Infective endocarditis | 2520 (0.20) | 2435 (0.20) | 85 (0.24) | 0.537 |
| Rheumatic heart disease | 37045 (3.01) | 35630 (2.99) | 1415 (3.95) | < 0.001 |
| All-cause bleeding | 88550 (7.20) | 85840 (7.19) | 2710 (7.56) | 0.239 |
| Previous cerebrovascular disease | 191990 (15.62) | 185995 (15.58) | 5995 (16.73) | 0.008 |
| Shock | 5505 (0.45) | 5340 (0.45) | 165 (0.46) | 0.873 |
| Procedures n (%) | | | | |
| Thrombolysis | 117045 (9.52) | 112810 (9.45) | 4235 (11.82) | < 0.001 |
| Thrombectomy | 37450 (3.05) | 35910 (3.01) | 1540 (4.30) | < 0.001 |
| Echocardiography | 120130 (9.77) | 108390 (9.08) | 11740 (32.76) | < 0.001 |
| Outcomes n (%) | | | | |
| In-hospital mortality | 42930 (3.49) | 42480 (3.56) | 450 (1.26) | < 0.001 |
| Prolonged hospitalisation (> 4 days) | 416570 (33.89) | 403185 (33.78) | 13385 (37.35) | < 0.001 |
| Routine Home Discharge | 443730 (37.79) | 425685 (37.38) | 18045 (51.29) | < 0.001 |
| Severe Stroke (NIHSS > 15) | 38990 (13.00) | 37950 (13.12) | 1040 (9.86) | < 0.001 |
| *missing, n (%)* | *929430 (75.61)* | *904135 (75.76)* | *25295 (70.58)* | *< 0.001* |

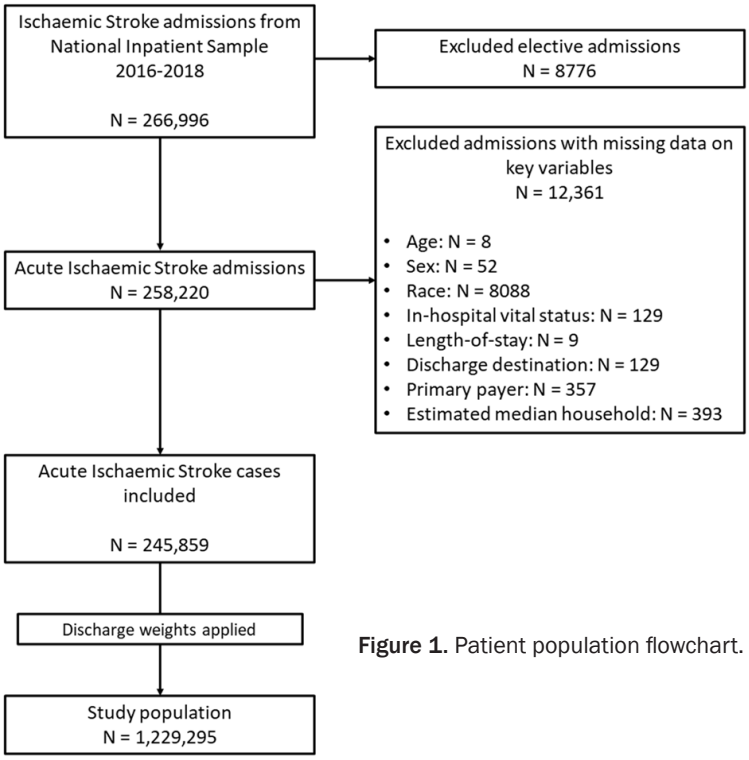


**Figure 1.** Patient population flowchart.

patients were less likely to have pre-existing diabetes mellitus, hypertension, heart failure, atrial fibrillation or renal failure than their counterparts without ASD. ASD patients were significantly more likely to undergo echocardiography during their hospitalisation (32.76% versus 9.08%) as well as thrombolysis (11.82% versus 9.45%) and thrombectomy (4.30% versus 3.01%) compared to their counterparts without ASD. In terms of raw outcomes, ASD patients had significantly lower rates of in-hospital mortality (1.26% versus 3.56%) and severe stroke (9.86% versus 13.12%), but higher rates of prolonged hospitalisation > 4 days (37.35% versus 33.78%) and routine home discharge (51.29% versus 37.38%) compared to their counterparts without ASD.

