


Frequency, predictors and cardiovascular outcomes associated with transthoracic echocardiographic findings during acute ischaemic stroke hospitalisation

Richa Sharma ¹, Scott Silverman,² Shaun Patel,² Lee H Schwamm,² Danita Yoerger Sanborn³

To cite: Sharma R, Silverman S, Patel S, *et al.* Frequency, predictors and cardiovascular outcomes associated with transthoracic echocardiographic findings during acute ischaemic stroke hospitalisation. *Stroke & Vascular Neurology* 2022;**7**:e001170. doi:10.1136/svn-2021-001170

Received 8 June 2021
Accepted 29 April 2022
Published Online First
13 June 2022

ABSTRACT

Objective To characterise the clinical utility of transthoracic echocardiography (TTE) at the time of acute ischaemic stroke (AIS).

Background The utility of obtaining a TTE during AIS hospitalisation is uncertain.

Methods We studied AIS hospitalisations at a single centre (2002–2016). TTE abnormalities were classified as findings associated with: high stroke risk (Category I), cardiac events (Category II) and of unclear significance (Category III). We performed logistic regressions to predict Category I, II and III abnormalities. The odds of 1 year recurrent stroke hospitalisation captured by ICD 9 and 10 codes as a function of Category I, II and III abnormalities were assessed. Improvement in predictive capacity for 1 year recurrent ischaemic stroke hospitalisation beyond stroke risk factors was evaluated by net reclassification improvement.

Results There were 5523 AIS hospitalisations. Nearly 81% of admission TTEs were abnormal (18.7% Category I, 32.7% Category II, 72.8% Category III). Older patients with coronary artery disease, atrial fibrillation, hypertension, diabetes, and patent intracranial and extracranial vessels were likely to have an abnormal TTE. Category I finding was associated with lower odds of 1-year recurrent stroke hospitalisation (OR 0.54, 95% CI 0.30 to 0.96). Category I data significantly improved the predictive value for 1-year recurrent ischaemic stroke hospitalisation beyond stroke risk factors (net reclassification improvement 0.1563, 95% CI 0.0465 to 0.2661).

Conclusions TTE abnormalities associated with stroke and cardiac event risk were commonly detected during AIS hospitalisation. Detection of Category I TTE findings reduced the risk of recurrent stroke, potentially due to neutralisation of the cardioembolic source by targeted therapy, indicating the clinical utility of TTE.

INTRODUCTION

Patients with acute ischaemic stroke (AIS) routinely undergo transthoracic echocardiography (TTE) during the inpatient encounter, however the clinical utility of this study in patients who had a stroke is unknown. Cardiac abnormalities can coexist in patients

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Transthoracic echocardiography (TTE) studies are routinely performed in patients hospitalised with acute ischaemic stroke (AIS). The utility of obtaining a TTE during AIS hospitalisation is uncertain.

WHAT THIS STUDY ADDS

⇒ We demonstrate that 18% of AIS TTE studies demonstrate high-risk cardioembolic sources of stroke and we identify clinical and radiographic predictors of these TTE findings. Detection of these abnormalities by TTE was associated with lower odds of 1 year recurrent stroke hospitalisation (OR 0.54, 95% CI 0.30 to 0.96) and improved the predictive capacity for 1 year recurrent ischaemic stroke hospitalisation beyond stroke risk factors.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, AND/OR POLICY

⇒ These findings may inform future guidelines and clinical practice regarding the utilisation of TTE during AIS hospitalisation to facilitate prevention of recurrent stroke.



© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

¹Department of Neurology, Yale University School of Medicine, New Haven, Connecticut, USA

²Department of Neurology, Massachusetts General Hospital, Boston, Massachusetts, USA

³Department of Cardiology, Massachusetts General Hospital, Boston, Massachusetts, USA

Correspondence to

Dr Richa Sharma;
richa.sharma@yale.edu

with ischaemic stroke due to shared vascular risk factors. One meta-analysis demonstrated a prevalence of asymptomatic coronary artery disease (CAD) of 52% among patients with AIS and a 3% risk of myocardial infarction (MI) within 1 year in patients without any cardiac history.¹ While some AIS and cardiac therapies overlap, others are uniquely aimed at each disease. Pharmacological, surgical and procedural interventions target certain cardiac conditions and decrease mortality, but are rarely used in patients without cardiac diagnoses.² Quantifying cardiac abnormality frequencies and their progression over time in patients with AIS is critical to inform when to obtain a TTE for the purpose of mitigating risk of future stroke and cardiovascular events.

Prior studies describe the epidemiology of cardiac abnormalities detected by TTE in patients with AIS, however, these are limited by solely assessing findings pertinent to stroke prevention, cross-sectional design, small samples sizes and lack of generalisability due to being performed outside of the USA.³⁻⁵ Reflecting the paucity of evidence linking TTEs obtained during AIS admission and clinical outcomes, the yield of echocardiography in the AIS context is denoted as uncertain in the current guidelines.⁶

Clinicians face uncertainty about whether TTE in patients with AIS informs management to prevent future stroke and cardiovascular events while attempting to practice resource stewardship. Patient-level predictors of having a TTE abnormality during AIS admission need to be more clearly defined. It is unknown which patients with AIS with a prior TTE study will have a newly detected finding. Finally, it is important to determine whether detecting the presence of specific TTE findings during AIS hospitalisation are associated with risk of future stroke, MI and heart failure hospitalisation.

In this study, we aim to (1) Explore the frequency of findings on AIS admission TTE and their rates of progression over time, (2) Identify patient-level predictors of having specific TTE findings during AIS admission and new TTE findings if a prior study was normal, and (3) Determine the odds of 1 year hospitalisation for recurrent stroke, MI and heart failure associated with having specific TTE findings at the time of AIS admission.

METHODS

Patient population

This retrospective study was performed at an academic institution from 2002 to 2016. The cohort was derived from the institution's Get-With-The-Guidelines-Stroke database, a quality improvement initiative in which hospitals enter clinical and radiographic data of all patients hospitalised with a stroke diagnosis.⁷ Patients with AIS are identified retrospectively by administrative discharge ICD-9 and ICD-10 codes and prospectively by daily review of clinical logs. Data abstraction, entry and adjudication are performed by trained study personnel. There are logic checks and form controls to minimise data entry errors. The covariates in this study were age, gender, race, admission year, history of atrial fibrillation (AF), CAD/prior MI, hypertension (HTN), hyperlipidaemia (HLD), diabetes mellitus (DM), carotid disease, peripheral vascular disease (PVD) excluding the carotid artery, prior stroke or transient ischaemic attack, smoking, chronic kidney disease (CKD), heart valve prosthesis, National Institutes of Health Stroke Scale (NIHSS) at presentation (dichotomised as minor and major stroke by NIHSS <4 and >4),⁸ presenting symptoms, and home medications.

