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# Emerging risk factors for stroke

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**Emerging risk factors such as aortic arch atheroma, patent foramen ovale, thrombophilia and hyperhomocysteinaemia may contribute to the mechanisms or causes of cryptogenic stroke, which currently accounts for 40% of all ischaemic strokes.**

Stroke causes 9% of all deaths worldwide and is the second most common cause of death after ischaemic heart disease.[1] In Australia, about 40,000 to 48,000 stroke events occur each year and stroke is responsible for nearly 7% of all deaths.[2]

Increasing age, hypertension, diabetes mellitus, atrial fibrillation, hypercholesterolaemia, cigarette smoking, excessive use of alcohol and physical inactivity are well known risk factors for ischaemic stoke.[3] An increased understanding of the underlying mechanisms and risk factors for stroke is very important for primary and secondary stroke prevention, and will help to identify ways of reducing the incidence of stroke. Several emerging risk factors for stroke, including aortic arch atheroma, patent foramen ovale, thrombophilia and hyperhomocysteinaemia, are attracting the attention of researchers. These risk factors may contribute to the mechanisms or causes of cryptogenic stroke (stroke of an unknown cause), which currently accounts for about 40% of all ischaemic strokes.[4,5]

This article summarises the evidence for each of these risk factors for stroke and discusses recommendations for management.

## Aortic arch atheroma

Aortic arch atheroma is first seen during early adult life, and its incidence and severity increases with age. It is highly prevalent in the community and was identified in 51.3% of patients aged 45 years and older who participated in the SPARC study.[6] This study is the largest prospective population-based study published to date and was designed to identify risk factors for stroke and cardiovascular disease using transoesophageal echocardiography and carotid ultrasonography.[6]

Severe aortic arch atheroma, defined as atheromatous plaques thicker than 4 mm or with mobile components (Figure 1), has been established as an important risk factor and mechanism for stroke.

**IN SUMMARY**

- **Stroke causes 9% of all deaths worldwide and is the second most common cause of death after ischaemic heart disease. In Australia, about 40,000 to 48,000 stroke events occur each year and stroke is responsible for nearly 7% of all deaths.**
- **There are several emerging risk factors for stroke, including aortic arch atheroma, patent foramen ovale, thrombophilia and hyperhomocysteinaemia.**
- **Patent foramen ovale may be an important contributor to cryptogenic strokes, particularly in patients aged less than 55 years. There is also a strong relation between severe aortic arch atheroma and stroke.**
- **For several of these risk factors, there are still concerns about optimal treatments. Unravelling the relation between stroke and these emerging risk factors may be important for future stroke prevention initiatives.**

**continued**

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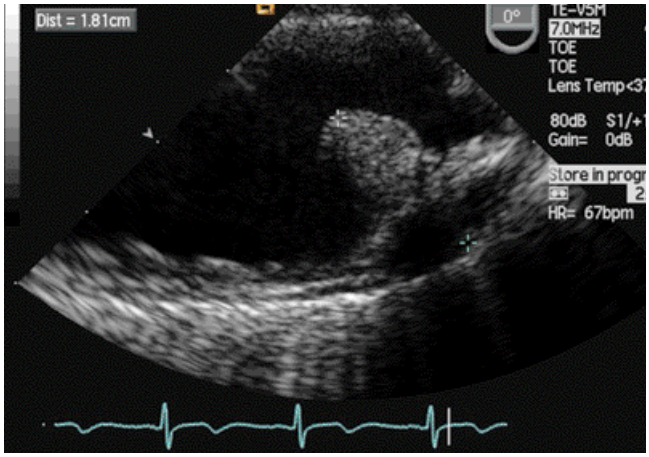


Figure 1. Transoesophageal echocardiogram showing a mobile atheroma of the aortic arch. The thickness of the atheroma was not measured because it was seen to be mobile.

