Living clinical guidelines for stroke: updates, challenges and opportunities

The Australian and New Zealand living stroke management guidelines provide timely, evidence-based updates to recommendations

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Continued growth in the number of published clinical studies has necessitated changes to the way evidence-based resources such as clinical guidelines are developed and updated. The Australian and New Zealand Clinical Guidelines for Stroke Management (https://informme.org.au/guidelines/clinical-guidelines-for-stroke-management) are based on continual evidence surveillance and timely updates to recommendations as new research is published. In this article, we outline the main updates to recommendations since the guidelines moved into a living mode in 2018, and discuss key challenges and benefits of living guidelines.

Background

Stroke is a leading cause of adult disability in Australia, with an estimated 27 428 incident strokes occurring each year, or one every 19 minutes.[1] Compared with urban areas, the incidence of stroke is 17% higher in rural communities, where access to specialist stroke care is less likely.[1] This makes the need for easily accessible, up-to-date, evidenced-based clinical practice guidelines for stroke care essential.

The first Australian clinical guidelines for stroke were published in 2003 (acute) and 2005 (post-acute). These were updated in 2007, 2010 and most recently in 2017 following traditional methods, including endorsement by the National Health and Medical Research Council (NHMRC). In 2017, the guidelines moved from being published in a static (pdf) format, to being published online using the Making GRADE the Irresistible Choice (MAGICapp) platform (https://magicevidence.org).[2]

Traditional cycles of guideline updates which involve recommendations based on the best available evidence at the time of publication are problematic because new evidence can mean that recommendations quickly become outdated. In 2018, the Stroke Foundation and Cochrane Australia were awarded funding to test a model of living guidelines for stroke management. These were the first Australian living clinical guidelines and are the first and only living stroke guidelines worldwide. Subsequent living guidelines include those for diabetes,[3] maternal and perinatal health,[4] and COVID-19.[5] The stroke guidelines are published online at https://informme.org.au/guidelines/clinical-guidelines-for-stroke-management, to guide day-to-day stroke care in Australia and New Zealand.

Development

The 2017 update of the static stroke guidelines consisted of 392 individual recommendations including practice points across eight chapters addressing 89 topics. Each topic was structured into a PICO (patient, intervention, comparator, outcome) format to address an aspect of care, for example, the use of cholesterol-lowering therapy for secondary prevention of stroke. The living stroke guidelines project commenced in July 2018. The structures in place for the 2017 static guidelines update were adapted and expanded to fit living guidelines methods. A full description of the methods is published elsewhere.[6]

In brief, each month the results of published new studies are reviewed by the project team. Where new evidence is deemed to potentially impact one or more recommendations, the project team works with clinical experts to update evidence-to-decision frameworks (benefits and harms and certainty of evidence component) using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) method (https://gdt.gradepro.org/app/handbook/handbook.html), and draft changes to recommendations and background text. Draft changes go through a rigorous review process, culminating in submission to the NHMRC for approval (median time from initiation to submission is about 6 months). Clinical indicators collected as part of the National Stroke Audit and the Australian Stroke Clinical Registry are monitored over time to evaluate adherence to aspects of the guidelines.

The living clinical guidelines for stroke are developed in accordance with NHMRC standards, including the use of the GRADE method for recommendations. The MAGICapp platform presents the recommendations and related information in a multilayered, transparent format. MAGICapp allows users to review all previous versions of each recommendation for full transparency. Any new or updated recommendations are flagged as such within the platform for a period of 6–12 months. A summary of updates is also maintained online (https://informme.org.au/guidelines/living-guidelines-updates).

Recommendations

Since the 2017 update to the static guideline, a total of 35 new or updated recommendations have been made. Just under half (16) of the changes are new recommendations (five strong, 10 weak, and one practice point), with updates to 19 recommendations (12 without change to the direction or grade of recommendation, six upgraded strength, and one downgraded strength [from weak recommendation for to weak recommendation against]). New and updated strong recommendations are presented in the Box. All new and updated recommendations are reported in

the Supporting Information and are described in brief below.