*Main analyses*

**Table 2** details the results of the logistic regressions assessing the relationship between ASD and AIS in-hospital outcomes. After extensive adjustment for age, sex and comorbidities, patients with ASD had 58% lower odds of in-hospital mortality (hazard ratio (95% confidence interval) = 0.42 (0.33-0.54)), 18% lower odds of severe stroke (0.82 (0.71-0.94)) as well as 20% higher odds of routine home discharge (1.20 (1.14-1.28)). Conversely, ASD patients had 28% higher odds of prolonged hospitalisation (1.28 (1.21-1.35)).

**Table 2.** Results of the multivariable logistic regressions delineating the association between atrial septal defects and in-hospital outcomes amongst acute ischaemic stroke admission in the National Inpatient Sample

| Outcome | Hazard Ratio (95% confidence interval) | *P* value |
|---|---|---|
| In-hospital mortality | 0.42 (0.33-0.54) | < 0.001 |
| Prolonged hospitalisation (> 4 days) | 1.28 (1.21-1.35) | < 0.001 |
| Routine Home Discharge | 1.20 (1.14-1.28) | < 0.001 |
| Severe Stroke (NIHSS > 15) | 0.82 (0.71-0.94) | 0.007 |

All logistic regression models were adjusted for age, sex, year of admission, hospital location/teaching status, hospital region, primary payer, Elixhauser comorbidities, other comorbidities (cancer, anaemia, dyslipidaemia, dementia, smoking, Parkinson disease, infective endocarditis, atrial fibrillation, previous transient ischaemic attack, pneumonia (including aspiration), rheumatic heart disease, coronary heart disease, all-cause bleeding, shock, previous stroke, thrombolysis, thrombectomy and the NIHSS score), except for the model assessing the severe stroke outcome, which did not include an NIHSS adjustment.

*Interaction with revascularisation therapies*

**Table 3** details the additional models including interaction terms between ASD and thrombolysis and thrombectomy respectively. There were no statistically significant interaction terms between ASD and either revascularisation modality for any of the studied outcomes.

## Discussion

In this National Inpatient Sample study representative of ~1.2 million hospital admissions across the United States, we describe for the first time the epidemiology of co-existing ASD across a large, representative, contemporary and unselected cohort of AIS patients. ASD patients were younger, more likely to be male, more likely to have co-existing valvular disease and pulmonary vascular disorders, but less likely to have traditional cardiovascular risk factors such as diabetes mellitus, hypertension, heart failure or atrial fibrillation. After adjustment for a wide range of important confounding patient characteristics, ASD was associated with significantly better in-hospital stroke outcomes, including a 58% decrease in mortality, 18% decrease in the odds of severe stroke (NIHSS > 15) and 20% increase in the odds of routine home discharge. Finally, we did not identify any interactions between these associations and utilisation of stroke revascularisation therapies.

Our results are consistent with the only prior large-scale study to have evaluated the relationship between ASD and outcomes after stroke [3]. This nationwide study from Sweden which included ~1800 ASD patients with AIS found that, in comparison to age- and sex-matched controls, ASD was associated with a 30% decrease in the risk of recurrent stroke and 50% decrease in post-stroke long-term mortality. Our findings support the hypothesis that the lower mortality observed amongst ASD patients become apparent from the early stages of the post-stroke period, even in an unselected cohort of AIS patients. Furthermore, our study delineates for the first time that this is driven not only by individual patient factors such as age and lower prevalence of traditional cardiovascular risk factors, but also by lower stroke severity. Importantly, these relationships may also driven by the different distribution of AIS aetiologies which may be observed amongst patients with ASD, who are more likely to experience embolic strokes [1]. We were however unable to test this hypothesis due to the lack of data on the Trial of Org 10172 in Acute Stroke Treatment (TOAST) [26] classification in our primary data source. Finally, despite the higher rate of administration of revascularisation therapies in AIS patients with ASD, the results of our study suggest that the association between ASD and better in-hospital outcomes was independent of administration of revascularisation therapies.

