Lifelong Learning

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# Transient Neurological Troubles in Patients with Type 2 Diabetes

**Transient neurological attacks, early warning signs of cerebrovascular disease, are usually differentiated by their history. As type 2 diabetes is an important risk factor for a transient ischaemic attack (TIA) and subsequent stroke, this article focuses on the acute, usually urgent management of this focal transient neurological problem and its prevention.**

Transient neurological attacks are warning signs that patients may have cerebrovascular disease. Although coronary heart disease is the most common cause of morbidity, disability and mortality in people with type 2 diabetes, transient ischaemic attacks (TIAs) and strokes are frequent cerebrovascular complications in such patients, particularly as they age. Type 2 diabetes is an important risk factor for TIA and/or stroke, especially in patients who have other components of the type 2 syndrome (hypertension, dyslipidaemia, prothrombosis).

Many of these patients have a great fear of having a stroke and see it as something that may strike them down without warning. They think that they cannot prevent it and worry about full functional recovery, fearing being left with a crippling disability, or dying. They may have good reason to fear a stroke more than a heart attack: 20% of those with a stroke die within a month and one-third of the survivors are disabled permanently.[1,2]

Measures can, however, be taken to reduce the frequency of TIAs and stroke, and to prevent a stroke closely following a TIA (about one in five people have a stroke within 90 days of a TIA).[3] It is also possible to intervene effectively in a developing stroke and to maximise functional recovery after a stroke.

This article focuses on the early warning sign of a stroke, the TIA, and provides practical guidance on the prompt recognition of this focal transient neurological attack and the interventions to reduce the likelihood of having a stroke within 90 days of a TIA.[3]

**About the author**

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## The case

*Bill is 68 years old and has had type 2 diabetes and dyslipidaemia for six years and hypertension for more than 15 years. All these conditions have been moderately controlled in the past few years (glycosylated haemoglobin [A1c], 7.5% to 8.5%; blood pressure, 140 to 150/90 to 95mmHg; LDL-cholesterol, 3 to 4mmol/L). Earlier today he found he could not move his left leg and his left arm became clumsy. Strength gradually returned and now, four hours later, is almost normal. Bill is reassured by your examination and says as he leaves: 'Well, at least it wasn't a stroke'.*

## Diagnosis

Potential causes of Bill's transient neurological symptoms are:

- TIA
- Residual weakness after a seizure
- Complicated migraine
- Hypoglycaemia.

The history, however, strongly suggests that Bill has had a TIA. The onset is unlike the acute onset for a seizure (and there is no stated history of seizures). A migraine can cause a transient neurological attack but would usually be associated with a headache, an aura and a previous history of migraine. Hypoglycaemia can be associated with focal neurological symptoms but usually occurs acutely and is associated with hunger and the classic sympathetic symptoms of tremor, sweating, tachycardia and anxiety.

Severe hypoglycaemia is not common in patients with type 2 diabetes but there is a series of 'red flags' that can alert patients with diabetes who are at high risk of hypoglycaemia. These factors are significant since intervention can reduce the frequency and depth of severe hypoglycaemia. They are:[4]

- History of hypoglycaemic episode
- Hypoglycaemic unawareness (autonomic neuropathy)
- Type 1 diabetes, long-standing type 2 diabetes
- Erratic lifestyle
- Bolus insulin/tight glycaemic targets
- Sleeping alone.

As it happens, Bill has none of these 'red flags'. Anyway, the clinical setting and history are consistent with a TIA: Bill has several of the major risk factors for cerebrovascular disease (ie, age over 60, hypertension, dyslipidaemia and diabetes) and the focal nature, acute onset and gradual offset of his symptoms are typical of a TIA (see the box on next page).[5]

## Risk factors for cerebrovascular disease*

- Age 60 years and older
- Hypertension
- Smoking
- Dyslipidaemia
- Known cardiovascular disease†
- Atrial fibrillation†
- Diabetes

* In order of the approximate contribution to the incidence in the general population.

† An ECG, which is part of the recommended cycle of diabetes care, would identify undiagnosed coronary heart disease and/or atrial fibrillation.