Acute medical and surgical management

The first living guideline recommendation, developed after the 2017 update but before the start of the funded living guidelines project, extended the time window for endovascular clot retrieval to 24 hours for specific clinical presentations.[11] Additionally, based on results from new studies,[12-14] the recommended time window for safe administration of alteplase has been extended to 9 hours post-stroke and a new recommendation made about safe use of alteplase for stroke of unknown onset time. Both recommendations are based on favourable perfusion imaging. Two new recommendations have been made for the use of tenecteplase as an alternative to alteplase within 4.5 hours of stroke onset[15] or for large vessel occlusions.[16] Ticagrelor in combination with aspirin commenced within 24 hours of symptom onset and continued for the first 30 days may now be used for acute antiplatelet therapy for people with minor ischaemic stroke or transient ischaemic attack,[17] although this should be considered secondary to a strong recommendation for aspirin plus clopidogrel for the first 21 days. The recommendation for oxygen therapy has been updated to include a specific threshold (92% blood oxygen saturation on room air), above which routine use of supplemental oxygen therapy is not recommended.[18] There is a new recommendation for the use of telestroke services to assist in patient assessment and decision making for the use of thrombolysis and/or endovascular clot retrieval for people presenting to hospitals where medical specialist services are not available.[19,20] Finally, there is a new recommendation that clarifies that patients not receiving nasogastric feeding do not require head elevation and may be managed in any position.[21]

Secondary prevention

Several recommendations have been updated regarding secondary prevention. The first specifies a target of < 1.8 mmol/L for low density lipoprotein levels for people with ischaemic stroke.[22] The recommendation for management of patent foramen ovale now specifies that where this is considered the likely cause of stroke, percutaneous closure should occur.[23] People who were taking antiplatelet therapy before experiencing an intracerebral haemorrhage may be safely recommenced, although the optimal timing for this is not clear.[24] Left atrial appendage occlusion may be considered for the management of atrial fibrillation if there is a genuine contraindication to anticoagulation.[25] Non-pharmacological interventions to reduce stroke risk factors include exercise training as well as individual support and counselling, and the final new recommendation suggests that people with stroke should follow a Mediterranean style diet.[26]

Rehabilitation

The most significant updated recommendation pertains to the use of selective serotonin reuptake inhibitors (SSRIs) to reduce disability after stroke. New large trials[27,28] found SSRIs did not reduce disability and were associated with a small risk of harm, and therefore are no longer recommended for routine use in this context but may still be relevant specifically to prevent or treat depression. The recommendations for management of motor weakness and difficulty standing have been updated. These updates include greater specificity in the types of training modalities that are recommended. Finally, new recommendations for specific interventions to improve memory function, and for the use of telehealth as an alternative mode of rehabilitation service delivery[29] have been made.

Managing complications

Due to an increase in the number of published high quality, albeit small trials, it is now recommended that acupuncture may be considered for the management of shoulder pain after stroke.[30] Minor changes have also been made in preventing or managing swelling in the arms or legs.

Discussion

Major updates to the guidelines over the past four years have occurred, ensuring the recommendations are current. Importantly, there have been no cases in which a recommendation for an intervention has been downgraded from a strong to a weak recommendation. Furthermore, no recommendation has been changed multiple times. Important new recommendations have been made regarding lifesaving therapy such as extension of the time window for endovascular clot retrieval and the administration of alteplase for thrombolysis.

The key benefit of living guidelines is the ability to rapidly update recommendations in response to new evidence. As a case example, results from the EXTEND trial demonstrating the safety and efficacy of thrombolysis up to 9 hours after stroke were published in May 2019,[12] followed soon after by a systematic review and individual patient data meta-analysis.[13] By November 2019, our updated recommendation had completed the full development, review and public consultation process and was endorsed by the NHMRC and disseminated to key end-user organisations; a total time of less than six months.

