

Response to the consultation on MSAC Application 1825 'Transcranial Doppler bubble test for patent foramen ovale'



1. What is the organisation's experience with the proposed health service or technology, or with the related health condition?

Stroke Foundation is a national charity that partners with the community to prevent stroke, save lives and enhance recovery. We do this through raising awareness, empowering health professionals to deliver high quality, best-practice care to stroke patients, facilitating research, and supporting survivors of stroke. We advocate for better systems, processes and resources to help health professionals deliver world class stroke care.

A stroke is a sudden interruption of blood flow to the brain, which can lead to damage to brain tissue, severe disabilities or loss of life. There are two main types of stroke: ischaemic (caused by a blockage in a blood vessel supplying the brain) and haemorrhagic (caused by vessel rupture and bleeding into the brain).

There are an estimated 45,785 stroke events in Australia annually and more than 440,000 survivors of stroke are living in our community.¹ The lifetime costs associated with strokes that occurred in Australia in 2023 exceed \$15 billion (\$350,000 per person), including healthcare, lost productivity and unpaid carer costs.¹ Research shows that without a concerted effort to improve stroke awareness and prevention, the number of annual stroke events in Australia is expected to reach 72,000 by 2050.¹

Cryptogenic stroke occurs when no cause is identified despite a thorough diagnostic work-up. It accounts for between 15 and 40 percent of ischaemic strokes,^{2,3} which are the most common type of stroke and account for approximately 80 percent of all strokes.⁴ Four in 10 people who have had a stroke will have another stroke within 10 years,² and recurrent stroke is more likely to be fatal or cause major disability.³ Without a clear cause, effective secondary stroke prevention can be difficult.

Stroke prevention remains the most effective means of reducing the impact of stroke in Australia, and Stroke Foundation is committed to reducing the number of preventable strokes in this country.

Between 25 and 50 percent of cryptogenic strokes can be attributed to patent foramen ovale (PFO), with young and middle-aged people (less than 60 years of age) disproportionately represented.⁵ The current diagnostic pathway relies on transthoracic echocardiogram (TTE) with bubble test, which has low sensitivity for PFO. As a result, many patients with PFO-associated stroke experience delayed diagnosis and may wait up to a year before receiving targeted treatment. During this time, some patients may have another stroke. In comparable high-income countries, transcranial doppler (TCD) bubble test is the standard of care because it has high sensitivity for PFO diagnosis. Therefore, Stroke Foundation supports the creation of a new MBS item number for the TCD bubble test, to improve access to this superior diagnostic investigation in Australia.

1. Kim J et al. on behalf of the Stroke Foundation. 2024. Economic Impact of Stroke Report 2024. Melbourne, Australia.
2. Leys D et al. Clinical outcome in 287 consecutive young adults (15 to 45 years) with ischemic stroke. *Neurology*. 2002. 59:26-33.
3. Kolominsky-Rabas PL et al. Epidemiology of ischemic stroke subtypes according to TOAST criteria: incidence, recurrence, and long-term survival in ischemic stroke subtypes: a population-based study. *Stroke*. 2001. 32:2735-2740.
4. Boehme AK, Esenwa C, Elkind MS. Stroke Risk Factors, Genetics, and Prevention. *Circ Res*. 2017. 120:472-495.

5. Chambers BR et al. Diagnosis and Management of Patent Foramen Ovale for Stroke Prevention: An Australian and New Zealand Consensus Statement Developed by a Modified Nominal Group Approach. *Med J Aust.* 2026. 224:e70199.
6. Hardie K et al. Ten-year risk of first recurrent stroke and disability after first-ever stroke in the Perth Community Stroke Study. *Stroke.* 2004. 35:731-735.
7. Rothwell PM. 2007. Making the most of secondary prevention. *Stroke.* 2007. 38:1726.

2. How does the health condition that the proposed health service or technology relates to affect individuals, families, and carers?

People with cryptogenic ischaemic stroke, and their families and carers, face significant stress and uncertainty because the cause of the stroke is unknown. This can make it harder to identify the right secondary prevention treatment and may lead to long-term, invasive heart rhythm monitoring.¹ Many survivors are also managing significant stroke-related disability and impacts to their psychosocial wellbeing.

Many people continue to experience health problems well after leaving hospital. Common post-stroke impacts include changes in strength, sensation, movement, coordination, speech and swallowing. These changes can affect a person's ability to walk, shower, use their hands and arms, communicate, and complete daily tasks. Stroke can also cause hidden disabilities, including fatigue and changes in cognition. Some survivors have difficulty with memory, learning, concentration, planning or sequencing tasks, which can affect activities such as getting dressed or driving.