## The ABCD2 guide to stroke following a TIA[6]

The ABCD2 score, a seven-point scale that assesses five clinical measures, can be used to predict the risk of a patient having a stroke within two days of having a TIA.

| Symbol | Feature | Criterion | Points |
|---|---|---|---|
| A | Age | 60 years or older | 1 |
| B | Blood pressure | 140/90mmHg or greater | 1 |
| C | Clinical picture of the TIA | Unilateral weakness | 2 |
| | | Speech impairment only | 1 |
| D | Duration | 60 minutes or longer | 2 |
| | | 10 to 59 minutes | 1 |
| D | Diabetes | Diagnosed with diabetes | 1 |

Sum ABCD2 score predicts risk of having a subsequent stroke within two days:

- score 0 to 3 = 1.0% (low risk)
- score 4 and above = 8% (high risk)

## TIAs and subsequent stroke

Bill is right to be pleased that he has had a TIA and not a stroke but might not be so happy if he realised that he is at high risk of having a stroke later and that approximately half of these strokes occur within the first 48 hours after the TIA. It is critically important to identify those at high risk of having a stroke, to investigate and to intervene promptly to prevent these early strokes.

The ABCD2 score is a validated model to predict the early risk of stroke after a TIA (see the box on this page).[6] In this scoring system, a cut point of 4 separates high risk (score of 4 and above, 8% two-day stroke risk) from low risk (score of 1 to 3, 1% two-day stroke risk).

Bill has all the indicators. With the maximum possible score of 7 points, he is in a very high risk category – at least 8% in the next 48 hours and a further 8% in the subsequent three months.

## TIA: Causes and investigations

It is important to identify the cause of a TIA because that will define further investigation and intervention. In general, there are five main causes (see the box on page 16).

Carotid artery dissection is unlikely in Bill's case; however, if he were younger than 50 it would be a possibility, particularly if associated with neck pain. Bill has a relatively high exercise tolerance and is unlikely to have the severe cardiac dysfunction associated with ventricular thrombus and embolism (eg, ejection fraction less than 50%). Atrial fibrillation (paroxysmal or continuous) is a real possibility because he is very likely to have ischaemic heart disease given his age, type 2 diabetes, hypertension and dyslipidaemia.[7]

Similarly, he is likely to have significant atherosclerotic arterial disease – aortic arch, carotid and intracerebral – and may have had an arterial embolus. Finally, he is also at risk of an intracerebral haemorrhage, given his age, type 2 diabetes and hypertension.

Initial investigation should be targeted to identify the likely cause and potential interventions (see the flowchart on page 16).[8] The emphasis is on triaging those at high risk of an early stroke and identifying the appropriate intervention(s). Given the practical difficulties of arranging the recommended urgent investigations in the community setting, perhaps the safest option is to have the assessing clinician discuss the management of TIA patients with a stroke physician who can help triage the patient and facilitate access to prompt, appropriate investigation.[9] An ECG may identify ischaemic heart disease and atrial fibrillation (if persistent). Computed tomography imaging (CT) of the brain will show an intracerebral haemorrhage and a CT angiogram will identify carotid and intracerebral vascular pathology, but neither will show signs of early cerebral infarction. MRI or magnetic resonance angiography give better anatomical definition. A positive diffusion-weighted MRI is equivalent to a troponin spike in differentiating the cerebral 'angina' of a TIA from the cerebral infarction of a stroke. A carotid ultra-sound will identify any carotid plaque and stenosis and guide surgical intervention, if appropriate.

## TIA: Management

Acute management (thrombolysis, surgical and medical therapy) is on specialist advice but ongoing prevention occurs in the community.

### Reducing the risk of future cerebrovascular events

Having a healthy lifestyle (addressing the SNAP risk factors – smoking, nutrition, alcohol, physical activity) and keeping vascular risk factors under control reduce an individual's overall vascular risk (see the box on this page).

Recent clinical trials have assessed the pros and cons of the various antiplatelet agents currently available.[10-13] Aspirin is the 'gold standard' antiplatelet agent and has the advantage of being cheap. Both clopidogrel and the combination of aspirin and dipyridamole have marginally better therapeutic efficacy than aspirin (extra absolute risk reduction 0.5% and 1%, respectively), but they are considerably more expensive and are more commonly associated with side effects.

## Causes of TIA

- Arterial embolus (aortic arch, carotid, intracerebral)
- Atrial fibrillation (ischaemic heart disease)
- Cardiac embolus (ejection fraction less than 50%)
- Carotid artery dissection (in patients younger than 50)
- Intracranial haemorrhage

Although the combination of aspirin and clopidogrel is recommended after coronary stenting, the combination is no more effective than aspirin alone after a TIA and is associated with increased haemorrhagic risk (as well as extra cost and side effects).[14,15] One practical approach is to start with aspirin plus dipyridamole and, if side-effects from dipyridamole occur, to continue with aspirin alone or switch to clopidogrel.

