

Supplemental Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable. Incidence of pediatric arterial ischaemic stroke in NSW, Australia

Year	NSW population for age<17 years ^a (n)	Arterial ischaemic stroke (AIS) (n)	AIS incidence per 100,000 persons	Large vessel occlusion (LVO) (n)	LVO incidence per 100,000 persons
2010	1543584	15	0.97	6	0.39
2011	1549483	11	0.71	3	0.19
2012	1562405	18	1.15	3	0.19
2013	1579244	13	0.82	2	0.13
2014	1595316	18	1.13	1	0.06
2015	1614297	16	0.99	2	0.12
2016	1635508	17	1.04	5	0.31
2017	1654082	23	1.39	9	0.54
2018	1666000	17	1.02	6	0.36
2019	1681294	17	1.01	2	0.12
Mean	1608121	16.5	1.02	3.9	0.24
95%CI	1572516 - 1643727	14.2 – 18.8	0.89 – 1.16	2.1 – 5.7	0.13 – 0.35
SD	49773	3.21	0.18	2.51	0.15
Median	1604807	17.0	1.02	3.0	0.19
IQR	1559175 - 1657062	14.5 – 18.0	0.93 – 1.13	2.0 – 6.0	0.12 – 0.37

^a NSW population data obtained from Australian Bureau of Statistics: National, state, and territory population – 3101.1, Table 51 – Estimated resident population by single year of age, New South Wales. Commonwealth of Australia, 2020²². Accessed via abs.gov.au on 1st September 2021.

All incidences measured in number of cases per 100,000 persons of age<17 years per year

Abbreviations: AIS – arterial ischaemic stroke, CI – confidence interval, IQR – interquartile ratio, LVO – large vessel occlusion, NSW – New South Wales, SD – standard deviation

eMethods 1. Selection criteria for mechanical thrombectomy in adults

In this study, we applied existing selection criteria for mechanical thrombectomy in adults from three sources to determine if paediatric patients with large vessel occlusion (LVO) would have been eligible for thrombectomy, other than age. The three sources were:

1. MR-CLEAN study¹ – applying to anterior circulation LVO presenting <6h since last seen well.
2. DAWN study² – applying to anterior circulation LVO presenting 6-24h since last seen well.
3. American Heart Association (AHA) 2019 Updated Guidelines for the Early Management of Patients with Acute Ischemic Stroke³ – applying to anterior and posterior circulation LVO.

In all cases, the criteria requiring age 18 years or older were not applied.

MR-CLEAN study – inclusion criteria¹:

MR-CLEAN – Multicentre Randomized CLinical trial of Endovascular treatment for Acute ischaemic stroke in the Netherlands¹

- Age 18 years or older (not applied)
- Acute ischemic stroke caused by an intracranial occlusion in the anterior arterial circulation
- Initiation of intraarterial treatment to be possible within 6 hours after stroke onset
- Occlusion of the distal intracranial internal carotid artery, middle cerebral artery (M1 or M2), or anterior cerebral artery (A1 or A2), established with CTA, MRA, or DSA
- NIHSS score of 2 or higher
- Administration of IV thrombolysis (alteplase) was allowed
- Inclusion of patients with additional extracranial internal carotid artery occlusion or dissection was left to the judgement of the treating physician

DAWN study – inclusion criteria²:

DWI Assessment with clinical mismatch in the triage of Wake-up and late presenting strokes undergoing Neurointervention with Trevo²

- Age 18 years or older (not applied)
- Interval between the time the patient was last known to be well and randomization of 6 to 24 hours
- Pre-stroke score of 0 or 1 on the modified Rankin Scale (mRS)
- No evidence of intracranial haemorrhage on CT or MRI
- No evidence of infarct involving more than one third of the territory of the middle cerebral artery on CT or MRI at baseline
- Evidence of occlusion of the intracranial internal carotid artery or M1 segment of the middle cerebral artery or both on CTA or MRA
- Mismatch between the severity of the clinical deficit and the infarct volume based on these criteria:
 - Group A: 80 years or older, NIHSS score 10 or higher, infarct volume < 21 mL on DWI or CTP
 - Group B: 18-79 years age, NIHSS score 10 or higher, infarct volume < 31 mL
 - Group C: 18-79 years age, NIHSS score 20 or higher, infarct volume 31-50 mL

AHA 2019 updated guidelines³:

- Class I recommendation: Patients should receive mechanical thrombectomy with a stent retriever if they meet all the following criteria: (1) prestroke mRS score of 0 to 1; (2) causative occlusion of the internal carotid artery or MCA segment 1 (M1); (3) age \geq 18 years (not applied); (4) NIHSS score of \geq 6; (5) ASPECTS of \geq 6; and (6) treatment can be initiated (groin puncture) within 6 hours of symptom onset.
- Class IIb recommendation: Although the benefits are uncertain, the use of mechanical thrombectomy with stent retrievers may be reasonable for carefully selected patients with AIS in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have causative occlusion of the MCA segment 2 (M2) or MCA segment 3 (M3) portion of the MCAs.
- Class IIb recommendation: Although the benefits are uncertain, the use of mechanical thrombectomy with stent retrievers may be reasonable for carefully selected patients with AIS in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have causative occlusion of the anterior cerebral arteries, vertebral arteries, basilar artery, or posterior cerebral arteries.
- Class I recommendation: In selected patients with AIS within 6 to 16 hours of last known normal who have LVO in the anterior circulation and meet other DAWN or DEFUSE 3 eligibility criteria, mechanical thrombectomy is recommended.
- Class IIa recommendation: In selected patients with AIS within 16 to 24 hours of last known normal who have LVO in the anterior circulation and meet other DAWN eligibility criteria, mechanical thrombectomy is reasonable.

eMethods 2. Study protocol

1. TITLE

Paediatric Large Vessel Occlusion Stroke Study (PLVOSS)

2. CO-ORDINATING PRINCIPAL INVESTIGATOR

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3. INVOLVED CENTERS

- i) The Children's Hospital at Westmead: Departments of Medical Imaging and Paediatric Neurology
- ii) Sydney Children's Hospital at Randwick: Department of Paediatric Neurology
- iii) John Hunter Children's Hospital: Department of Paediatric Neurology
- iv) Royal Prince Alfred Hospital: Department of Neurology

4. SITE-SPECIFIC PRINCIPAL INVESTIGATORS

- i) The Children's Hospital at Westmead: Dr Kartik Bhatia (see above) – Medical Imaging. Dr Christopher Troedsen, Paediatric Neurologist
- ii) Sydney Children's Hospital at Randwick: Dr Ian Andrews, Paediatric Neurologist
- iii) John Hunter Children's Hospital: Dr Christina Miteff, Paediatric Neurologist
- iv) Royal Prince Alfred Hospital: Dr John Worthington, Head of Stroke Neurology

5. BACKGROUND

Mechanical thrombectomy for acute ischemic stroke due to large vessel occlusion (LVO) is now the standard of care in adults up to 24 hours following symptom onset after seven randomized controlled trials demonstrated its benefit over IV thrombolysis alone^{1,2,4-8}. However, none of these trials included patients < 18 years of age. The evidence base in children and adolescents is limited to an individual patient-data meta-analysis⁹, single small prospective case series¹⁰, multiple small retrospective case series/single-arm cohort studies¹¹⁻¹³, and case reports. On this evidence base, the 2019 American Heart Association/American Stroke Association guidelines for management of paediatric stroke state that no strong recommendation can be made on the use of thrombectomy in children, but that it may be considered in select circumstances¹⁴. A previous attempt at undertaking a randomized controlled trial purely for the use of just IV thrombolysis in children (Thrombolysis in Pediatric Stroke: TIPS study) was abandoned due to insufficient patient recruitment resulting in loss of funding¹⁵.

Undertaking a randomized controlled trial for thrombectomy in children with acute stroke would therefore be:

- 1) **Not feasible** – the trial would be unlikely to recruit sufficient patients in a reasonable time period for meaningful statistical analysis, AND
- 2) **Not ethical** – it would be unethical to randomize a child to non-interventional treatment for acute stroke when the evidence base in adults is so strong (in adults the number needed to treat is 2.6¹⁶, which is better than coronary angioplasty for myocardial infarction or IV antibiotics for acute mastoiditis).

There is an increasing trend to offering both IV thrombolysis and mechanical thrombectomy to children with acute LVO stroke who fulfill existing adult selection criteria, in order to avoid poor long-term neurological outcomes which are lifelong and can be associated with significant disability⁹. The existing Australian consensus guidelines for paediatric stroke management allow for consideration of endovascular therapy in patients who fulfill existing adult criteria, which all require confirmation of a LVO on vascular imaging¹⁷. However, there are large gaps in the existing knowledge base which prevent appropriate resource allocation to allow such treatments. In particular, the following data are unknown based on the existing literature:

- i) What is the frequency (and proportion of all stroke cases) of LVO in paediatric patients?
- ii) What are the long-term neurological outcomes in children with a confirmed anterior circulation LVO? There is some data on posterior circulation LVO outcomes¹⁸.
- iii) What proportion of paediatric patients with acute LVO stroke would fulfill existing adult criteria for mechanical thrombectomy?