Whilst the results of our study bring further clarity towards this important research question, further research efforts are required in order to fully characterise the epidemiology of AIS amongst patients with ASD. Firstly, further studies including large cohorts of unselected stroke patients with long post-discharge follow-up are warranted to also delineate these relationships longitudinally. Furthermore, studies with granular echocardiographical data are warranted in order to delineate the ASD/PFO characteristics which are most strongly associated with these outcomes, including co-existence of ASA. This is particularly important as these clinical scenarios are likely to have different implications in the primary and secondary preventative settings. While ASD detection is important, given the long-term adverse effects of untreated ASDs on cardiovascular haemody-

**Table 3.** Results of the multivariable logistic regressions delineating the association between atrial septal defects and in-hospital outcomes amongst acute ischaemic stroke admission in the National Inpatient Sample, including interaction terms for revascularisation therapies

| Intravenous Thrombolysis | | | |
|---|---|---|---|
| Outcome | Thrombolysis HR (95% CI) | No thrombolysis HR (95% CI) | *P* value of interaction term |
| In-hospital mortality | 0.37 (0.19-0.72) | 0.43 (0.33-0.56) | 0.667 |
| Prolonged hospitalisation (> 4 days) | 1.52 (1.45-1.59) | 1.29 (1.22-1.37) | 0.494 |
| Routine Home Discharge | 1.21 (1.02-1.44) | 1.21 (1.32-1.28) | 0.941 |
| Severe Stroke (NIHSS > 15) | 0.82 (0.63-1.08) | 0.82 (0.71-0.96) | 0.973 |
| Endovascular Thrombectomy | | | |
| Outcome | Thrombectomy HR (95% CI) | No thrombectomy HR (95% CI) | *P* value of interaction term |
| In-hospital mortality | 0.22 (0.10-0.51) | 0.46 (0.36-0.59) | 0.097 |
| Prolonged hospitalisation (> 4 days) | 1.40 (1.07-1.85) | 1.28 (1.21-1.35) | 0.504 |
| Routine Home Discharge | 1.07 (0.78-1.46) | 1.21 (1.14-1.29) | 0.437 |
| Severe Stroke (NIHSS > 15) | 0.82 (0.59-1.15) | 0.82 (0.71-0.95) | 0.992 |

All logistic regression models were adjusted for age, sex, year of admission, hospital location/teaching status, hospital region, primary payer, Elixhauser comorbidities, other comorbidities (cancer, anaemia, dyslipidaemia, dementia, smoking, Parkinson disease, infective endocarditis, atrial fibrillation, previous transient ischaemic attack, pneumonia (including aspiration), rheumatic heart disease, coronary heart disease, all-cause bleeding, shock, previous stroke and the NIHSS score), except for the models assessing the severe stroke outcome, which did not include an NIHSS adjustment.

namics and outcomes [27], PFO screening is not currently warranted in the general population, especially given its likely high prevalence and likely 'innocent bystander' role in stroke pathogenesis in people with traditional cardiovascular risk factors [28]. This may however differ for patients with PFO and coexistent ASA, who have a three-fold increase in the risk of incident stroke compared to people with PFO without ASA [29]. The different acute stroke outcomes between these patient populations will therefore further inform the different primary screening recommendations for these inter-atrial defects.

Our study is powered by several important strengths. We included a sample representative of 1.2 million unselected hospitalisations across the United States reflecting contemporary clinical practice. Furthermore, this allowed us to include ~35,000 ASD patients with AIS, rendering this the largest study of this patient population to date. We were also able to adjust our analyses for a wide variety of important potential confounders, including utilisation of evidence-based revascularisation therapies.