Findings from a survey of Australians who have had a stroke, and their carers, reported that the most common health problems experienced by individuals several years after their stroke included fatigue (78%), and mobility (76%), emotional (68%), memory (68%) and concentration (67%) problems.² Of those who were working prior to their stroke, almost three quarters (71%) reported a change in their work activities since their stroke and 57 percent reported that the change was moderate to extreme.² Specifically, individuals lose an average of 3.8 full time weeks of work each year due to stroke.³ More than one third (36%) of respondents reported a loss in income since having their stroke and almost half (48%) were receiving some form of benefit.² The majority (57%) of people who had a partner or spouse reported that their stroke had a negative impact on their relationship and 34 percent reported that this change was moderate to extreme.²

The survey results also provided evidence there was a significant impact experienced by carers of people with stroke.⁴ Carers may accompany people with stroke to medical appointments, and care for them at home, playing a critical role in their recovery. In Australia, costs related to informal care over a lifetime for people who had a stroke in 2023 were almost \$4 billion.⁵

Of those caregivers who were working prior to taking on a carer role, 40 percent reported a moderate to extreme reduction in the amount of work they were able to perform.⁴ Almost half (47%) of the carers who participated in leisure activities prior to taking on a carer role reported a moderate to severe reduction in the number or type of leisure activities in which they were able to participate. Almost a third (31%) of carers who were the partner or spouse of a person with stroke reported moderate to extreme changes in their relationship.⁴ A significant proportion of carers reported moderate to extreme changes in their relationships with other family members (20%), and with other people outside the family such as friends (32%).⁴ As a consequence of these pressures, carers of people with stroke commonly experience a decline in their own physical and mental health and a reduced quality of life.⁶⁻⁸

Importantly, the impact of stroke on areas such as work and finances can be even more devastating for individuals with cryptogenic stroke, the majority of whom are working age.⁹

1. Yaghi S, Elkind MS. Cryptogenic stroke: A diagnostic challenge. *Neurol Clin Pract.* 2014. 4:386-393.

2. Monash University Stroke and Ageing Research Centre (STARC). 2013. Australian Stroke Survivor and Carer Needs Assessment Survey.
3. Deloitte Access Economics. 2020. The economic impact of stroke in Australia, 2020.
4. Andrew NE et al. The relationship between caregiver impacts and the unmet needs of survivors of stroke. *Patient Prefer Adherence*. 2015. 9:1065-1073.
5. Kim J et al. on behalf of the Stroke Foundation. 2024. Economic Impact of Stroke Report 2024. Melbourne, Australia.
6. Han B, Haley WE. Family caregiving for patients with stroke. *Stroke*. 1999. 30:1478–1485.
7. Salter K et al. Impact of caring for individuals with stroke on perceived physical health of informal caregivers. *Disabil Rehabil*. 2010. 32:273–281.
8. Rigby H, Gubitz G, Phillips S. A systematic review of caregiver burden following stroke. *Int J Stroke*. 2009. 4:285–292.
9. Putaala J et al. Searching for Explanations for Cryptogenic Stroke in the Young: Revealing the Triggers, Causes, and Outcome (SECRETO): Rationale and design. *Eur Stroke J*. 2017. 2:116-125.

3. How is the health condition that the proposed health service or technology relates to currently managed in Australia? That is, prevented, diagnosed, treated and/or monitored?

Currently, patients with ischaemic stroke undergo a variety of diagnostic investigations to determine the cause of their stroke. These investigations include brain imaging (CT and MRI), vascular imaging (ultrasound, CTA or MRA) to exclude extracranial and intracranial arterial stenosis, ECG monitoring to exclude atrial fibrillation, and blood tests to exclude vasculitis and thrombophilia. Following this diagnostic work-up, a patient with suspected embolic ischaemic stroke (where a blood clot or other debris forms elsewhere in the body, and then travels in the blood to lodge in a brain artery) with no identified cause, is eligible for a TTE with bubble test to determine if their stroke has been caused by a PFO.

The TTE with bubble test has low sensitivity for PFO (approximately 45%),^{1, 2} and is therefore a poor diagnostic test despite being non-invasive and widely available.³ Most patients who have a positive TTE with bubble test, and many who have a negative test, are then referred for transoesophageal echocardiography (TOE) for further investigation. TOE is more sensitive than the TTE with bubble test, but is invasive and requires sedation, which can reduce test sensitivity.³ TOE is also the gold standard for identifying high-risk PFO anatomical features, which are associated with recurrent stroke and may indicate benefit from PFO closure.⁴ Patients without high-risk PFO features can usually be treated medically with antiplatelet medications.