The answering of these questions would allow for a more comprehensive and efficient allocation of resources for acute paediatric stroke management in NSW (and worldwide).

6. RESEARCH AIMS and QUESTIONS

Primary aim:

- i) To determine the long-term clinical outcome in children who suffer from an ischaemic stroke secondary to large vessel occlusion (LVO) - defined as occlusion of the intracranial components of the internal carotid artery, the M1 or M2 segments of the middle cerebral artery, A1 or A2 segments of the anterior cerebral artery, intracranial component of the vertebral artery, basilar artery, and P1 or P2 segments of the posterior cerebral artery. Chronic stenosis (e.g. due to Moya-moya) does not count as LVO unless the case presents with acute thrombotic occlusion.

Secondary aims:

- i) To determine the frequency of LVO stroke in children in New South Wales (NSW).
- ii) To determine the proportion of all diagnosed ischaemic strokes in children in NSW that have an LVO.
- iii) To determine the proportion of all stroke presentations in children (including stroke mimics) that have an LVO.
- iv) To determine the main aetiologies causing LVO stroke in children in NSW.
- v) To assess for differences in outcome between children with LVO stroke who underwent reperfusion therapy (IV thrombolysis or mechanical thrombectomy) compared with those who did not.
- vi) To determine the proportion of children with LVO-stroke whose clinical and imaging findings at presentation (other than age) would fulfill inclusion criteria for the MR-CLEAN¹ (when less than 6 hours after onset) or DAWN² (6-24 hours after onset) studies on mechanical thrombectomy.

7. HYPOTHESES

Primary hypothesis:

- i) That the long-term neurological outcomes in children with non-reperused LVO stroke are significantly worse than those with non-LVO ischaemic stroke.

Secondary hypotheses:

- i) We hypothesize that the long-term neurological outcomes in children who suffer from a non-reperused LVO stroke are poor (i.e. moderate to severe disability or death) in the majority (>50%) of cases.
- ii) That there is a substantial proportion of children with LVO stroke who fulfill existing adult criteria for mechanical thrombectomy.
- iii) That children with LVO stroke who underwent reperfusion therapy have better clinical outcomes than those who did not.

8. METHODOLOGY

8.1. Study design

Retrospective multi-centre cohort study involving all paediatric hospitals in NSW over the period 2010-2019 inclusive.

Consent would be waived given the retrospective nature of the study, the long-time-period being assessed, the likelihood that a significant proportion of patients will have moved interstate or overseas since their admission, and the risk of creating a biased sample if there is a predominance of patients and families with good outcomes responding relative to those with poor outcomes.

8.2. Patient search

Retrospective databases for ischaemic stroke admissions already exist separately at Sydney Children's Hospital Randwick, John Hunter Children's Hospital, and Royal Prince Alfred Hospitals (3 of our 4 sites). No database currently exists at Children's Hospital at Westmead.

For this retrospective cohort, the de-identified paediatric (age < 18 years at time of admission) ischaemic stroke cases from the three existing hospital databases would be pooled. In addition, utilizing the assistance of the Management Support Analysis Unit at Children's Hospital at Westmead, we will undertake a retrospective search for all cases of paediatric ischaemic stroke admitted in the Sydney Children's Hospital Network from 1st January 2010 – 31st December 2019 utilizing the ICD-10 codes of I63, I65, and I66:
I63 (Cerebral infarction) including all subsections I63.0 – I63.9,
I65 (occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction) including all subsections I65.0-I65.9, and
I66 (occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction) including all subsections I66.0-I66.9.

Pooling the de-identified data from these four sites will yield the retrospective cohort. To ensure data integrity, the SCHN search results will be cross-referenced with the existing SCH Randwick database to ensure all cases have been captured in the network.

INCLUSION CRITERIA for SEARCH:

- i) Date range 1st January 2010 – 31st December 2019
- ii) Age range <18 years at time of diagnosis
- iii) Inpatient hospital admission at one of the four study centres
- iv) ICD-10 (2019 version) admission diagnostic codes:
I63 (Cerebral infarction) including all subsections I63.0 – I63.9,
I65 (occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction) including all subsections I65.0-I65.9 – if infarction identified, and
I66 (occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction) including all subsections I66.0-I66.9 – if infarction identified.