Patients who are prescribed antiplatelet agents should be advised of likely side effects and told that they should not stop the agent if the side effects occur but should seek immediate medical review so an alternative agent can be used. They should also be advised not to take any other medication without seeking advice from a doctor or pharmacist, in case the new medication, prescription or nonprescription (eg, fish oils, gingko biloba), increases haemorrhagic risk. [14]

'Resistance' to therapy with aspirin and other antiplatelet agents (when a stroke occurs despite therapy) may occur. However, it is important to remember that, when an antiplatelet agent is used to 'prevent' a stroke after a TIA, only some events will be prevented and most events will still occur despite appropriate and effective antiplatelet therapy (see the table on page 17). Such an event may prompt a switch to a more effective agent (from aspirin alone to aspirin plus dipyridamole or to clopidogrel), but even this more effective schedule can only prevent a further small number of events (1% and 0.5%, respectively).

### Establishing an action plan for future cardiovascular events

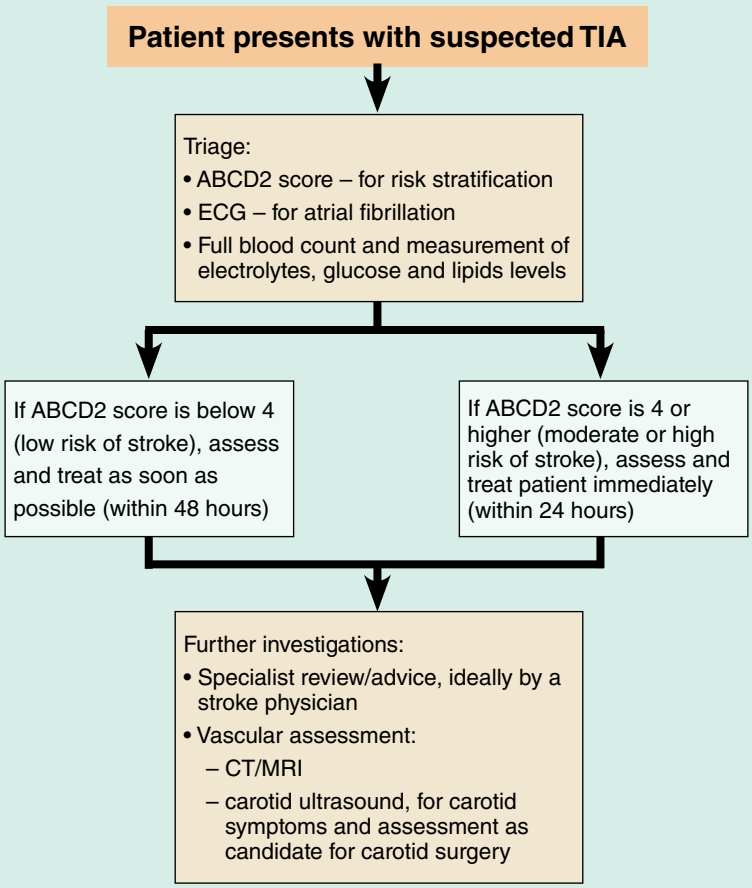
As noted, prompt recognition, assessment, investigation and intervention for a TIA can significantly reduce the risk of a future stroke in both the short (48 hours) and long term. The community and medical professionals have accepted the importance of heart attacks and the need to respond urgently to symptoms such as chest pain. Furthermore, it is widely recognised that modern heart attack treatments save lives and prevent further disability; most people go home functioning well after a short hospital stay. People at risk of a heart attack are therefore usually aware that they should seek help immediately if they have certain symptoms.

On the other hand, the idea of a 'brain attack' does not seem to have quite the same impact as the idea of a 'heart attack'. Therefore, an important part of the management of a TIA is to explain that the symptoms of a TIA may go away but the underlying problems remain, that preventive therapy is important and that any future warning symptoms should prompt urgent presentation for assessment and treatment.

### Implications for other circulations

Most TIAs and subsequent strokes are caused by cerebrovascular disease and most cerebrovascular disease is associated with vascular disease in the other circulations: ophthalmic, coronary, aortic (including renal) and peripheral. After acute management and establishing measures to deal with future risk of cerebrovascular events, it is appropriate to review and monitor these circulations by history (eg, previous angina,

**Transient ischaemic attack: triage and investigation[8]**




ABBREVIATIONS: CT = computed tomography; ECG = electrocardiogram; MRI = magnetic resonance imaging

## Recommendations for vascular health in patients with diabetes

### SNAP lifestyle

All people will benefit from targeting the behavioural risk factors affecting health.