We acknowledge some limitations, which mainly stem from the administrative nature of our primary data source. Having relied on ICD-10 codes to delineate our primary exposure, we were unable to differentiate between ASDs and PFOs. This is an important limitation of our study, as the risk profile may be highly heterogeneous between the two groups and therefore these also warrant to be evaluated separately. Similarly, we lacked echocardiographical information regarding the exact nature or size of the ASDs, which may be important risk modifiers in these relationships. Similarly, we lacked data on stroke subtypes according to the TOAST classification and were therefore unable to use this to stratify our analyses. Finally, the NIHSS variable was also derived from ICD-10 codes and subsequently had a high degree of missing data. While we undertook missing data analysis of this variable which indicated multiple imputation as an appropriate methodological approach to minimise the impact of this, our results need to be interpreted with caution in the light of these considerations.

In conclusion, in this study including a sample representative of 1.2 million unselected AIS admissions across the United States between 2016-2018 of whom ~35,000 had co-existing ASD, we found that ASD was significantly associated with markedly better in-hospital outcomes. Compared to their counterparts without ASD, ASD patients had 58% lower odds of in-

hospital mortality and 20% higher odds of routine home discharge. These results were likely driven by the individual patient factors such as age and lower prevalence of traditional cardiovascular risk factors, but also by lower stroke severity amongst ASD patients. Further research is warranted to clarify the anatomical characteristics of inter-atrial shunts which are most strongly associated with these relationships but also whether ASD determines similar post-stroke outcomes over longer-term follow-up.

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## Disclosure of conflict of interest

None.

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**Supplementary Table 1.** International Classification of Disease - tenth edition (ICD-10) codes used to extract admission co-morbidities (other than Elixhauser comorbidities) and procedures

| Co-morbidities | ICD-10 codes (Diagnosis) |
|---|---|
| Transient ischaemic attack | G45.x |
| Smoking | F17.2x |
| Dyslipidaemia | E78.0-E78.6 |
| Dementia | F01.x-F03.x |
| Pneumonia | J12.x-J18.x |
| Aspiration pneumonia | J69.x |
| Atrial fibrillation | I48.x |
| Coronary heart disease | I20.x-I25.9 |
| Parkinson's disease | G20 |
| Infective endocarditis | I33.x |
| Rheumatic heart disease | I00-I09.x |
| All-cause bleeding | D69.8; D69.9; G97.x; H11.3x; H31.3x; H35.6x; H43.1x; H92.2x; I31.2; I60.x-I62.x; I85.01; I85.11; K25.x-K29.x; K31.811; K62.5; K92.0-K92.2; I97.418; I97.42; I97.618-I97.621; J60.x-J62.x; N93.8; N93.9; N95.0; R04.x; R31.0; R31.9; R58; S06.4x-S06.6x |
| Shock | R57.x |
| Previous cerebrovascular disease | Z86.73 |
| Procedures | ICD-10 codes (Procedural) |
| Thrombolysis | 03CG3ZZ; 03CG4ZZ; 03CK3Z7; 03CK3ZZ; 03CK4ZZ; 03CL3Z7; 03CL3ZZ; 03CL4ZZ; 03CP3Z7; 03CP3ZZ; 03CP4ZZ; 03CQ3Z7; 03CQ3ZZ; 03CQ4ZZ |
| Thrombectomy | 03CG3ZZ; 03CG4ZZ; 03CK3Z7 |
| Echocardiography | B24; B244YZZ; B244ZZ3; B244ZZ4; B244ZZZ; B245YZZ; B245ZZ3; B245ZZ4; B245ZZZ; B246YZZ; B246ZZ3; B246ZZ4; B246ZZZ; B24BYZZ; B24BZZ3; B24BZZ4; B24BZZZ; B24CYZZ; B24CZZ3; B24CZZ4; B24CZZZ; B24DYZZ; B24DZZ3; B24DZZ4; B24DZZZ |

ICD-10, International Classification of Disease - tenth edition.

