Appendix 1 (as supplied by the authors)

Value of routine echocardiography in the management of stroke Appendix

Appendix to: Fralick M, Goldberg N, Rohailla S, et al. Value of routine echocardiography in the management of stroke.
CMAJ 2019. doi: 10.1503/cmaj.190111.

Additional details about the GEMINI database

Data were collected from the GEMINI database (the General Medicine Inpatient Initiative), which has previously been described in detail in *CMAJ Open*.[1] GEMINI collects administrative and clinical data for all patients hospitalized under general internal medicine at seven hospitals in Toronto and Mississauga, Ontario, since April 1, 2010. Administrative data are collected directly from hospitals and include data about patient demographics, clinical diagnoses, and resource use, as reported to the Canadian Institute for Health Information. Clinical data are extracted from information technology systems within each hospital, and include laboratory tests, diagnostic imaging, in-hospital medications, and at the two sites included in this study, echocardiography. All data are subjected to quality control checks, including statistical process control methods and manual review of a random sample of patient records at each hospital to identify data extraction errors.

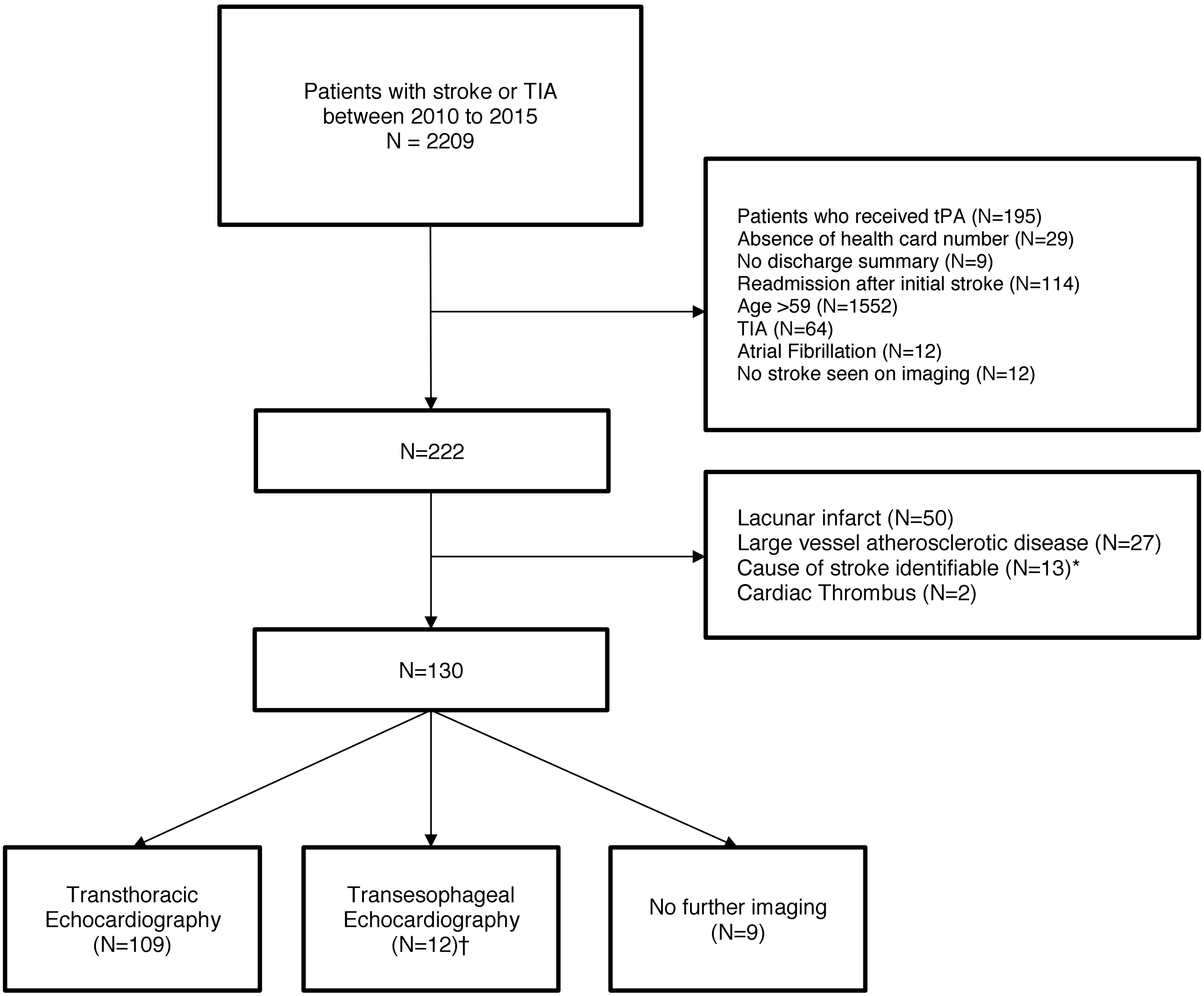
Identifying patients with cryptogenic stroke