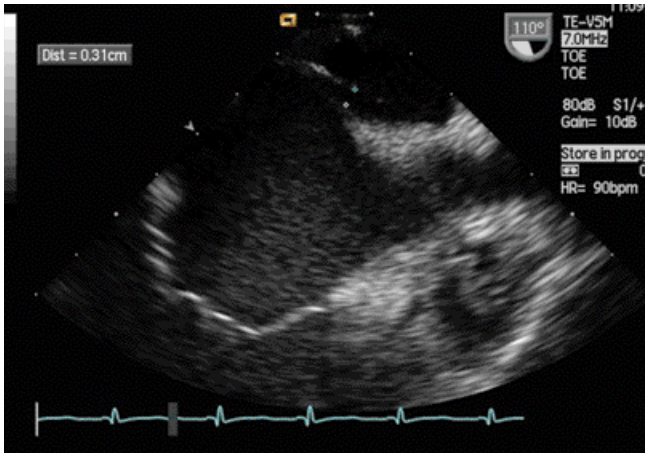


Figure 2. Transoesophageal echocardiogram of an interatrial septum showing a patent foramen ovale measuring 3.1 mm in dimension (using calipers).

Data from a meta-analysis provided evidence that the odds of stroke in patients with severe arch atheroma was 3.76 (95% confidence interval [CI], 2.58–5.48). A remarkable degree of homogeneity between studies was found ($\chi^2$=0.73; p=0.98), providing strong evidence of the important role of arch atheroma in the pathogenesis of stroke.[7] The results from the French Study of Aortic Plaques in Stroke Group indicated that severe atheroma was also an independent risk factor for the recurrence of stroke in a COX proportional hazards model (hazard ratio [HR], 3.5; 95% CI, 2.1–5.9).[4]

### Treatment

Given the high risk of stroke in people with aortic arch atheroma, experts have concerns that standard antiplatelet treatment may be insufficient and have, therefore, advocated the use of combination antiplatelet treatment (aspirin and clopidogrel) or warfarin. However, there is still no consensus on secondary prevention strategies in patients with arch atheroma who have experienced a stroke.

The MATCH trial is a randomised, double-blind, placebo-controlled trial comparing aspirin (75 mg/day) plus clopidogrel (75 mg/day) with clopidogrel alone in 7599 high-risk patients who have had a recent ischaemic stroke or transient ischaemic attack (TIA). The trial did not show any additional clinical value of adding aspirin to clopidogrel in these patients.[8] There is also evidence from another large randomised trial, CHARISMA, showing that the use of combination therapy with aspirin and clopidogrel was not significantly more effective than aspirin alone for secondary prevention in patients who have had a stroke. In this latter study, the risk of moderate to severe bleeding was increased.[9]

The ARCH trial, a large randomised controlled trial, is currently under way. This trial is testing whether aspirin plus clopidogrel combination therapy is superior to adjusted-dose warfarin in preventing recurrent vascular events in patients who have had a recent TIA or minor stroke or in those with peripheral embolism associated with severe aortic arch atheroma.[4] The findings from this trial should provide guidance as to whether antiplatelet or anticoagulation therapy is the preferred treatment for these patients.

### Recommendations

Recommendations for patients with aortic arch atheroma are listed below.

- Transoesophageal echocardiography is the preferred method for detecting aortic arch atheroma. It should be considered in patients who have had an ischaemic stroke in which no underlying cause is evident after other standard investigations (e.g. electrocardiography, carotid duplex ultrasound).
- Patients with aortic arch atheroma should be treated with standard antiplatelet therapy or considered for enrolment in a clinical trial.

## Patent foramen ovale

Patent foramen ovale, a common cardiac anomaly, is a flap-like opening of the atrial septum between the septum primum and secundum, which is caused by lack of closure and fusion of a foramen ovale (Figure 2).[5] Patent foramen ovale affects about 25% of the adult population.[10]

### Relation with stroke

An increased risk of first ever stroke has not been established in any prospective cohort stroke study in participants with or without a patent foramen ovale. Indeed, a patent foramen ovale was found not to be a risk factor for cerebral ischaemia in patients aged over 50 years

in a case-control study in Melbourne.[11] However, an increased prevalence of patients with a patent foramen ovale who have had a cryptogenic stroke has been found in multiple studies over the past few years, particularly in patients younger than 55 years of age.[12] Several factors have been reported to be associated with this increased risk of cryptogenic stroke in patients with a patent foramen ovale (Table 1).[13] However, there is still debate concerning the characteristics of a patent foramen ovale that determine the risk of stroke.