Hospitalisations were included in this cohort if age at admission was ≥ 18 years, AIS was diagnosed during hospitalisation and a TTE was performed during the AIS hospitalisation. Of the 8859 consecutive admissions to

our hospital with AIS, a total of 5523 met these criteria. Subgroups consisted of admissions with (1) Prior, most recently performed TTE available in hospital system's records (n=1106), (2) TTE performed ≥ 3 months after AIS hospitalisation (n=1077), and (3) TTE performed most recently prior to the AIS hospitalisation and at ≥ 3 months after the AIS hospitalisation (n=373).

Radiographic features

Radiographic information was extracted by natural language processing of radiology reports from each stroke admission encounter using Python programming language (Python Software Foundation, <https://www.python.org/>). All radiology reports were created by board-certified radiologists. We applied predefined regular expression sequences for specific radiographic findings to radiology reports of neuroimaging obtained during AIS admission including CT head without contrast, CT angiogram of head and neck, brain MRI, MR angiogram head and neck, carotid ultrasound, and conventional angiogram. Our Python codebase is uploaded on GitHub and available by request. We collected information about cortical location of stroke, supratentorial (defined as structures rostral to and including the thalamus) and infratentorial location of stroke, and the presence of any moderately or severely stenotic or occluded intracranial artery or extracranial carotid or vertebral arteries. We determined the accuracy of this automated method of radiology chart review by selecting 100 observations for each variable and blindly comparing values ascribed by human (RS) versus machine algorithm review of the radiology report.

Echocardiographic features

All patients in this cohort underwent a two-dimensional TTE during admission for an AIS. TTEs were performed by trained hospital sonographers and interpreted by board-certified echocardiographers. TTE images were collected per Intersocietal Accreditation Commission of Echocardiography standards and included colour Doppler, continuous wave and pulse wave data. Images were analysed in apical two-chamber and four-chamber views as well as parasternal long-axis and short-axis views.

We classified TTE findings into three mutually exclusive categories based on the reading echocardiographer's hard-coded interpretations in the database: (1) Features associated with a high risk of cardioembolic stroke (Category I), (2) Abnormalities warranting timely cardiac workup and treatment not necessarily related to stroke management (Category II), and (3) Possible indicators of stroke aetiology and/or cardiac disease with no immediate therapeutic consequence but may warrant further monitoring and long-term risk factor management (Category III). High-risk cardioembolic sources are abnormalities outlined in the 1993 TOAST (Trial of Org 10172 in Acute Stroke Treatment) publication⁹ plus the presence of a patent foramen ovale (PFO) which are associated with evidence-based secondary stroke



prevention treatments.^{10–12} Category I features included: left ventricular (LV) thrombus, PFO (ascertained by Doppler and/or agitated saline contrast), atrial septal aneurysm, intracardiac tumour, left-sided endocarditis and left-sided valvular prosthesis. Category II abnormalities were: depressed ejection fraction (EF),^{13,14} LV aneurysm,¹⁵ LV segmental wall motion abnormality,¹⁶ aortic stenosis¹⁷ and regurgitation¹⁸ (moderate and severe by colour Doppler), and mitral stenosis¹⁹ and regurgitation²⁰ (moderate and severe by colour Doppler). Category III findings included: dilated left atrium (LA),^{21,22} LV hypertrophy (LVH),²³ mitral annular calcification (MAC),²⁴ Lambl's excrescence²⁵ and aortic atheroma.²⁶

Outcomes

The outcomes of incident hospitalisation for recurrent ischaemic stroke and cardiac events were ascertained within the time frame of the day after AIS hospitalisation discharge to 1 year after discharge in the full cohort. We queried the Massachusetts General Hospital's Research Patient Database Repository for discrete hospitalisations that occurred within the health system with a principal diagnoses of ischaemic stroke (ICD-9 434.xx, 436.xx; ICD-10 I63.3-I63.9), MI (ICD-9 410.xx; ICD-10 I21.xx, I22.xx) and heart failure (ICD-9 428.xx; ICD-10 I50.xx).²⁷ We counted only the first incident hospitalisation for each of the individual outcomes of recurrent ischaemic stroke, MI and heart failure within 1 year after AIS discharge.

Statistical analysis

Comparison of TTE abnormalities in patients who had an ischaemic stroke across time

Statistical analyses were performed in SAS software V.9.4 (Cary, North Carolina, USA). Baseline demographic and clinical characteristics are presented as percentages and means as appropriate. Among patients with both TTEs prior to and during AIS admission, exact McNemar's testing was used to determine whether there was a significant difference in the proportion of patients with each prespecified cardiac abnormality at the two time points. This test was selected due to the lack of independence between repeated measures within the same group of patients.^{28,29} Statistical significance was set at $p < 0.05$. This test was also applied among patients with both an inpatient TTE and TTE > 3 months after admission. Among patients with TTEs available prior to, during, and ≥ 3 months after admission, we compared the proportions of patients with each cardiac abnormality at each time point by Cochran's Q test.

Logistic regression modelling

To identify predictors of Category I, II and III abnormalities detected on AIS admission TTE, multivariable logistic regression models were developed using clinical and imaging covariates available at the time of or soon after presentation including age, gender, race, prior medical comorbidities and medication use, NIHSS at presentation, and radiographic findings (cortical infarct location,

infratentorial infarct location, and vessel stenosis or occlusion). We excluded patients with prior history of heart failure from this analysis since heart failure was one of the TTE outcomes of interest. Among patients without a history of heart failure ($n=5228$), we modelled the likelihood of observing any of the prespecified TTE findings. We also modelled the likelihood of having a TTE abnormality in each of the three categories with specific management implications. Parsimonious models were created by stepwise selection (p values of entry and exit: 0.05). These models were also generated in a subgroup of patients with no prior history of heart failure, mechanical heart valve or AF ($n=4234$) since there are well-defined management approaches with these diagnoses and AIS. We created a multivariable logistic regression model to identify independent predictors of having a new TTE finding if a prior TTE showed no abnormalities. Finally, we ascertained the odds of (1) Incident hospitalisation for recurrent ischaemic stroke, (2) MI, and (3) Heart failure within 1 year of the index AIS hospitalisation in all patients with AIS regardless of baseline heart failure status as a function of having a Category I, II and III TTE abnormality detected by the AIS TTE by univariate logistic regression modelling.