We identified patients with acute ischemic stroke using the International Classification of Diseases, 10th revision (ICD-10) diagnostic criteria codes for ischemic stroke (i63.x, i64.x, h34.1x) and transient ischemic attack (G45.0x, G45.1x, G45.2x, G45.3x, G45.8x, G45.9x). To identify patients with a cryptogenic stroke, two trained clinicians manually reviewed the medical records for all patients diagnosed with an acute ischemic stroke and then, similar to the clinical trials[2-4], we excluded the following patients:

- Age > 59 years
- transient ischemic attack (based on ICD-10 diagnosis codes)
- lacunar infarct (based on manual review of imaging reports, which could have included CT or MRI)
- intracranial tumour/mass (based on manual review of imaging reports)
- intracranial hemorrhage (based on manual review of imaging reports)

- aortic dissection (based on manual review of imaging reports)
- atrial fibrillation (based on electrocardiogram, Holter monitoring, or a diagnosis of atrial fibrillation)
- large vessel atherosclerotic disease (defined as carotid stenosis > 50% on the ipsilateral side as the patient's stroke, based on manual review of carotid vessel imaging reports including carotid doppler, CT-angiogram, MR-angiogram)
- cardiac thrombus (based on a review echocardiographic findings)
- aortic valve vegetation or atrial myxoma (primarily based on a review transthoracic echo findings)
- clotting disorder (adjudicated by one to two physicians as needed after reviewing discharge summary and medical record)

Appendix Figure 1. Consort diagram for identifying patients with potential cryptogenic stroke.



Note: * For example: vasculitis, hypercoagulability, intracranial hypotension

† 1 patient with cryptogenic stroke had a transesophageal echocardiogram but not on a transthoracic echocardiogram

Appendix Table 1: Characteristics of patients with cryptogenic stroke (N=130) and echocardiogram findings	
Age – yr (SD)	49.8 (SD)
Male Sex – no. (%)	82 (63.1%)
Medical History – no. (%)	
Hypertension	58 (44.6)
Dyslipidemia	15 (11.5)
Diabetes mellitus	33 (25.4)
Coronary artery disease	6 (4.6)
Congestive heart failure	2 (1.5)
Previous Stroke/TIA	13 (10.0)
Transthoracic Echocardiography (TTE) – no. (%)	109 (83.8%)
Patent foramen ovale	19 (17.4%)^
*****Small	4
Moderate	1
Large	0
Left ventricle aneurysm	5 (4.6%)^
Left ventricle EF < 35%	3 (2.8%)^
Transesophageal echocardiography (TEE) – no. (%)	12 (9.2%)
Number of patients with PFO detected only on TEE	2

Legend: SD = standard deviation * Size only available from 5 reports

^ The percentage of patients with cryptogenic stroke and TTE (N=109) who had PFO

PFO: Patent foramen ovale

Identifying additional patients with a potential hospital admission diagnosis of stroke

Patients who were initially considered to have a stroke but were subsequently diagnosed with another condition would not be captured in our cohort if their most responsible discharge diagnosis was not stroke or TIA. Additional chart review was performed for these patients. For example, a patient initially diagnosed with stroke may be diagnosed with a ventricular thrombus based on TTE findings. Their discharge diagnosis could be coded as ventricular thrombus, rather than stroke. Missing these patients in our cohort would underestimate the diagnostic utility of TTE. In order to quantify any such misclassification, we also reviewed all patients initially diagnosed with a stroke or TIA while in the emergency department whose discharge diagnosis was not stroke or TIA.