The mechanisms responsible for stroke in patients with a patent foramen ovale may be a paradoxical embolism in those with a right to left shunt (from a peripheral source – e.g. deep vein thrombosis), thrombus formation in relation to the lesion or associated hypercoagulability.[10]

## Diagnosis and treatment

Several diagnostic tests can be used to detect the presence of a patent foramen ovale. These include transthoracic echocardiography, transoesophageal echocardiography with contrast, and an indirect method using transcranial doppler to detect embolic signals in the middle cerebral artery.[10] Transoesophageal echocardiography is reported to have a 99% accuracy for detecting a patent foramen ovale and is accepted as the 'gold standard' method for diagnosing patients with this condition.[5]

In some studies, stroke recurrence rates have been shown to be higher in patients with a patent foramen ovale who have had cryptogenic stroke than in the general stroke population. Annual stroke recurrence rates in such patients have been reported to range from between 3.8% (for those with a patent foramen ovale alone) to 16% (for those with a patent foramen ovale and atrial septal aneurysm), indicating the need for appropriate secondary prevention.[10]

Optimal treatment for patients with a patent foramen ovale has not been defined, but options currently include medical treatment and interventions to close the atrial septal defect. The choice of any treatment option should be balanced with its associated potential hazards, including the risk of stroke.[10] Medical treatment includes antiplatelet agents (aspirin, clopidogrel) and anticoagulants (warfarin).[10] One large randomised controlled trial, PICSS, was designed to evaluate the efficacy of aspirin and warfarin in patients with a patent foramen ovale who have experienced a stroke. Among all patients with a patent foramen ovale, no significant difference in time to primary end points (recurrent ischaemic stroke or death from any cause) was observed between those treated with warfarin and those treated with aspirin ($p=0.15$; HR, 1.59; 95% CI, 0.85–2.97). However, a significantly higher risk of minor bleeding was demonstrated in patients treated with warfarin (HR, 2.64; $p<0.001$).[14]

Interventional treatment options for patients with a patent foramen ovale include open surgical patent foramen ovale closure and the less invasive percutaneous patent foramen ovale closure. The authors of one study reported a lower one-year recurrence rate (5%) for embolic events after percutaneous patent foramen ovale closure than after open surgical closure (7%).[15] Percutaneous patent foramen ovale closure has now largely replaced surgical closure; however, its risks and benefits still need to be evaluated for each patient.

To our knowledge, no results from randomised controlled trials comparing transcatheter patent foramen ovale closure and medical therapy have yet been reported. However, two major randomised controlled trials are currently underway.[16] Findings from the RESPECT trial (760 patients) and CLOSURE 1 trial (900 patients) will provide some guidance for future treatment of these patients.

As a relation between an initial stroke and the presence of a patent foramen ovale has not been established at this stage, there is no justification for patients to undergo patent foramen ovale closure for primary stroke prevention. It is suggested that it is not necessary to close a patent foramen ovale unless the patient has a contraindication to, or has a recurrent event while taking, medical therapy.[14]

The current expert recommendation is that standard antiplatelet therapy should be used in a patient who has had an initial stroke and has a patent foramen ovale without associated atrial septal aneurysm. Percutaneous patent foramen ovale closure should be considered in patients with a patent foramen ovale with spontaneous right to left shunt and associated atrial septal aneurysm because there is an increased risk of cryptogenic stroke in these patients.[17]

**Table 1. Factors possibly associated with risk of cryptogenic stroke in patients with a patent foramen ovale[13]**

- Age less than 55 years
- Large patent foramen ovale (>2 mm)
- Large right to left shunt magnitude
- Right to left shunt at rest
- Coexisting atrial septal aneurysm
- Pelvic deep venous thrombosis
- Factor V Leiden mutation
- Prothrombin gene G20210A mutation

## Recommendations

The following points are recommendations for diagnosing and treating patients with a patent foramen ovale.