Net reclassification improvement analysis

We sought to evaluate the additive value of Category I findings in predicting incident hospitalisation for recurrent ischaemic stroke within the 1 year follow-up period. We calculated the net reclassification index and its two-sided 95% CI to understand the incremental predictive capacity of Category I TTE biomarker data above the baseline characteristics collected during AIS admission.³⁰ These characteristics were the following: age, sex, race, and history of prior stroke, HTN, HLD, diabetes, AF and heart failure.

RESULTS

There were 5523 hospitalisations in the cohort (table 1). More than half were male, and the mean age of patients was 68.6 years. The majority of the cohort was Caucasian (86%) with HTN (68%), AF (20%), HLD (40%) and DM (23%). Average admission NIHSS was 8. Nearly 33% reported taking an antithrombotic (29% an antiplatelet, 4.9% an anticoagulant). Seventy-two per cent had cortical infarcts, 27% had infratentorial infarcts, and 30% had significant head or neck stenosis or occlusion of a head or neck artery. The accuracy of our automated method of radiology data extraction in a random sample of 100 selected for each variable was 98% for neuroanatomical location and 99% for vessel abnormality.

Nearly 81% of admission TTEs had at least one abnormality of interest. The most frequent admission TTE findings were: dilated LA (44%), MAC (37%), LVH (26%), aortic atheroma (17%), PFO (16%), segmental LV wall motion abnormality (14%), moderate or severe mitral regurgitation (11%), and $EF \leq 35\%$ (7.4%). In the cohort

Table 1 Characteristics of the study cohort

Variable	N (%) or mean (SD) (total n=5523)
Gender (male)	2996 (54.3)
Age at admission	68.6 (15.2)
Race	
Caucasian	4727 (85.6)
African-American	305 (5.5)
Asian	175 (3.2)
American-Indian	5 (0.1)
Native Hawaiian/Pacific Islander	9 (0.2)
Unknown/other	314 (5.7)
Year of admission	
2002–2007	1321 (23.9)
2007–2010	1230 (22.3)
2010–2013	1202 (21.8)
2013–2016	1770 (32.1)
Comorbidities	
Atrial fibrillation/flutter	1119 (20.3)
Coronary artery disease/prior myocardial infarction	1185 (21.5)
Carotid stenosis	221 (4.0)
Diabetes	1292 (23.4)
Dyslipidaemia	2216 (40.1)
Hypertension	3744 (67.8)
Prior stroke	579 (10.5)
Prior transient ischaemic attack	183 (3.3)
Peripheral vascular disease	237 (4.3)
Smoker	826 (15.0)
Prosthetic heart valve	46 (0.8)
Heart failure	295 (5.3)
Chronic kidney disease	181 (3.3)
Home medications	
Antithrombotics	1843 (33.4)
Antiplatelet	1574 (28.5)
Anticoagulant	269 (4.9)
Antihypertensive	3547 (64.2)
Statin	2209 (40.0)
Presenting symptoms	7.5 (7.1)
Aphasia	1657 (30.0)
Gaze deviation	1271 (23.0)
Field cut	1404 (25.4)
Facial weakness	2754 (49.9)
Ataxia	698 (12.6)
Motor	4379 (79.3)
Neglect	936 (16.9)
Radiographic findings	
Cortical infarct	3977 (72.0)

Continued

Table 1 Continued

Variable	N (%) or mean (SD) (total n=5523)
Infratentorial infarct	1512 (27.4)
Arterial moderate/severe stenosis or occlusion in the head or neck	1673 (30.3)
TTE findings	
Tumour	2 (0.04)
Vegetation	14 (0.3)
Patent foramen ovale	884 (16.0)
Atrial septal aneurysm	70 (1.3)
Left atrium, dilated	2411 (43.7)
LV aneurysm	91 (1.7)
LV thrombus	59 (1.1)
LV hypertrophy	1436 (26.0)
LV wall motion abnormality	791 (14.3)
EF ≤15%	72 (1.3)
EF ≤35%	406 (7.4)
Lambli's excrescence	117 (2.1)
Mitral annular calcification	2023 (36.6)
Aortic atheroma	950 (17.2)
Cardiac valvular prosthesis	90 (1.6)
Moderate or severe aortic regurgitation	108 (2.0)
Moderate or severe mitral regurgitation	609 (11.0)
Moderate or severe aortic stenosis	111 (2.0)
Moderate or severe mitral stenosis	98 (1.8)
EF, ejection fraction; LV, left ventricular; TTE, transthoracic echocardiography.	

without a prior history of heart failure, a total of 4157 out of 5228 (79.5%) admission TTEs demonstrated at least one abnormality. There were 981 (18.7%) admission TTEs with a Category I finding, 1711 (32.7%) with a Category II finding and 3806 (72.8%) with a Category III finding. Among patients with no history of heart failure, mechanical cardiac valve or AF (n=4234), there were 3227 admission TTEs with any prespecified abnormality (76.2%), 854 with a Category I abnormality (20.1%), 1062 with a Category II abnormality (25.1%) and 2642 with a Category III abnormality (62.4%).

Comparison of TTE abnormalities in patients who had a stroke across time

Among patients with TTEs both before and during AIS admission, the proportion of patients with the following abnormalities increased significantly on the subsequent TTE: PFOs (p<0.01), dilated left atria (p<0.01), LV thrombi (p=0.03), LVH (p=0.01), EF ≤15% and <35% (p<0.01 and p<0.01, respectively), Lambli's excrescence (p<0.01), MAC (p<0.01), aortic atheroma (p<0.01) and cardiac valvular prostheses (p<0.01) (table 2). Median time from prior TTE to the inpatient TTE was 539 days

Table 2 Findings on TTE during inpatient hospitalisation for ischaemic stroke versus a most recent prior TTE (*left*) and inpatient TTE versus follow-up TTE (*right*)