We identified 582 patients with an initial diagnosis of ischemic stroke or TIA in the emergency department who were admitted to hospital and subsequently discharged with a different most responsible discharge diagnosis. Four patients (0.7%) had a most responsible discharge diagnosis of acute or subacute infectious endocarditis and 1 (0.2%) had a diagnosis of a benign heart neoplasm. The most common discharge diagnoses among the remaining patients were intracerebral hemorrhage (13%), syncope (12%), seizure (8%), infection other than endocarditis (7%), malignancy (5%), delirium (5%), and generalized malaise (5%).

Inter-rater agreement (Cohen's Kappa)

Manually extracted data were analyzed for consistency using Cohen's Kappa calculated for each variable. A Kappa value of 0.61 – 0.80 indicates "substantial agreement" and 0.81 – 0.99 indicates "almost perfect agreement".[5] Manually extracted sources of data for this study included: electronic admission note (including home medications), in-hospital pharmacy records, in-hospital laboratory and medical imaging systems, and the electronic discharge summary (including discharge medications, referrals, and follow-up plan)

The inter-rater agreement between data extractors for TTE results was near perfect: thrombus (κ=0.90), PFO (κ=0.98), vegetation (κ=0.90), and myxoma (κ=0.97) (appendix). The inter-rater agreement for data manually extracted from the patient's chart ranged from near perfect to moderate: atrial fibrillation (κ=0.91), antiplatelet prescribed on discharge (κ=0.90), anticoagulation use prior to admission (κ=0.83), anticoagulation use on discharge (κ=0.75), prior stroke (κ=0.75), antiplatelet use prior to admission (κ=0.67), and prior stroke (κ=0.64).

Additional Details for Length of Stay Analysis

	Unadjusted		Quantile regression	
	Difference in length of stay (95% CI)*	p-value	Difference in length of stay (95% CI)	p-value
Age	0.05 (0.029, 0.06)	<0.01	0.04 (0.02, 0.05)	<0.01
Male Sex	-0.63 (-1.17, -0.08)	0.03	-0.46 (-0.89, -0.04)	0.03
Atrial fibrillation	2.17 (1.27, 3.06)	<0.01	1.61 (0.60, 2.62)	<0.01
Hypertension	0.79 (0.20, 1.38)	0.008	0.56 (0.09,1.03)	0.02
Dyslipidemia	-1.04 (-1.73, -0.35)	0.003	-1.00 (-1.45,-0.55)	< 0.01
Prior stroke or TIA	0.04 (-0.71, 0.79)	0.9	0.15 (-0.32,0.63)	0.5
Diabetes mellitus	0.71 (0.04, 1.38)	0.04	0.70 (0.18,1.22)	0.01
Coronary artery disease	0.63 (-0.46, 1.71)	0.3	0.38 (-0.37,1.12)	0.3
Heart failure	5.17 (2.66, 7.68)	<0.01	3.67 (1.40,5.94)	< 0.01
Prior antiplatelet	-0.83 (-1.41, -0.26)	0.004	-0.44 (-0.91, 0.02)	0.06
Prior anticoagulant	0.63 (-0.34, 1.59)	0.2	-1.28 (-2.47,-0.10)	0.03
Echocardiogram	3.13 (2.66,3.59)	< 0.01	3.01 (2.58, 3.44)	<0.01

Note: The median length of stay was used rather than mean length of stay since length of stay was not normally distributed. *Age was maintained as a continuous variable in years and thus the regression output represents the difference in the median length of stay in days for every 1-year increase in age. The overall interpretation is that patients who had an echocardiogram had a median length of stay that was 3.01 days longer than patients who did not have an echocardiogram.

References

1. Verma AA, Guo Y, Kwan JL, et al. Patient characteristics, resource use and outcomes associated with general internal medicine hospital care: the General Medicine Inpatient Initiative (GEMINI) retrospective cohort study. *CMAJ open*. 2017;5(4):E842-E849. Doi:10.9778/cmajo.20170097.
2. 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(11):1011-1021. doi:10.1056/NEJMoa1705915.
3. Søndergaard L, Kasner SE, Rhodes JF, et al. Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke. *N Engl J Med*. 2017;377(11):1033-1042. doi:10.1056/NEJMoa1707404.
4. 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(11):1022-1032. doi:10.1056/NEJMoa1610057.
5. Viera AJ, Garrett JM. Understanding interobserver agreement: the kappa statistic. *Fam Med*. 2005;37(5):360-363.