In Australia, timely diagnosis of PFO in the public hospital system can be challenging for patients with cryptogenic ischaemic stroke. Patients may wait up to two months for a TTE with bubble test. In some cases, TTE is performed without the bubble test, meaning the test must be repeated and reviewed at a later outpatient appointment. Many patients then require TOE and another outpatient review. This pathway can delay targeted treatment for up to a year. During this time, some patients may have another stroke. The delay and ongoing uncertainty can also cause significant stress and anxiety for patients, families and carers.

The comparator (TTE with bubble test) and the diagnostic pathway described in the PICO document are accurate and reflect how patients with cryptogenic ischaemic stroke who are suspected of having a PFO are currently managed in Australia.

1. Katsanos AH et al. Transcranial Doppler versus transthoracic echocardiography for the detection of patent foramen ovale in patients with cryptogenic cerebral ischemia: A systematic review and diagnostic test accuracy meta-analysis. *Ann Neurol*. 2016. 79:625-635.
2. Mojadidi MK et al. Accuracy of conventional transthoracic echocardiography for the diagnosis of intracardiac right-to-left shunt: a meta-analysis of prospective studies. *Echocardiogr*. 2014. 31:1036–1048.

3. Rubin MN et al. Robot-Assisted Transcranial Doppler Versus Transthoracic Echocardiography for Right to Left Shunt Detection. *Stroke*. 2023. 54:2842-2850.
4. Wang L, Sun H, Shen H. Anatomical Significance of the Patent Foramen Ovale by Real-Time 3D TEE in Cryptogenic Stroke and Migraine. *Echocardiogr*. 2024. 41:e70018.

4. Is the population(s) for the proposed health service or technology appropriate?

The TCD bubble test is performed in patients with cryptogenic ischaemic stroke, mostly under 60 years of age, who have previously undergone a specific diagnostic work-up (described in our response to Question 3). Consistent with the proposed eligibility criteria, this test may also be used in older patients (60 years and over) with no vascular risk factors, who have failed to demonstrate atrial fibrillation following prolonged ECG monitoring.

The proposed population and eligibility criteria described in the PICO document are appropriate and are consistent with the characteristics of participants in published studies relevant to this application.

5. Is the proposed approach to delivery of the health service or technology appropriate?

Following a specific diagnostic work-up (described in our response to Question 3), a patient with suspected embolic ischaemic stroke, with no identified cause, would generally be eligible for a TCD bubble test to determine if their stroke has been caused by a PFO.

The TCD bubble test is highly sensitive (96%) and specific (92%) for diagnosing PFO compared with the TTE with bubble test and TOE.¹ It is non-invasive, allows body positioning to improve sensitivity, and costs less than the TTE with bubble test and TOE.² Patients who have a positive TCD bubble test are referred for TOE to confirm PFO and assess anatomical features associated with high-risk PFOs. These features are linked with recurrent stroke and may indicate benefit from PFO closure.³ Patients without high-risk PFO features can usually be treated medically with antiplatelet medications. A positive TCD bubble test removes the need for the TTE with bubble test in most patients, while a negative test avoids the need for both TTE and TOE. This would free up TTE and TOE capacity for patients with other conditions, reduce wait times and deliver cost savings to the health system.

In the few public hospitals that currently offer the TCD bubble test, the test can be performed more quickly than the TTE with bubble test and TOE. Many patients can have the test while still in hospital, and those discharged after their stroke episode can usually access it relatively quickly. Earlier diagnosis helps patients receive targeted treatment sooner, reducing the risk of recurrent stroke, death and disability, and reducing health system costs.

Implementation will need to account for workforce, equipment and training requirements. The TCD bubble test is operator-dependent and limited by the availability of sonographers and other health professionals with appropriate expertise.⁴ The test must be performed using a dedicated, registered TCD ultrasound machine operated by an accredited vascular sonographer. A medical practitioner or certified health professional must also be present to consent the patient, cannulate the arm vein, draw blood, prepare and inject the agitated saline contrast, and instruct the patient to perform the Valsalva manoeuvre. The test is currently offered at three highly specialised tertiary stroke units in Australia: the Austin Hospital (Melbourne, VIC), Royal Adelaide Hospital (Adelaide, SA) and John Hunter Hospital (Newcastle, NSW). The Austin Hospital offers two-day training workshops each year for stroke units seeking to adopt the TCD bubble test. These factors will influence the rate of uptake and will need to be addressed in order to support equitable access across metropolitan, regional and rural services.