TTE features	Comparison of findings of inpatient TTE and most recent prior TTE (n=1106)			Comparison of findings of inpatient TTE and first follow-up TTE (n=1077)		
	Most recent prior TTE N (%)	Inpatient TTE N (%)	P value	Inpatient TTE N (%)	Follow-up TTE N (%)	P value
Tumour (left-sided)	0 (0)	0 (0.0)	1.000	0 (0.00)	0 (0.00)	1.000
Vegetation (left-sided)	1 (0.09)	5 (0.45)	0.219	4 (0.4)	1 (0.1)	0.250
Patent foramen ovale	88 (8.0)	131 (11.8)	<0.001	258 (24.0)	128 (11.9)	<0.001
Atrial septal aneurysm	1 (0.2)	10 (2.9)	0.250	20 (1.9)	5 (0.5)	<0.001
Left atrium, dilated	589 (53.3)	632 (57.1)	0.007	490 (45.5)	555 (51.5)	<0.001
LV aneurysm	18 (1.6)	25 (2.3)	0.265	20 (1.9)	20 (1.9)	1.000
LV thrombus	6 (0.54)	16 (1.45)	0.031*	18 (1.7)	12 (1.1)	0.327
LV hypertrophy	331 (29.9)	368 (33.3)	0.014*	289 (26.8)	273 (25.4)	0.284
LV wall motion abnormality	201 (18.2)	214 (19.4)	0.287	157 (14.6)	184 (17.1)	0.026
EF ≤15%	2 (0.2)	13 (1.2)	0.001*	16 (1.5)	6 (0.6)	0.031
EF ≤35%	66 (6.0)	104 (9.4)	<0.001	95 (8.8)	92 (8.5)	0.810
Lambert's excrescence	14 (1.3)	30 (2.7)	0.003*	14 (1.3)	18 (1.7)	0.524
Mitral annular calcification	485 (43.91)	545 (49.3)	<0.001	366 (34.0)	406 (37.7)	0.003
Aortic atheroma	193 (17.5)	244 (22.1)	0.003*	174 (16.2)	159 (14.8)	0.342
Prosthesis	30 (2.7)	46 (4.2)	0.009*	22 (2.04)	25 (2.32)	0.607
Moderate or severe aortic regurgitation	27 (2.4)	40 (3.6)	0.053	21 (2.0)	28 (2.6)	0.248
Moderate or severe mitral regurgitation	155 (14.0)	177 (16.0)	0.067	116 (10.8)	155 (14.4)	<0.001
Aortic stenosis	37 (3.4)	34 (3.1)	0.804	26 (2.4)	32 (3.0)	0.489
Mitral stenosis	25 (2.3)	26 (2.4)	1.000	19 (1.8)	19 (1.8)	1.000

*Median days between most recent prior TTE and inpatient TTE is 539 days (IQR 162–1317 days); median days between inpatient TTEs and follow-up TTE is 481 days (IQR 212–1065 days)
EF, ejection fraction; LV, left ventricular; TTE, transthoracic echocardiography.

(IQR: 162–1317). Among those with an inpatient and follow-up TTE, there was an increase in the proportion of patients with: dilated LA ($p<0.01$), segmental LV wall motion abnormality ($p=0.03$), MAC ($p<0.01$), and moderate and severe mitral regurgitation ($p<0.01$).

In the subgroup ($n=373$) with TTEs across all three time points (prior to AIS admission, during the inpatient AIS period and ≥ 3 months after the admission) (figure 1), higher proportions were noted with dilated LA ($p<0.01$), EF $\leq 35\%$ ($p<0.01$), PFOs ($p<0.01$), atrial septal aneurysms ($p=0.04$), MAC ($p<0.01$), a new prosthetic valve ($p<0.01$), and moderate and severe mitral regurgitation ($p=0.01$) over time.

Multivariable modelling

Table 3 presents independent, patient-level predictors of an abnormal TTE during admission in the cohort without a prior history of heart failure including older age (OR 2.01, 95% CI 1.73 to 2.34), CAD/prior MI (OR 3.44, 95% CI 2.64 to 4.47), AF (OR 3.15, 95% CI 2.40 to 4.14), diabetes (OR 1.28, 95% CI 1.06 to 1.54), HTN (OR 1.32, 95% CI 1.14 to 1.54), and patent head and neck vessels

(OR 1.18, 95% CI 1.01 to 1.38) (c -statistic 0.71). There was a higher likelihood of a Category I finding among those who were younger, Caucasian, had no history of AF, HTN, or DM, had an infratentorial infarct, had a low severity stroke, and had patent head and neck vessels (c -statistic 0.68). The odds of having a Category II TTE abnormality were higher among patients who were older, had a history of CAD, AF, HTN, or PVD, had a higher NIHSS, and had patent head and neck vessel (c -statistic 0.73). Significant predictors of a Category III finding included older age, male sex, a history of CAD, AF, HTN, DM, or CKD, and a higher NIHSS.

Among patients with no history of heart failure, mechanical cardiac valve or AF ($n=4234$), older age, Caucasian race, history of CAD, HTN or DM, and patent head and neck vessels were patient-level risk factors for having any of the prespecified TTE abnormalities (c -statistic 0.68, table 4). Younger, Caucasian patients with no history of HTN, DM, or antiplatelet use, NIHSS <4 , infratentorial infarct, and patent head and neck vessels were more likely to have a Category I finding (c -statistic 0.67). A Category