While it is hard to estimate the direct and definitive impact of rapid guideline updates, based on trial outcomes and reported patient numbers, we estimate that about 320 Australians each year may be saved from premature death or disability following a severe stroke based on the updated recommendations for endovascular clot retrieval from 6–24 hours after symptom onset (unpublished data). Rapid guideline updates as part of a living model are almost certain to have played a significant role by expediting local and state-wide system changes. Further work to quantify the impact, including the potential economic impact and return-on-investment, of the living guidelines compared with traditional guideline updates is planned. Since 2007, we have had national, standardised systems of monitoring adherence to the clinical guideline recommendations

Summary of new and updated strong recommendations

	Specific recommendations	New or updated	Summary of change
Acute medical and surgical management			
Thrombolysis	For patients with potentially disabling ischaemic stroke who meet perfusion mismatch criteria in addition to standard clinical criteria, intravenous alteplase (0.9 mg/kg, maximum 90 mg) should be administered up to 9 hours after the time the patient was last known to be well, or from the midpoint of sleep for patients who wake with stroke symptoms, unless immediate endovascular thrombectomy is planned	New	Extends the time window recommended for thrombolysis treatment up to 9 hours after time of stroke where imaging findings suggest benefit
	For patients with potentially disabling ischaemic stroke due to large vessel occlusion who meet specific eligibility criteria, intravenous tenecteplase (0.25 mg/kg, maximum 25 mg) or alteplase (0.9 mg/kg, maximum of 90 mg) should be administered up to 4.5 hours after the time the patient was last known to be well	New	Addition of a new recommended antithrombotic agent (tenecteplase)
Neurointervention	For patients with ischaemic stroke caused by a large vessel occlusion in the internal carotid artery, proximal middle cerebral artery (M1 segment), or with tandem occlusion of both the cervical carotid and intracranial large arteries, endovascular thrombectomy should be undertaken when the procedure can be commenced between 6 and 24 hours after they were last known to be well if clinical and computed tomography perfusion or magnetic resonance imaging features indicate the presence of salvageable brain tissue	New	Extends the time window for endovascular clot retrieval to 24 hours, in specific circumstances
Acute antithrombotic therapy	Aspirin plus clopidogrel should be commenced within 24 hours and used in the short term (first 3 weeks) in patients with minor ischaemic stroke or high risk transient ischaemic attack to prevent stroke recurrence	Updated	New evidence of benefit of dual antiplatelet therapy to prevent secondary stroke[7]
Acute telehealth services	In hospitals without onsite 24/7 stroke medical specialist availability, telestroke systems should be used to assist in patient assessment and decision making regarding acute thrombolytic therapy and possible transfer for endovascular therapy. This system should include the ability for stroke medical specialists to access remote brain imaging scans and preferably include the use of videoconferencing facilities or, if not possible, ensure that the diagnosis and management discussions between local clinicians, families and patients occur via a telephone consultation	New	This recommendation aims to ensure all Australians have access to best practice acute therapies after stroke, regardless of where they live
Secondary prevention			
Cholesterol lowering therapy	In patients with ischaemic stroke, cholesterol lowering therapy should target low density lipoprotein cholesterol < 1.8 mmol/L for secondary prevention of atherosclerotic cardiovascular disease	New	New trial evidence shows that more intensive lowering of low density lipoprotein levels reduces recurrent cardiovascular events[8]
Patent foramen ovale management	In patients with ischaemic stroke aged < 60 years in whom a patent foramen ovale is considered the likely cause of stroke after thorough exclusion of other aetiologies, percutaneous closure of the patent foramen ovale is recommended	Updated	Two new trials, long term follow-up of a previous trial and a new meta-analysis have confirmed the benefits of patent foramen ovale closure where it is considered the likely cause of stroke[9]
Rehabilitation			
Weakness	For stroke survivors with reduced strength in their arms or legs, progressive resistance training should be provided to improve strength	Updated	Based on a new systematic review, there is now sufficient evidence to specify the type of strength training that is most efficacious[10]

in Australia. Specifically, these systems include the National Stroke Audit (detailed cross-sectional audits of acute care and inpatient rehabilitation every alternate year) and the Australian Stroke Clinical Registry, whereby adherence to the national acute care standards is continuously monitored, including patient outcomes 90–180 days after stroke. These data permit reliable assessment of practice change and health outcomes over time to inform economic and other impact assessments. However, preliminary findings of the independent evaluation indicate that end users of the living stroke management guidelines report have increased trust in and likelihood of accessing and following the guidelines compared with the traditional, periodically updated guideline model (Wiles L, Zurynski Y, Hibbert P, et al. Living stroke guidelines evaluation. Australian Institute of Health Innovation, 2021. Unpublished report).