**Supplementary Table 2.** Descriptive statistics of the initially extracted sample representative of 1,229,295 patients admitted with a primary diagnosis of ischaemic stroke, stratified by whether the National Institute of Health Stroke Scale data were missing

| | Total | Not missing | Missing | *P* value |
|---|---|---|---|---|
| N | 1229295 | 299865 | 929430 | |
| Age, y | | | | |
| median (IQR) | 71.00 (60.00-81.00) | 72.00 (61.00-82.00) | 72.00 (61.00-82.00) | < 0.001 |
| Length of stay, d | | | | |
| median (IQR) | 3.00 (2.00-6.00) | 3.00 (2.00-5.00) | 3.00 (2.00-6.00) | < 0.001 |
| Sex | | | | |
| Women n (%) | 621605 (50.57) | 149105 (49.72) | 472500 (50.84) | < 0.001 |
| Comorbidities n (%) | | | | |
| Congestive Heart Failure | 196000 (15.94) | 46595 (15.54) | 149405 (16.07) | 0.006 |
| Valvular Disease | 124410 (10.12) | 30280 (10.10) | 94130 (10.13) | 0.879 |
| Pulmonary circulation disease | 9405 (0.77) | 2200 (0.73) | 7205 (0.78) | 0.309 |
| Peripheral vascular disease | 119155 (9.69) | 28825 (9.61) | 90330 (9.72) | 0.535 |
| Paralysis | 127880 (10.40) | 51815 (17.28) | 76065 (8.18) | < 0.001 |
| Other neurological disorders | 6580 (0.54) | 1480 (0.49) | 5100 (0.55) | 0.118 |
| Chronic pulmonary disease | 196070 (15.95) | 46505 (15.51) | 149565 (16.09) | 0.002 |
| Diabetes mellitus (without chronic complications) | 222090 (18.07) | 48030 (16.02) | 174060 (18.73) | < 0.001 |
| Diabetes mellitus (with chronic complications) | 256110 (20.83) | 62430 (20.82) | 193680 (20.84) | 0.932 |
| Hypothyroidism | 177380 (14.43) | 41755 (13.92) | 135625 (14.59) | 0.001 |
| Renal failure | 206730 (16.82) | 45720 (15.25) | 161010 (17.32) | < 0.001 |
| Liver disease | 20890 (1.70) | 4700 (1.57) | 16190 (1.74) | 0.004 |
| Peptic ulcer disease | 8185 (0.67) | 1835 (0.61) | 6350 (0.68) | 0.075 |
| AIDS | 2680 (0.22) | 715 (0.24) | 1965 (0.21) | 0.218 |
| Lymphoma | 6265 (0.51) | 1420 (0.47) | 4845 (0.52) | 0.153 |
| Metastatic cancer | 19920 (1.62) | 4330 (1.44) | 15590 (1.68) | < 0.001 |
| Solid tumour without metastasis | 22300 (1.81) | 5275 (1.76) | 17025 (1.83) | 0.262 |
| Rheumatoid arthritis/collagen vascular disease | 33870 (2.76) | 8060 (2.69) | 25810 (2.78) | 0.271 |
| Coagulopathy | 45225 (3.68) | 10750 (3.58) | 34475 (3.71) | 0.211 |
| Obesity | 169955 (13.83) | 44815 (14.95) | 125140 (13.46) | < 0.001 |
| Weight loss | 50540 (4.11) | 10965 (3.66) | 39575 (4.26) | < 0.001 |
| Fluid and electrolyte disorders | 275845 (22.44) | 60845 (20.29) | 215000 (23.13) | < 0.001 |
| Chronic blood loss | 4470 (0.36) | 1125 (0.38) | 3345 (0.36) | 0.602 |
| Deficiency anaemia | 148365 (12.07) | 33130 (11.05) | 115235 (12.40) | < 0.001 |
| Alcohol abuse | 53925 (4.39) | 13345 (4.45) | 40580 (4.37) | 0.411 |
| Drug abuse | 31655 (2.58) | 7430 (2.48) | 24225 (2.61) | 0.125 |
| Psychoses | 30035 (2.44) | 7145 (2.38) | 22890 (2.46) | 0.291 |
| Depression | 141370 (11.50) | 34770 (11.60) | 106600 (11.47) | 0.491 |
| Hypertension | 1056115 (85.91) | 258575 (86.23) | 797540 (85.81) | 0.045 |
| Cancers | 43340 (3.53) | 9900 (3.30) | 33440 (3.60) | 0.001 |