Another limitation is that approximately 10 percent of patients have temporal bone structures that are too thick to allow adequate transmission of ultrasound signals, preventing a clear TCD reading. For these patients, the alternative diagnostic pathway is a TTE with bubble test, which is less sensitive.

The TCD bubble test requires the patient to perform a forceful Valsalva manoeuvre to temporarily reverse pressure in the heart and force bubbles across the PFO. Patients who are uncooperative or physically (e.g. facial or respiratory muscle weakness) or cognitively impaired, may be unable to perform this manoeuvre, leading to false-negative results.

The intervention (TCD bubble test) described in the PICO document is accurate, and the proposed approach to its delivery, if supported, is appropriate.

1. Katsanos AH et al. Transcranial Doppler versus transthoracic echocardiography for the detection of patent foramen ovale in patients with cryptogenic cerebral ischemia: A systematic review and diagnostic test accuracy meta-analysis. *Ann Neurol*. 2016. 79:625-635.
2. Rubin MN et al. Robot-Assisted Transcranial Doppler Versus Transthoracic Echocardiography for Right to Left Shunt Detection. *Stroke*. 2023. 54:2842-2850.
3. Wang L, Sun H, Shen H. Anatomical Significance of the Patent Foramen Ovale by Real-Time 3D TEE in Cryptogenic Stroke and Migraine. *Echocardiogr*. 2024. 41:e70018.
4. Alexandrov AV et al; American Society of Neuroimaging Practice Guidelines Committee. Practice standards for transcranial Doppler (TCD) ultrasound. Part II. Clinical indications and expected outcomes. *J Neuroimaging*. 2012. 22:215-224.

6. What is the expected effect of the proposed health service or technology (if supported) on the lives of people with the health condition, their families, and carers?

Patient health benefits

The more widespread use of the TCD bubble test in Australian stroke units will result in:

- a more timely diagnosis of PFO-associated stroke
- patients with PFO-associated stroke receiving the targeted treatment they need in a more timely manner
- fewer PFO-associated recurrent strokes and associated death and disability
- reduced stress and anxiety for patients (and their families and carers) as a result of knowing the cause of their stroke.

Safety issues and adverse events

The TTE with bubble test and TCD bubble test have an excellent safety profile, with complication rates well below one percent.¹ For both tests, the main risks relate to injection of agitated saline contrast. If microbubbles cross a PFO and enter the cerebral circulation, they can cause temporary neurological symptoms. For example, in patients with severe migraines with aura, the injection may trigger a migraine attack. There is an extremely low theoretical risk of TIA or stroke, which is statistically negligible in a diagnostic setting. In addition, the agitation process requires brief exposure to air, carrying a theoretical, but extremely rare, risk of micro air emboli.

Health system resources and costs

The more widespread use of the TCD bubble test in Australian stroke units will result in:

- fewer referrals for the TTE with bubble test and TOE, freeing up these tests for patients with other conditions
- reduced wait times for the TTE with bubble test and TOE
- cost savings to the health system as a result of fewer TTE with bubble tests and TOEs (the cost of the TCD bubble test is less than both of these tests).

The potential outcomes described in the PICO document are appropriate. They could be strengthened by including safety issues and adverse events.

1. Tsivgoulis G et al. Safety of transcranial Doppler 'bubble study' for identification of right to left shunts: an international multicentre study. *J Neurol Neurosurg Psychiatry*. 2011. 82:1206-1208.

7. Are there disadvantages to the proposed health service or technology, if supported and implemented as proposed?

The main implementation challenges are relatively minor and are manageable with appropriate planning. They are summarised below and discussed in more detail in our response to Question 5:

- the need for specialised, dedicated ultrasound devices and highly trained sonographers to operate them
- anatomical limitations, with approximately 10 percent of patients having temporal bone structures that are too thick to allow adequate transmission of ultrasound signals, preventing a clear TCD reading and meaning the that test cannot be completed reliably
- challenges in executing the required Valsalva manoeuvre.

8. Does the organisation support public funding for the health service or technology, as it is proposed to be delivered?

Please choose the most appropriate answer and tell us your reasons for choosing it below.

- ☐ Do not support
- ☒ **Support**
- ☐ Unsure/Other

Stroke Foundation supports public funding for the TCD bubble test, which would improve access to a more sensitive, non-invasive diagnostic test for eligible patients with cryptogenic ischaemic stroke. It would support earlier identification of PFO-associated stroke, help patients receive appropriate secondary stroke prevention sooner, reduce uncertainty for patients and their families and carers, and improve use of health system resources.