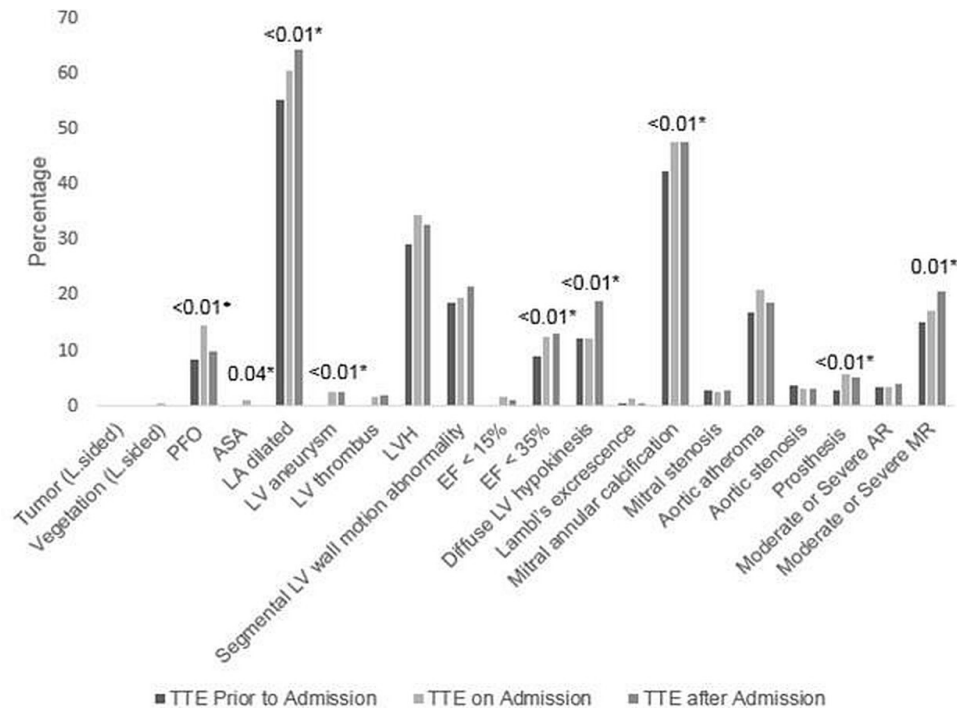


Figure 1 Cardiac abnormalities across serial transthoracic echocardiography (TTE). Percentages of patients with TTE abnormalities prior to ischaemic stroke admission, at the time of admission and after admission. (N=373). *Median time from first to the third TTE: 1094 days (IQR 559–1900). AR, aortic regurgitation; EF, ejection fraction; LV, left ventricular; MR, mitral regurgitation; PFO, patent foramen ovale.

II abnormality was associated with patients who were older, had a history of CAD and HTN, a higher NIHSS, a cortical infarct, and patent head and neck vessels (c-statistic 0.72). Older, male patients with a history of CAD, HTN or DM, and higher NIHSS were more likely to have a Category III finding (c-statistic 0.72).

We created a model predicting the odds of a new prespecified TTE finding (n=83) during AIS admission if a prior TTE in our system was unremarkable (n=891) (table 5). Older patients with CAD, PVD, CKD, no history of HLD and no known carotid disease were likely to develop a novel TTE finding at the time of AIS (c-statistic 0.71).

There were a total of 124 hospitalisations for recurrent stroke, 21 hospitalisations for MI and 28 hospitalisation for heart failure within 1 year of the index AIS hospitalisation. In univariate logistic regression modelling of all patients with AIS, the odds of an incident hospitalisation for recurrent ischaemic stroke within 1 year of discharge from the index AIS hospitalisation was significantly higher among patients with a Category I finding detected by the AIS TTE versus patients without a Category I finding (OR 0.54, 95% CI 0.30 to 0.96, $p=0.0347$, table 6). There was no significant difference in hospitalisations for MI (OR 1.45, 95% CI 0.53 to 3.97, $p=0.4701$) or heart failure (OR 1.01, 95% CI 0.38 to 2.65, $p=0.9895$) by Category I status. The odds of a recurrent stroke hospitalisation within 1 year of AIS were similar by Category II status (OR 0.77, 95% CI 0.51 to 1.16), but the odds of hospitalisation for MI (OR 2.46, 95% CI 1.04 to 5.80) and heart failure (OR

5.62, 95% CI 2.47 to 12.79) within 1 year were significantly higher among patients with Category II findings. There was no association between the odds of hospitalisation for any of the three conditions as a function of Category III status.

There was significant net reclassification improvement with the additional input of Category I TTE data to baseline characteristics (net reclassification index 0.1563; 95% CI 0.0465 to 0.2661) for predicting recurrent ischaemic stroke hospitalisation. The addition of Category I TTE data to baseline characteristics compared with the model comprised of baseline characteristics alone resulted in 79% of events being correctly reclassified ($p<0.001$) and 63% of non-events being reclassified ($p<0.001$).

DISCUSSION

Our study assesses TTE findings identified during an AIS hospitalisation. About 19% of studies demonstrated an abnormality associated with a high risk of cardioembolic stroke, 33% with an abnormality warranting cardiac management not specifically related to stroke and 72% with findings with no significant immediate implication but which may prompt further monitoring and long-term risk factor management to prevent a future cerebrovascular or cardiovascular event. Some findings were more frequently observed over time. Patient-level risk factors for an abnormal TTE include age, vascular risk factors, having cortical or infratentorial acute infarcts, and patent head and neck vessels. Only 9% of admission TTEs



Table 3 Multivariable logistic regression models predicting an abnormal TTE finding (*left*), a Category I finding (*left-centre*), a Category II finding (*right-centre*) and a Category III finding (*right*) among those with no prestroke history of heart failure

Covariates	TTE abnormality n=4157		Category I abnormality n=981		Category II abnormality n=1519		Category III abnormality n=3535		Model c- statistic		
	OR (95% CI)	P value	Model c- statistic	OR (95% CI)	P value	Model c- statistic	OR (95% CI)	P value			
Older age	2.01 (1.73 to 2.34)	<0.001	0.71	0.53 (0.45 to 0.62)	<0.001	0.68	1.74 (1.50 to 2.01)	<0.001	0.73	2.83 (2.48 to 3.24)	<0.001
Male gender										1.22 (1.07 to 1.39)	0.004
Caucasian				1.36 (1.10 to 1.70)	0.005						
Coronary artery disease/prior MI	3.44 (2.64 to 4.47)	<0.001					3.73 (3.21 to 4.34)	<0.001		2.02 (1.66 to 2.45)	<0.001
Atrial fibrillation	3.15 (2.40 to 4.14)	<0.001		0.61 (0.48 to 0.77)	<0.001		1.75 (1.49 to 2.05)	<0.001		3.41 (2.71 to 4.29)	<0.001
Prior antihypertensive medication	1.32 (1.14 to 1.54)	<0.001		0.67 (0.57 to 0.79)	<0.001		1.22 (1.05 to 1.42)	0.009		1.84 (1.60 to 2.11)	<0.001
Diabetes mellitus	1.28 (1.06 to 1.54)	0.010		0.76 (0.63 to 0.93)	0.007					1.45 (1.23 to 1.71)	<0.001
Chronic kidney disease										1.62 (1.02 to 2.58)	0.041
Prior antiplatelet use				0.74 (0.62 to 0.89)	0.002						
Admission NIHSS ≥4				0.63 (0.54 to 0.73)	<0.001		1.44 (1.26 to 1.65)	<0.001		1.17 (1.03 to 1.33)	0.017
Cortical infarct							1.38 (1.18 to 1.61)	<0.001			
Infratentorial infarct				0.81 (0.68 to 0.96)	0.0139						
Patent intracranial and extracranial arteries	1.18 (1.01 to 1.38)	0.043		1.50 (1.26 to 1.78)	<0.001		1.29 (1.12 to 1.49)	<0.001			

MI, myocardial infarction; NIHSS, National Institutes of Health Stroke Scale; TTE, transthoracic echocardiography.