- Transoesophageal echocardiography is the 'gold-standard' test to detect a patent foramen ovale and should be ordered by specialists when necessary.
- Individualised treatment includes:
  - aspirin in patients with a patent foramen ovale and who have had an initial cryptogenic stroke

## Stroke studies mentioned in this article

**ARCH trial**
Aortic Arch Related Cerebral Hazard trial

**CHARISMA trial**
Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance trial

**CLOSURE 1 trial**
Evaluation of the STARflex Septal Closure System in Patients with a Stroke or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a PFO trial
www.closurei.com/patient/citrial.html

**HOPE-2 trial**
Homocysteine Lowering with Folic Acid and B Vitamins in Vascular Disease trial

**MATCH trial**
Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent Transient Ischemic Attacks or Ischemic Stroke trial

**PICSS**
Patent Foramen Ovale in Cryptogenic Stroke Study

**RESPECT trial**
Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment trial
www.amplatzer.com/us/Respect/index.html

**SPARC study**
Stroke Prevention: Assessment of Risk in a Community study

**VISP trial**
Vitamin Intervention for Stroke Prevention trial

**VITATOPS trial**
Vitamins to Prevent Stroke trial
vitatops.highway1.com.au/index.htm

## Table 2. Investigating patients for inherited thrombophilia (FURY)

Patients with thrombophilia will need to be referred to a specialist for further investigation for inherited thrombophilia if they:

- have a family history of thrombosis (F), or
- have a thrombus in an unusual location (U), or
- have recurrent episodes of thrombosis (R), or
- are young (less than 40 years of age) (Y)

  - warfarin therapy in patients with a patent foramen ovale who have had an initial cryptogenic stroke and in whom there is a strong suspicion of paradoxical embolism, such as deep vein thrombosis or pulmonary embolus. Warfarin should also be considered in patients with a patent foramen ovale and thrombophilia and who have had a cryptogenic stroke with recurrent stroke events.
- Percutaneous patent foramen ovale closure is not currently recommended as first-line management in patients with a patent foramen ovale and who have had an initial stroke.
- Percutaneous patent foramen ovale closure should be considered in patients with a patent foramen ovale who have recurrent stroke and in whom medical treatment has failed or is contraindicated.

## Thrombophilia

Thrombophilia is defined as an enhanced tendency to form intravascular thrombi, which may be arterial or venous. Hypercoagulation is a term often used as an alternative for thrombophilia.[18]

## Table 3. Acquired hypercoagulable disorders associated with stroke

- Antiphospholipid antibody syndrome
- Heparin-induced thrombocytopenia
- Thrombotic thrombocytopenic pupura
- Hyperhomocysteinaemia

### Relation with stroke

Inherited thrombophilia is caused by mutations of genes that are involved in the generation and regulation of procoagulants or anticoagulants. Among these conditions, the factor V Leiden and prothrombin gene G20210A mutations have been shown to be associated with stroke. However, these associations are only significant in children and adults less than 40 years of age.[18] Patients with thrombophilia will need further investigation for inherited thrombophilia by a specialist if they have certain risk factors (Table 2).[18]

Of the acquired thrombophilias, the presence of antiphospholipid and heparin antibodies and elevated levels of homocysteine are commonly associated with stroke.[19] Antiphospholipid antibodies have been demonstrated to be an independent risk factor for ischaemic stroke, imparting a relative risk of between 3 to 5. Antiphospholipid antibodies promote thrombosis via unclear mechanisms, which may relate to platelet activation, impaired fibrinolysis, endothelial cell damage or impaired function of proteins involved in the regulation of coagulation.[20] Table 3 lists some of the known acquired hypercoagulable disorders associated with stroke.

Antiphospholipid antibody syndrome (APAS) describes the required association between antiphospholipid antibodies and a syndrome of hypercoagulability. Patients with APAS have recurrent venous and/or atrial thromboses that can affect nearly every organ system, and may result in recurrent TIAs and strokes.[20]

### Recommendations

Aspirin may provide protection from thrombosis in women with the APAS and previous pregnancy loss. Warfarin should be used as secondary prevention following a thrombotic event.