Importantly, living guidelines provide currency of advice. The experience with stroke as well as other guidelines[3-5] demonstrates that the rigour of the methods does not need to be compromised when living modes are adopted. The GRADE method is as appropriate for living guidelines as for traditional, periodic guidelines. NHMRC support is also vital in ensuring living guidelines continue to meet its standards.

Sustainability remains the key challenge for the living stroke guidelines. Collaboration with major stroke guideline groups in Europe and North America may improve guideline efficiency and sustainability, but although discussions have been undertaken, no formal projects have been forthcoming as only a few groups currently use the GRADE method. However, there has been strong collaboration and sharing of knowledge and experience with other national guideline groups as part of the Australian Living Evidence Consortium (https://livingevidence.org.au/). Compared with the costs of updating the stroke guidelines every five years, our initial experience indicates the living model is likely to have similar overall costs, but with the significant benefits of increased trust and use from clinicians. Ongoing, secure funding for this new model is now required for stroke along with similar guidelines for other high burden diseases.

The Australian and New Zealand living guidelines for stroke management are the first of their kind globally. A number of important changes have occurred in the guideline recommendations. Our model of continual evidence surveillance and timely updates to recommendations is feasible, but sustainability remains a challenge. Now that we have started down this road, the message from guideline end users is that a return to the old model of static updates is no longer acceptable, and ongoing long term investment in living guidelines must be prioritised.

It is important to note that due to the living nature of these guidelines, the information presented in this article is correct at the time of writing but may have been updated since.

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1 Deloitte Access Economics. No postcode untouched: stroke in Australia 2020. Stroke Foundation, 2020. http://maps.strokefoundation.com.au/wp-content/themes/dlstroke/downloads/No%20Postcode%20Untouched%202020%20Final%20report.pdf (viewed Jan 2022).

2 MAGIC Evidence Ecosystem Foundation. https://magicevidence.org (viewed Jan 2022).

3 White H, Tendal B, Elliott J, et al. Breathing life into Australian diabetes clinical guidelines. *Med J Aust* 2020; 212: 250-251. https://www.mja.com.au/journal/2020/212/6/breathing-life-australian-diabetes-clinical-guidelines

4 Vogel JP, Dowswell T, Lewin S, et al. Developing and applying a 'living guidelines' approach to WHO recommendations on maternal and perinatal health. *BMJ Glob Health* 2019; 4: e001683.

5 Tendal B, Vogel JP, McDonald S, et al. Weekly updates of national living evidence-based guidelines: methods for the Australian living guidelines for care of people with COVID-19. *J Clin Epidemiol* 2021; 131: 11-21.

6 Hill K, English C, Campbell BCV, et al. Feasibility of national living guideline methods: the Australian Stroke Guidelines. *J Clin Epidemiol* 2021; 142: 184-193.

7 Hao Q, Tampi M, O'Donnell M, et al. Clopidogrel plus aspirin versus aspirin alone for acute minor ischaemic stroke or high risk transient ischaemic attack: systematic review and meta-analysis. *BMJ* 2018; 363: k5108.

8 Amarenco P, Kim JS, Labreuche J, et al. A comparison of two LDL cholesterol targets after ischemic stroke. *N Engl J Med* 2020; 382: 9-19.

9 Turc G, Calvet D, Guérin P, et al. closure, anticoagulation, or antiplatelet therapy for cryptogenic stroke with patent foramen ovale: systematic review of randomized trials, sequential meta-analysis, and new insights from the CLOSE study. *J Am Heart Assoc* 2018; 7: e008356.

10 Dorsch S, Ada L, Alloggia D. Progressive resistance training increases strength after stroke but this may not carry over to activity: a systematic review. *J Physiother* 2018; 64: 84-90.