| | | | | |
|---|---|---|---|---|
| Dyslipidaemia | 725100 (58.99) | 185575 (61.89) | 539525 (58.05) | < 0.001 |
| Dementia | 147135 (11.97) | 30650 (10.22) | 116485 (12.53) | < 0.001 |
| Smoking | 231380 (18.82) | 61645 (20.56) | 169735 (18.26) | < 0.001 |
| Parkinson's disease | 18015 (1.47) | 3960 (1.32) | 14055 (1.51) | 0.001 |
| Pulmonary embolism | 7910 (0.64) | 1890 (0.63) | 6020 (0.65) | 0.644 |
| Infective endocarditis | 2520 (0.20) | 555 (0.19) | 1965 (0.21) | 0.239 |
| Arrhythmias (other than AF) | 103450 (8.42) | 26140 (8.72) | 77310 (8.32) | 0.010 |
| Atrial fibrillation | 310530 (25.26) | 78345 (26.13) | 232185 (24.98) | < 0.001 |
| Transient ischaemic attack | 9695 (0.79) | 2155 (0.72) | 7540 (0.81) | 0.035 |
| Aspiration pneumonia | 39460 (3.21) | 8450 (2.82) | 31010 (3.34) | < 0.001 |
| Pneumonia | 31940 (2.60) | 6090 (2.03) | 25850 (2.78) | < 0.001 |
| Congenital heart disease | 38280 (3.11) | 11255 (3.75) | 27025 (2.91) | < 0.001 |
| Aortic disease | 33985 (2.76) | 8635 (2.88) | 25350 (2.73) | 0.124 |
| Primary payer | | | | |
| Medicare | 813110 (66.14) | 195770 (65.29) | 617340 (66.42) | < 0.001 |
| Medicaid | 110920 (9.02) | 26140 (8.72) | 84780 (9.12) | < 0.001 |
| Private insurance | 228740 (18.61) | 58765 (19.60) | 169975 (18.29) | < 0.001 |
| Self-pay | 46640 (3.79) | 11975 (3.99) | 34665 (3.73) | < 0.001 |
| No charge | 4045 (0.33) | 1095 (0.37) | 2950 (0.32) | < 0.001 |
| Other | 25840 (2.10) | 6120 (2.04) | 19720 (2.12) | < 0.001 |
| Ethnicity | | | | |
| White | 853450 (69.43) | 211825 (70.64) | 641625 (69.03) | < 0.001 |
| Black | 220270 (17.92) | 54880 (18.30) | 165390 (17.79) | < 0.001 |
| Hispanic | 87950 (7.15) | 18340 (6.12) | 69610 (7.49) | < 0.001 |
| Asian/Pacific Islander | 32390 (2.63) | 6835 (2.28) | 25555 (2.75) | < 0.001 |
| Native American | 4890 (0.40) | 940 (0.31) | 3950 (0.42) | < 0.001 |
| Other | 30345 (2.47) | 7045 (2.35) | 23300 (2.51) | < 0.001 |
| Year of admission | | | | |
| 2016 | 439515 (35.75) | 18555 (6.19) | 420960 (45.29) | < 0.001 |
| 2017 | 461665 (37.56) | 128190 (42.75) | 333475 (35.88) | < 0.001 |
| 2018 | 328115 (26.69) | 153120 (51.06) | 174995 (18.83) | < 0.001 |
| Quartiles of household income for patient's ZIP Code (based on current year) | | | | |
| 0-25th percentile | 384775 (31.30) | 90760 (30.27) | 294015 (31.63) | 0.092 |
| 26th to 50th percentile | 324225 (26.37) | 80010 (26.68) | 244215 (26.28) | 0.092 |
| 51st to 75th percentile | 288890 (23.50) | 72055 (24.03) | 216835 (23.33) | 0.092 |
| 76th to 100th percentile | 231405 (18.82) | 57040 (19.02) | 174365 (18.76) | 0.092 |
| All Patient Refined DRG: Severity of Illness Subclass | | | | |
| No class specified | 15 (0.00) | < 11 | < 11 | < 0.001 |
| Minor loss of function (includes cases with no comorbidity or complications) | 98975 (8.05) | 19815 (6.61) | 79160 (8.52) | < 0.001 |
| Moderate loss of function | 600870 (48.88) | 143065 (47.71) | 457805 (49.26) | < 0.001 |
| Major loss of function | 404680 (32.92) | 102390 (34.15) | 302290 (32.52) | < 0.001 |
| Extreme loss of function | 124755 (10.15) | 34590 (11.54) | 90165 (9.70) | < 0.001 |