EXCLUSION CRITERIA

The following patient groups would be excluded to create a database comprised of acute arterial ischaemic stroke case for the analysis, because the following groups have markedly different aetiologies, presentations, treatments, and outcomes:

- Neonatal stroke (age < 28 days) except if the stroke is iatrogenic in nature
- Haemorrhagic stroke
- Venous ischaemic/infarction (e.g. due to venous sinus thrombosis)
- Group B Streptococcal meningitis related stroke
- Herniation syndromes from traumatic brain injury resulting in stroke
- Global hypoxic-ischaemic injury (e.g. cardiac arrest, drowning) – these cases will be maintained separately for future analysis of this cohort

8.3. De-identification

For each patient identified at each hospital, a unique study ID number will be created for the purposes of de-identification and privacy protection. The ID number would contain a capital letter to indicate the hospital (W = Westmead, S = Sydney Children's Hospital at Randwick, J = John Hunter, and R = Royal Prince Alfred Hospital) followed by the number in chronological order based on the timing of the first relevant imaging (1, 2, 3, ...). Within each patient, each separate admission for stroke would be indicated by a lower-case letter (a, b, c, ...) to account for patients who have suffered multiple stroke episodes. An example: For the third child treated at John Hunter Hospital within the 2010-2019 cohort, undergoing their first admission for a stroke episode, the study ID would be J3a.

For each patient, the first and last name, date of birth, and hospital MRN (i.e. the identifiable data) would be kept in a separate password protected Master Log excel spreadsheet, with a separate Master Log at each site – this will ensure that private identifiable data does not leave

the original hospital. These identifiable data would not be shared across sites and would remain within the research network drives of the relevant hospitals. The only purpose of maintaining the Master Log would be to link clinical and imaging data at the time of data acquisition and to link the study ID with the identifiable data, and only de-identified data would be shared across sites for the purposes of the study. The Master Log at each site would be kept in a separate folder and with a different password to the de-identified Data Sheet excel spreadsheet used for data collection and analysis.

8.4. Outcome measures

The paediatric modified Rankin Scale score (ped-mRS) will be derived by the study investigators from the recorded clinical data using eMR/Powerchart based on the last available clinical follow-up. The clinical data to be used to derive the ped-mRS must be a recorded clinical or functional assessment by a paediatric neurologist, neurosurgeon, or rehabilitation physician. Ped-mRS score 0-2 (none, minimal, or mild disability) will be classified as a good outcome and 3-6 (moderate to severe disability or death) as a poor outcome for secondary outcome analysis.

8.5. Imaging analysis

All CT angiogram (CTA), MR angiogram (MRA), and Digital Subtraction Angiography (DSA) studies from identified cases will be analysed independently by the same paediatric interventional neuroradiologist (Dr Kartik Bhatia) for the presence or absence of large vessel occlusion (LVO). LVO cases will then be independently assessed by two paediatric neuroradiologist reviewers blinded to the clinical presentation or outcome of the patients – Dr R Goetti and Dr P Muthusami. The reviewers will record the presence/absence of LVO on the imaging, the side of LVO, and the location of the primary (most proximal) occlusion (e.g. M1, M2 etc.). In the event of disagreement between the two assessors, resolution will be via analysis by the co-ordinating principal investigator (Dr Kartik Bhatia).

Other imaging data to be acquired includes the following:

- Infarct location(s) (cerebral cortex, deep white matter, basal ganglia, thalamus, brainstem, cerebellum) and side (left, right, midline, bilateral) – preferably based on diffusion weighted imaging on MRI. Where MRI is not available, delayed non-contrast CT imaging can be utilized (performed more than 48 hours after symptom onset).
- Infarct volume (using $a \times b \times c/2$ estimation) derived from diffusion weighted imaging, or where unavailable based on delayed non-contrast CT imaging
- Presence or absence of underlying chronic stenosis or dissection within the vessel of interest.
- Timing of each imaging study relative to the onset of stroke symptoms/recognition.
- If image-guided intervention (i.e. mechanical thrombectomy) has been performed, the duration of the procedure, timing of arterial access relative to onset time and diagnosis time respectively, number of passes, technique used (direct aspiration, stent-retriever, balloon-guide, combination), and final angiographic outcome using the modified Thrombolysis in Cerebral Ischaemia (mTICI) score.
- For patients with a LVO, assessment for whether the imaging fulfills the selection criteria for either the MR-CLEAN¹ (if presenting < 6 hours after onset) or DAWN² (6-24 hours after onset) studies that form the basis for existing adult criteria for mechanical thrombectomy.
- For posterior circulation LVO, assessment for whether the imaging fulfills American Heart Association guidelines³ for mechanical thrombectomy (Class IIb recommendation).