Table 4 Multivariable logistic regression models predicting an abnormal TTE finding (*left*), a Category I finding (*left-centre*), a Category II finding (*right-centre*) and a Category III finding (*right*) among those with no prestroke history of heart failure, mechanical heart valve or atrial fibrillation (n=4234)

Covariates	TTE abnormality n=3227			Category I abnormality n=854			Category II abnormality n=1062			Category II abnormality n=2642		
	OR (95% CI)	P value	c-statistic	OR (95% CI)	P value	c-statistic	OR (95% CI)	P value	c-statistic	OR (95% CI)	P value	c-statistic
Older age	2.05 (1.75 to 2.39)	<0.001	0.68	0.50 (0.43 to 0.59)	<0.001	0.67	1.81 (1.54 to 2.13)	<0.001	0.72	2.90 (2.52 to 3.33)	<0.001	0.72
Male gender										1.19 (1.03 to 1.36)	0.016	
Caucasian	1.22 (1.01 to 1.48)	0.049		1.31 (1.04 to 1.64)	0.007							
Coronary artery disease/prior MI	3.53 (2.66 to 4.68)	<0.001					4.17 (3.50 to 4.97)	<0.001		2.27 (1.85 to 2.79)	<0.001	
Prior antihypertensive medication	1.32 (1.13 to 1.55)	<0.001		0.65 (0.55 to 0.76)	<0.001		1.28 (1.08 to 1.52)	0.004		2.05 (1.78 to 2.37)	<0.001	
Diabetes mellitus	1.29 (1.06 to 1.57)	0.011		0.73 (0.59 to 0.90)	0.004					1.46 (1.23 to 1.74)	<0.001	
Prior antiplatelet use				0.75 (0.62 to 0.92)	0.005							
Admission NIHSS >4				0.61 (0.52 to 0.71)	<0.001		1.55 (1.32 to 1.81)	<0.001		1.19 (1.04 to 1.36)	0.013	
Cortical infarct							1.44 (1.21 to 1.72)	<0.001				
Infratentorial infarct				0.80 (0.67 to 0.95)	0.012							
Patent intracranial and extracranial arteries	1.22 (1.03 to 1.43)	0.019		1.49 (1.24 to 1.80)	<0.001		1.23 (1.04 to 1.44)	0.015				

MI, myocardial infarction; NIHSS, National Institutes of Health Stroke Scale; TTE, transthoracic echocardiography.

Table 5 Multivariable logistic regression model predicting a new abnormal TTE finding (n=83) in those with a prior normal TTE (n=891)

Patient characteristics	New TTE abnormality detected OR (95% CI)	P value	Model c-statistic
Older age	3.78 (1.85 to 7.74)	0.003	0.71
Prior use of cholesterol-lower medication	0.44 (0.27 to 0.73)	0.002	
History of coronary artery disease	1.73 (1.04 to 2.89)	0.036	
History of carotid disease	0.11 (0.01 to 0.80)	0.029	
Peripheral vascular disease	2.65 (1.27 to 5.54)	0.009	
Chronic kidney disease	2.53 (1.26 to 5.08)	0.009	

TTE, transthoracic echocardiography.

demonstrated a new abnormal finding compared with a prior TTE study. Older and unhealthier patients with no known carotid disease and a prior normal TTE have higher odds of a new TTE abnormality during AIS admission. Having a TTE finding detected at the time of AIS which has been associated with high stroke risk was associated with a significantly lower rate of ischaemic stroke hospitalisation within 1 year. Conversely, detection of a TTE feature associated with high risk of cardiac events was associated with a significantly elevated odds of hospitalisation for MI and heart failure within 1 year. There was no 1 year risk of stroke or cardiac events associated with TTE findings with no significant immediate clinical implication. Finally, there was significant incremental predictive value of Category I data above baseline demographic and clinical characteristics for 1 year recurrent ischaemic stroke hospitalisation risk. These findings confirm the important role of inpatient TTEs at the time of AIS admission particularly in patients with a high-risk profile to prompt interventions to prevent future cerebrovascular and cardiac events.

Two other studies have evaluated TTE findings in the AIS context. Abreu *et al* observed that 37% of patients with AIS had TTE findings that would warrant anticoagulation³ while Fralick *et al* noted that only 14% of TTEs in patients with AIS identified clinically actionable findings for secondary stroke prevention.³¹ These percentages lie within the range of the prevalences of potential cardioembolic sources identified by TTE in our study. Our study, however, also uniquely describes abnormalities associated

with both future neurological and cardiac events. Given the high proportions of AIS TTEs with abnormalities in the three prespecified categories in our study, a TTE during the AIS encounter may be a pivotal screening and diagnostic opportunity to promote brain and heart health. For instance, a new diagnosis of low EF merits may prompt not only anticoagulation for secondary stroke prevention but also cardiology consultation and prescription of evidence-based cardioprotective medications which may not be administered as first-line therapy for routine management by stroke care providers. A concomitant finding of LVH or aortic atheroma may also prompt more aggressive risk factor management to promote the health of both vascular beds. As such, the diagnostic implications from a TTE during an AIS admission may have significant immediate and downstream effects.

Our study uniquely explores TTE findings during AIS hospitalisation and their association with future stroke and cardiovascular events within 1 year of the index AIS. The ascertainment by TTE of findings linked with high stroke risk was associated with significantly lower odds of hospitalisation for ischaemic stroke within a year. The addition of Category I TTE biomarker data significantly improved the predictive capacity for recurrent ischaemic stroke beyond traditional vascular risk factors. These echocardiographic features have been designated as high risk in the stroke literature and there are clear evidence-based secondary stroke prevention treatment algorithms. The identification of any of these stroke risk related TTE abnormalities during AIS admission likely

Table 6 Odds of hospitalisation for recurrent ischaemic stroke, myocardial infarction and heart failure as a function of TTE finding categories

1 year outcomes	Category I finding OR (95% CI) p=	Category II finding OR (95% CI) p=	Category III finding OR (95% CI) p=
Hospitalisation for recurrent ischaemic stroke (n=124)	0.54 (0.30 to 0.96) p=0.0347	0.77 (0.51 to 1.16) p=0.2091	1.25 (0.84 to 1.87) p=0.2772
Hospitalisation for myocardial infarction (n=21)	1.45 (0.53 to 3.97) p=0.4701	2.46 (1.04 to 5.80) p=0.0398	0.91 (0.36 to 2.24) p=0.8238
Hospitalisation for heart failure (n=28)	1.01 (0.38 to 2.65) p=0.9895	5.62 (2.47 to 12.79) p<0.0001	>99 (<0.01 to >999.99) p=0.9527

TTE, transthoracic echocardiography.

prompted targeted stroke guideline-directed intervention to neutralise effectively the risk of future stroke from that specific source such as treatment of endocarditis with antibiotics or initiation of anticoagulation for an LV thrombus.