| | | | | |
|---|---|---|---|---|
| Bedsize Categories (Beginning in 1998) | | | | |
| Small | 202600 (16.48) | 39640 (13.22) | 162960 (17.53) | < 0.001 |
| Medium | 361380 (29.40) | 78805 (26.28) | 282575 (30.40) | < 0.001 |
| Large | 665315 (54.12) | 181420 (60.50) | 483895 (52.06) | < 0.001 |
| Location/teaching status of hospital | | | | |
| Rural | 91710 (7.46) | 12460 (4.16) | 79250 (8.53) | < 0.001 |
| Urban nonteaching | 279700 (22.75) | 52035 (17.35) | 227665 (24.50) | < 0.001 |
| Urban teaching | 857885 (69.79) | 235370 (78.49) | 622515 (66.98) | < 0.001 |
| Region of hospital | | | | |
| Northeast | 244660 (19.90) | 65550 (21.86) | 179110 (19.27) | < 0.001 |
| Midwest | 293405 (23.87) | 87905 (29.31) | 205500 (22.11) | < 0.001 |
| South | 525865 (42.78) | 124895 (41.65) | 400970 (43.14) | < 0.001 |
| West | 165365 (13.45) | 21515 (7.17) | 143850 (15.48) | < 0.001 |
| Control/ownership of hospital | | | | |
| Government, nonfederal | 135110 (10.99) | 34740 (11.59) | 100370 (10.80) | 0.009 |
| Private, not-profit | 940360 (76.50) | 233970 (78.03) | 706390 (76.00) | 0.009 |
| Private, invest-own | 153825 (12.51) | 31155 (10.39) | 122670 (13.20) | 0.009 |
| Disposition of patient, uniform coding | | | | |
| Routine | 443730 (36.10) | 108870 (36.31) | 334860 (36.03) | < 0.001 |
| Transfer to Short-term Hospital | 34195 (2.78) | 6645 (2.22) | 27550 (2.96) | < 0.001 |
| Transfer Other: Includes Skilled Nursing Facility (SNF), Intermediate Care Facility (ICF), Another Type of Facility | 517610 (42.11) | 129205 (43.09) | 388405 (41.79) | < 0.001 |
| Home Health Care (HHC) | 178525 (14.52) | 42535 (14.18) | 135990 (14.63) | < 0.001 |
| Against Medical Advice (AMA) | 12070 (0.98) | 2710 (0.90) | 9360 (1.01) | < 0.001 |
| Died | 42930 (3.49) | 9900 (3.30) | 33030 (3.55) | < 0.001 |
| Discharge alive, destination unknown | 235 (0.02) | < 11 | 235 (0.03) | < 0.001 |