11 Albers GW, Marks MP, Kemp S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med* 2018; 378: 708-718.

12 Ma H, Campbell BCV, Parsons MW, et al. Thrombolysis guided by perfusion imaging up to 9 hours after onset of stroke. *N Engl J Med* 2019; 380: 1795-1803.

13 Campbell BCV, Ma H, Ringleb PA, et al. Extending thrombolysis to 4·5-9 h and wake-up stroke using perfusion imaging: a systematic

review and meta-analysis of individual patient data. *Lancet* 2019; 394: 139-147.

14 Thomalla G, Simonsen CZ, Boutitie F, et al. MRI-Guided thrombolysis for stroke with unknown time of onset. *N Engl J Med* 2018; 379: 611-662.

15 Huang X, MacIsaac R, Thompson JL, et al. Tenecteplase versus alteplase in stroke thrombolysis: an individual patient data meta-analysis of randomized controlled trials. *Int J Stroke* 2016; 11: 534-543.

16 Campbell BCV, Mitchell PJ, Churilov L, et al. Tenecteplase versus alteplase before thrombectomy for ischemic stroke. *N Engl J Med* 2018; 378: 1573-1582.

17 Johnston SC, Amarenco P, Denison H, et al. Ticagrelor and aspirin or aspirin alone in acute ischemic stroke or TIA. *N Engl J Med* 2020; 383: 207-217.

18 Chu DK, Kim LH-Y, Young PJ, et al. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. *Lancet* 2018; 391: 1693-1705.

19 Lazarus G, Permana AP, Nugroho SW, et al. Telestroke strategies to enhance acute stroke management in rural settings: a systematic review and meta-analysis. *Brain Behav* 2020; 10: e01787.

20 Bladin CF, Kim J, Bagot KL, et al. Improving acute stroke care in regional hospitals: clinical evaluation of the Victorian Stroke Telemedicine program. *Med J Aust* 2020; 212: 371-377. https://www.mja.com.au/journal/2020/212/8/improving-acute-stroke-care-regional-hospitals-clinical-evaluation-victorian

21 Anderson CS, Arima H, Lavados P, et al. Cluster-randomized, crossover trial of head positioning in acute stroke. *N Engl J Med* 2017; 376: 2437-2447.

22 Amarenco P, Kim JS, Labreuche J, et al. A comparison of two LDL cholesterol targets after ischemic stroke. *N Engl J Med* 2020; 382: 9.

23 Turc G, Calvet D, Guérin P, et al. Closure, anticoagulation, or antiplatelet therapy for cryptogenic stroke with patent foramen ovale: systematic review of randomized trials, sequential meta-analysis, and new insights from the CLOSE study. *J Am Heart Assoc* 2018; 7: e008356.

24 RESTART Collaboration. Effects of antiplatelet therapy after stroke due to intracerebral haemorrhage (RESTART): a randomised, open-label trial. *Lancet* 2019; 393: 2613-2623.

25 Osmancik P, Herman D, Neuzil P, et al. Left atrial appendage closure versus direct oral anticoagulants in high-risk patients with atrial fibrillation. *J Am Coll Cardiol* 2020; 75: 3122-3135.

26 English C, MacDonald-Wicks L, Patterson A, et al. The role of diet in secondary stroke prevention. *Lancet Neurol* 2021; 20: 150-160.

27 AFFINITY Trial Collaboration. Safety and efficacy of fluoxetine on functional outcome after acute stroke (AFFINITY): a randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2020; 19: 651-660.

28 EFFECTS Trial Collaboration. Safety and efficacy of fluoxetine on functional recovery after acute stroke (EFFECTS): a randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2020; 19: 661-669.

29 Laver KE, Adey-Wakeling Z, Crotty M, et al. Telerehabilitation services for stroke. *Cochrane Database Syst Rev* 2020; (1): CD010255.

30 Liu S, Zhang CS, Cai Y, et al. Acupuncture for post-stroke shoulder-hand syndrome: a systematic review and meta-analysis. *Front Neurol* 2019; 10: 433. ■

Supporting Information

Additional Supporting Information is included with the online version of this article.