Among patients with TTE findings associated with high risk for a cardiac event, there was no increased odds of future stroke events, but there was a two times and five times higher risk of MI and heart failure, respectively. There may be two explanations for this observation. First, the risk of a cardiac event among patients with these TTE findings is elevated by definition and may reflect the natural course of cardiovascular disease. While this may be the case, there were multiple guideline-directed medical therapies available to modify the risk of cardiovascular events during this epoch that may not be in the toolkit of stroke providers. It is possible that under-recognition of the clinical significance of Category II findings may result in underutilisation of guideline-directed medical therapies, rendering the course of their sequela of cardiovascular outcomes unmitigated.

While the rates of recurrent hospitalisation events were low at 3.1%, importantly if considered solely from a payer's standpoint, the estimated cost of a TTE only (estimated at \$634 per study) in patients with a Category I or II abnormality detected during AIS admission in our cohort was \$1585000 while the estimated cost of hospitalisation for all three events within 1 year of the AIS was \$2923564.^{32 33} In contrast, the estimated total cost of ubiquitously obtaining TTEs in all patients with AIS in our cohort would have been \$3501582. These findings suggest that obtaining TTEs in patients with AIS particularly with a high pretest probability of having a Category I or II finding may be of clinical utility without compromising resource stewardship.

The use of a repeat TTE during AIS admission is often questioned when there is an existing recent TTE available. Our study demonstrates that among patients with a prior normal TTE who are admitted for AIS, nearly 9% have an abnormal finding on the TTE during admission. Predictors of a novel TTE finding include vascular comorbidities and no history of carotid disease. One explanation of this paradoxical finding is that among those with known carotid disease, the causative aetiology may be more likely large artery atherosclerosis rather than cardioembolism from a new cardiac lesion that developed in the interim. While the rareness of a new finding suggests a potentially limited role for a repeat TTE at the time of stroke if a prior TTE study is available and carotid disease is present, further study is needed to validate this observation.

We noted several patterns in our longitudinal analyses. Vascular risk factors were independent predictors of new TTE findings. LA dilation was one of the most common Category III TTE abnormalities and the proportion of patients with LA dilation increased with time. A link between LA dilation prevalence and vascular risk factors has been noted in prior studies.^{34 35} The observed progression of LA dilation in patients who had an ischaemic stroke is hypothesis-generating in terms of the temporal relationship linking

atrial cardiopathy, AF and ischaemic stroke. There was a greater proportion of patients with depressed EF and wall motion abnormality over time, suggesting a need to consider screening high-risk patients to prevent further cardiovascular events. Finally, follow-up TTEs were more likely to detect a new diagnosis of moderate or severe mitral regurgitation. The association between severe mitral regurgitation and mortality if untreated can be up to 50% compared with 14% with valve repair or replacement, highlighting the importance of its timely detection and management.²⁰

There are several limitations of our study. One consideration is the unknown generalisability of our results to patients in other geographical regions. Survival and detection biases are inherent in a retrospective study. We attempted to minimise detection bias by only including patients with TTE available at each of the time points of interest, however this approach can be subject to confounding by indication. The indications for the TTE studies were not precisely known and may explain the higher proportion of patients observed with a PFO during the inpatient AIS admission study compared with a prior TTE due to differences in ascertainment techniques used for specific indications. There is likely variability by sonographers and echocardiographers in the threshold for discerning and reporting a TTE abnormality, depending on indication for the TTE at the time it was ordered. Outcomes were ascertained by administrative billing codes which have variable sensitivity and specificity. There are also presumably unmeasured confounders at the patient level including the prevalence of medical comorbidities at the time of a prior and follow-up TTE. The TTE categories in this study are broad; further investigation is necessary to pinpoint specific TTE findings that can be implicated with outcomes.

SUMMARY

We observe a high prevalence of prespecified cardiac abnormalities detected by echocardiogram at the time of acute stroke hospitalisation associated with ischaemic stroke and cardiovascular event risk. The proportion of patients who had a stroke with certain abnormalities increases with time. We identify predictors of specific TTE abnormalities at the time of admission and having a new specific TTE abnormality if a prior TTE was normal. Finally, the presence of a high stroke risk TTE abnormality at the time of ischaemic stroke hospitalisation was associated with a significantly reduced odds of recurrent ischaemic stroke upto 1 year after the index ischaemic stroke, while a high cardiac risk TTE abnormality was associated with significantly higher odds of MI and heart failure hospitalisations. The addition of Category I TTE biomarker data significantly improved prediction of recurrent ischaemic stroke risk. These findings demonstrate utility of TTE as a diagnostic test performed during the AIS admission, particularly in patients with a high pretest probability of TTE findings associated with high risk of stroke and cardiac events. Further study is necessary to determine criteria for appropriate utilisation of TTE during AIS hospitalisation to inform our current standard of care.

Twitter Lee H Schwamm @braindoc_mgh

Acknowledgements The authors thank the staff who have participated in the development and maintenance of their institutional Get-With-The-Guidelines data repository.

Contributors RS's role was study conception and design, data analysis and manuscript writing.

Funding There was no specific funding source for this study, but effort by Dr Sharma and Dr Schwamm (Principal Investigator for the StrokeNet Northeast Regional Coordinating Centre) was supported, in part, by funding from the NINDS StrokeNet Network (NINDS U10 NS086729).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Massachusetts General Hospital Institutional Review Board. The IRB waived the need to obtain informed consent.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The data that support the findings of this study are available from the corresponding author upon reasonable request by investigators.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iD