Lifestyle recommendations for improving cardiovascular health are to follow a SNAP lifestyle:

**S** quit Smoking

**N** better Nutrition – low fat (saturated and trans fats) and often lower total energy

**A** moderate Alcohol consumption – maximum of two standard drinks/day

**P** more Physical activity – at least 30 minutes of moderate activity daily.

### ABCS control

People with diabetes also need to target specific clinical risk factors, specifically glycaemia and the ABCS of diabetes care:

**A** glycosylated haemoglobin (A1c) – ideal is below 7.0%

**B** Blood pressure – ideal is below 140/90 mmHg in general, and below 130/80 mmHg for individuals at high risk

**C** Cholesterol – ideal is a total cholesterol level of below 4mmol/L

**S** Salicylates – the taking of cardioprotective doses of aspirin (80 to 150mg) daily should be considered for people with diabetes who have a high cardiovascular risk.

TABLE

## Antiplatelet agents

| Agent | Side effects* | Notes |
|---|---|---|
| Aspirin | Allergy | RRR, 22%; ARR, 2%; NNT, 5010 |
| Clopidogrel | Diarrhoea, rash | Superior to aspirin alone (by 0.5%; NNT, 200)[11] |
| Dipyridamole | Headache and/or nausea in 20% | Plus aspirin superior to aspirin alone (by 1.0%; NNT, 10012 Equivalent to clopidogrel)[13] |

ABBREVIATIONS: NNT = number needed to treat; RRR = relative risk reduction.

* All antiplatelet agents increase the risk of haemorrhage.

claudication) and examination (ie, ophthalmoscopy, ECG, abdominal palpation and auscultation, and ankle brachial pressure index). Further investigations, including arterial imaging, and specialist advice may be indicated.

## Summary

- Although people with type 2 diabetes are less commonly affected by cerebrovascular disease than by coronary heart disease, type 2 diabetes is an important risk factor for TIA and/or stroke, especially in those who have other components of the type 2 syndrome (hypertension, dyslipidaemia, prothrombosis). Moreover, these patients often fear a stroke more than a heart attack.
- Usually, the history identifies the cause of a transient neurological trouble. The association with other risk factors for cerebrovascular disease, and its acute onset and gradual offset, differentiate a TIA from a seizure, migraine or hypoglycaemic episode.
- Acute management is guided by the ABCD2 score (age, blood pressure, neurological clinical features, symptom duration and diabetes). Higher scores (4 and over) prompt urgent investigation and neurological review (within 24 hours). Lower scores prompt semi-urgent investigation and review within 48 hours. Investigations include biochemistry, lipids, ECG, brain CT or MRI and carotid artery imaging.
- Initial treatment (thrombolysis, surgical and medical therapy) is on specialist advice but on-going prevention occurs in the community. Prevention focuses on reducing the risk of cardiovascular disease in general by tackling lifestyle and medical cardiovascular risk factors, and reducing the risk of future cerebrovascular events in particular (antiplatelet therapy).
- Aspirin is a very commonly prescribed antiplatelet agent with a 2% absolute risk reduction but both clopidogrel and the combination of aspirin and dipyridamole are more effective, with further absolute risk reduction of 0.5% and 1.0% respectively. The combination of aspirin and clopidogrel is no more effective than aspirin alone and increases haemorrhagic risk.
- An important part of the management of a TIA patient is to stress that it is an early warning of a stroke, that lifestyle and medical management can reduce this risk and that patients, family or caregivers should be aware of the symptoms and signs of a TIA or stroke so that intervention can start as soon as possible.

*References are available on request.*

## 'Resistance' to antiplatelet agents

An ABCD2 score of 4 and above after a TIA suggests there is an 8% or greater risk of the patient having a stroke in the next 48 hours and a 16% or greater risk of stroke in the next 12 months. If aspirin relatively reduces stroke risk by 22%, (see Table), this will be an absolute reduction of three events per 100 in the first year (22% of 16 events); the other 13 will still occur.

Switching to clopidogrel or aspirin plus dipyridamole further reduces this absolute risk by 0.5% and 1%, respectively, to 3.5 or four events, respectively (see Table). The majority of stroke events will still occur despite the best antiplatelet therapy.