8.6. Clinical data analysis

The following clinical data points will be obtained from the eMR/Powerchart for each acute stroke admission:

- Sex
- Age in months if < 36 months and in years if >3 years of age at time of stroke onset
- Time of symptom onset if witnessed or last seen well
- Time of arrival to paediatric hospital

- Time diagnostic imaging completed
- If IV thrombolysis was administered, the time and dosage of tPA given
- Baseline paediatric NIHSS (National Institute of Health Stroke Scale) score at presentation if available
- Paediatric NIHSS score at 24 hours after presentation and at any other available timepoints after that, if available
- Paediatric mRS at 3 months, and if available at 12 months in order to classify the long-term neurological outcome as good (none or mild disability: pediatric mRS 0-2) or poor (moderate to severe disability or death: mRS 3-6). Measurement within 4 weeks of the 3-month point may be included.
- Final mRS available and timing of that assessment.
- Final aetiology of the stroke as determined by the treating neurology team (cardio-embolic, iatrogenic, dissection, focal cerebral arteriopathy, vasculitis, Moya-Moya disease, paradoxical embolus, hypercoagulable state, stroke mimic such as migraine or post-ictal paralysis, idiopathic).
- Anticoagulation and/or anti-thrombotic treatment administered and timing of onset of such treatment relative to stroke onset (as well as duration of treatment).

8.7. Pooling of de-identified data

For this retrospective cohort of 2010-2019, the de-identified data from all four centres will be pooled (as described above using the three existing databases and the retrospective search of SCHN) but will still be identifiable by hospital using the study ID coding system described above.

8.8. Statistical analysis

Descriptive statistics will be utilized to analyse the results of each major variable. Comparative assessment of long-term neurological outcomes between patients with and without LVO will be undertaken using ordinal regression analysis to determine the odds ratio (α -value of 0.05) assessing for a worse functional outcome on the ped-mRS comparing three groups: non-LVO, LVO untreated by thrombolysis or thrombectomy, and LVO treated by thrombectomy or thrombolysis.

A secondary outcome assessment of clinical outcome would be by dichotomizing outcomes into good and poor (as described above in outcome measures) and then using a chi-squared test with an α -value of 0.05 for the primary outcome.

8.9. Reporting of results

The results of the retrospective data will be reported in two ways:

- i) Publication in a peer-reviewed journal using de-identified data
- ii) Creation of a report outlining the annual number of paediatric patients with LVO stroke in NSW, and the number that would potentially fulfill existing adult criteria for mechanical thrombectomy, to assist with future workforce and resource planning.

9. DATA/PRIVACY MANAGEMENT PLAN

For each patient identified across the four sites, a unique study ID number will be created for the purposes of de-identification and privacy protection. The ID number would contain a capital letter to indicate the hospital (W = Westmead, S = SCH Randwick, J = John Hunter, R = RPA Hospital) followed by the number in chronological order based on the first relevant imaging (1, 2, 3, ...). Within each patient, each separate admission for stroke would be indicated by a lower-case letter (a, b, c, ...) to account for patients who have suffered multiple stroke episodes. An example: For the third child treated at John Hunter Hospital within the 2010-2019 cohort, undergoing their first admission for a stroke episode, the study ID would be J3a.

For each patient, the first and last name, date of birth, and hospital MRN (i.e. the identifiable data) would be kept in a password protected Master Log excel spreadsheet, with a separate Master Log at each site. These identifiable data would NOT be shared across sites and *would remain within the research network drives of the relevant hospitals*. The purpose of maintaining the Master Log would be to identify clinical/imaging data from the eMR and RIS/PACS at the time of data acquisition and to

link the study ID with the identifiable data for data integrity purposes, but only de-identified data would be shared across sites for the purposes of the study. The Master Log at each site would be kept in a separate folder and with a different password to the de-identified Data Sheet excel spreadsheet used for data collection and analysis.

Identifiable data will not be removed from the research network drives of any of the four centres.

Upon completion of all data analyses, all data will be maintained in their existing password-protected status on the research network drives for 15 years (for ethics and data assurance purposes) before being deleted as per standard data and privacy management protocols.

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