## Hyperhomocysteinaemia

Hyperhomocysteinaemia, defined as fasting plasma homocysteine levels exceeding the 90th or 95th centile limits of a normal population (normal range, 5 to 15 μmol/L in a fasting state), is an independent modifiable risk factor for cardiovascular events.[21] For every 5 μmol/L increment in homocysteine levels, the risk of stroke or TIA is increased by about 1.5 times (95% CI, 1.3–1.9).[22] A high level of homocysteine causes oxidative stress, damages the endothelium and enhances thrombogenicity, which might be the mechanisms for increased risk of stroke.

### Treatment

Homocysteine is derived from the metabolism of methionine. The metabolism of dietary methionine requires at least two principal enzymes and three vitamins (folate, vitamin $B_{12}$ and vitamin $B_6$). Inadequate amounts of any of these nutrients may lead to elevated concentrations of homocysteine, which can be lowered with folic acid and vitamin $B_{12}$ supplementation. A meta-analysis of 12 clinical trials including 1114 individuals with renal failure showed that 0.5 to 5 mg daily of folic acid lowered homocysteine levels by 25% (95% CI, 23–28%) and 0.02 to 1 mg daily of vitamin $B_{12}$ further reduced homocysteine levels by about 7% (95% CI, 3–10%).[23] Although vitamin $B_6$ supplementation (2 to 50 mg daily) did not show any additional effect, it may be effective when combined with folic acid.

Since hyperhomocysteinaemia is an independent modifiable risk factor for stroke, homocysteine-lowering therapy may have a beneficial effect in stroke prevention. However, the use of such therapy in stroke prevention remains contentious.[21]

In the VISP trial, 3680 patients with a history of nondisabling stroke were treated with homocysteine-lowering therapy (folic acid, vitamin $B_{12}$ and vitamin $B_6$). No significant effects were found on vascular outcomes during the two years of follow up.[24]

Investigators of the HOPE-2 trial randomly assigned 5522 patients to either combined daily administration of 2.5 mg folic acid, 50 mg vitamin $B_6$ and 1 mg vitamin $B_{12}$ or to matching placebo for five years. This study demonstrated no beneficial effects of homocysteine-lowering therapy on major vascular events, and there was also no evidence to support the use of folic acid and vitamin B supplementation as preventive treatment.[25]

A meta-analysis of randomised controlled trials designed to assess the effects of folic acid supplementation on cardiovascular events showed a benefit of vitamin therapy on the risk of stroke. Although not significant, the relative risk of stroke in patients taking vitamin therapy was 0.86 (95% CI, 0.71–1.04) compared with a relative risk of myocardial infarction in those taking vitamin therapy of 1.04 (95% CI, 0.92–1.17). This supports the possibility that stroke might be more closely related than myocardial infarction to homocysteine levels.[26] More recently, a detailed assessment of the results of the HOPE-2 trial has been undertaken, showing a significant reduction in the incidence of stroke in patients taking vitamin therapy (relative risk, 0.75; 95% CI, 0.59–0.97; p=0.03). This suggests that therapy to lower homocysteine levels may have the potential to prevent stroke as stroke and other vascular events could respond differently to vitamin therapy.[24]

The results of the VITATOPS trial, a large multicentre international clinical trial of secondary stroke prevention with folic acid, vitamin $B_6$ and vitamin $B_{12}$, may help to clarify the question of whether vitamin therapy to lower total homocysteine levels reduces the risk of stroke.

## Recommendations

The American Heart Association guidelines for stroke prevention suggest a good dietary intake of foods that are rich in folic acid, vitamin $B_6$ and vitamin $B_{12}$ for primary stroke prevention, as well as supplemental multivitamins for individuals with hyperhomocysteinaemia who have had a prior stroke.

## Conclusion

At present, there is variable evidence that the emerging risk factors presented in this article may be causally associated with an increased incidence of stroke. Patent foramen ovale may be an important contributor to cryptogenic strokes, particularly in patients aged less than 55 years. There is also a strong relation between severe aortic arch atheroma and stroke. For several of these risk factors, there are still concerns about optimal treatments. Unravelling the relation between stroke and these emerging risk factors may be important for future stroke prevention initiatives. MT

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