Richa Sharma <http://orcid.org/0000-0003-0798-2353>

REFERENCES

- 1 Gunnoo T, Hasan N, Khan MS, *et al*. Quantifying the risk of heart disease following acute ischaemic stroke: a meta-analysis of over 50,000 participants. *BMJ Open* 2016;6:e009535.
- 2 Fonarow GC, Yancy CW, Hernandez AF, *et al*. Potential impact of optimal implementation of evidence-based heart failure therapies on mortality. *Am Heart J* 2011;161:1024–30.
- 3 Abreu TTde, Mateus S, Correia J. Therapy implications of transthoracic echocardiography in acute ischemic stroke patients. *Stroke* 2005;36:1565–6.
- 4 Khan MA, Khealani B, Hameed B, *et al*. Diagnostic yield of transthoracic echocardiography for stroke patients in a developing country. *J Pak Med Assoc* 2008;58:375–7.
- 5 Rem JA, Hachinski VC, Boughner DR, *et al*. Value of cardiac monitoring and echocardiography in TIA and stroke patients. *Stroke* 1985;16:950–6.
- 6 Powers WJ, Rabinstein AA, Ackerson T, *et al*. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American heart Association/American stroke association. *Stroke* 2019;50:STR000000000000211.
- 7 Schwamm LH, Fonarow GC, Reeves MJ, *et al*. Get with the Guidelines-Stroke is associated with sustained improvement in care for patients hospitalized with acute stroke or transient ischemic attack. *Circulation* 2009;119:107–15.
- 8 Fischer U, Baumgartner A, Arnold M, *et al*. What is a minor stroke? *Stroke* 2010;41:661–6.
- 9 Adams HP, Bendixen BH, Kappelle LJ, *et al*. Classification of subtype of acute ischemic stroke. definitions for use in a multicenter clinical trial. TOAST. trial of ORG 10172 in acute stroke treatment. *Stroke* 1993;24:35–41.
- 10 Mas J-L, Derumeaux G, Guillon B, *et al*. Patent foramen ovale closure or anticoagulation vs. antiplatelets after stroke. *N Engl J Med* 2017;377:1011–21.
- 11 Søndergaard L, Kasner SE, Rhodes JF, *et al*. Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke. *N Engl J Med* 2017;377:1033–42.
- 12 Saver JL, Carroll JD, Thaler DE, *et al*. Long-Term outcomes of patent foramen ovale closure or medical therapy after stroke. *N Engl J Med* 2017;377:1022–32.
- 13 Bristow MR, Gilbert EM, Abraham WT, *et al*. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. MOCHA Investigators. *Circulation* 1996;94:2807–16.
- 14 Krum H, Sackner-Bernstein JD, Goldsmith RL, *et al*. Double-Blind, placebo-controlled study of the long-term efficacy of carvedilol in patients with severe chronic heart failure. *Circulation* 1995;92:1499–506.
- 15 Hassapoyannes CA, Stuck LM, Hornung CA, *et al*. Effect of left ventricular aneurysm on risk of sudden and nonsudden cardiac death. *Am J Cardiol* 1991;67:454–9.
- 16 Cicala S, de Simone G, Roman MJ, *et al*. Prevalence and prognostic significance of wall-motion abnormalities in adults without clinically recognized cardiovascular disease: the strong heart study. *Circulation* 2007;116:143–50.
- 17 Schwarz F, Baumann P, Manthey J, *et al*. The effect of aortic valve replacement on survival. *Circulation* 1982;66:1105–10.
- 18 Dujardin KS, Enriquez-Sarano M, Schaff HV, *et al*. Mortality and morbidity of aortic regurgitation in clinical practice. A long-term follow-up study. *Circulation* 1999;99:1851–7.
- 19 Horstkotte D, Niehues R, Strauer BE. Pathomorphological aspects, aetiology and natural history of acquired mitral valve stenosis. *Eur Heart J* 1991;12 Suppl B:55–60.
- 20 Montant P, Chenot F, Robert A, *et al*. Long-Term survival in asymptomatic patients with severe degenerative mitral regurgitation: a propensity score-based comparison between an early surgical strategy and a conservative treatment approach. *J Thorac Cardiovasc Surg* 2009;138:1339–48.
- 21 Benjamin EJ, D'Agostino RB, Belanger AJ, *et al*. Left atrial size and the risk of stroke and death. The Framingham heart study. *Circulation* 1995;92:835–41.
- 22 Yaghi S, Moon YP, Mora-McLaughlin C, *et al*. Left atrial enlargement and stroke recurrence: the Northern Manhattan stroke study. *Stroke* 2015;46:1488–93.
- 23 Bots ML, Nikitin Y, Salonen JT, *et al*. Left ventricular hypertrophy and risk of fatal and non-fatal stroke. EUROSTROKE: a collaborative study among research centres in Europe. *J Epidemiol Community Health* 2002;56 Suppl 1:i8–13.
- 24 Benjamin EJ, Plehn JF, D'Agostino RB, *et al*. Mitral annular calcification and the risk of stroke in an elderly cohort. *N Engl J Med* 1992;327:374–9.
- 25 Freedberg RS, Goodkin GM, Perez JL, *et al*. Valve strands are strongly associated with systemic embolization: a transesophageal echocardiographic study. *J Am Coll Cardiol* 1995;26:1709–12.
- 26 Wehrum T, Dragonu I, Strecker C, *et al*. Aortic atheroma as a source of stroke - assessment of embolization risk using 3D CMR in stroke patients and controls. *J Cardiovasc Magn Reson* 2017;19:67.
- 27 Goldstein LB. Accuracy of ICD-9-CM coding for the identification of patients with acute ischemic stroke: effect of modifier codes. *Stroke* 1998;29:1602–4.
- 28 McNEMAR Q. Note on the sampling error of the difference between correlated proportions or percentages. *Psychometrika* 1947;12:153–7.
- 29 Kent DM, Ruthazer R, Weimar C, *et al*. An index to identify stroke-related vs incidental patent foramen ovale in cryptogenic stroke. *Neurology* 2013;81:619–25.
- 30 Pencina MJ, D'Agostino RB, D'Agostino RB, *et al*. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med* 2008;27:157–72.
- 31 Fralick M, Goldberg N, Rohailla S, *et al*. Value of routine echocardiography in the management of stroke. *CMAJ* 2019;191:E853–9.
- 32 Masoudi FA, Viragh T, Magid DJ, *et al*. Trends in Medicare payment rates for noninvasive cardiac tests and association with testing location. *JAMA Intern Med* 2019;179:1699–706.
- 33 Wang G, Zhang Z, Ayala C, *et al*. Costs of hospitalization for stroke patients aged 18–64 years in the United States. *J Stroke Cerebrovasc Dis* 2014;23:861–8.
- 34 Ou Q, Chen Y, Yu S, *et al*. Prevalence of left atrial enlargement and its risk factors in general Chinese population. *BMC Cardiovasc Disord* 2016;16:53.
- 35 Stritzke J, Markus MRP, Duderstadt S, *et al*. The aging process of the heart: obesity is the main risk factor for left atrial enlargement during aging the MONICA/KORA (monitoring of trends and determinations in cardiovascular disease/cooperative research in the region of Augsburg) study. *J Am Coll Cardiol* 2009;54:1982–9.