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THE MANAGEMENT OF STROKE

-  **Stroke is a leading cause of death and major disability worldwide**
-  **Thrombolytic therapy within 3 hours of symptom onset greatly reduces mortality and morbidity in ischaemic stroke**
-  **Up to 30% of patients presenting with a TIA may be at risk of developing a stroke within 30 days**
-  **Active management of modifiable risk factors is vital in the primary and secondary prevention of stroke**

INTRODUCTION

Stroke is one of the commonest causes of death and a major cause of disability worldwide.^{1,2} The World Health Organisation (WHO) has estimated that, each year, 15 million people suffer a stroke globally, of whom 5 million die and another 5 million are left permanently disabled.³ Between 2003 and 2007, Ireland had on average 44 deaths/100,000 population due to stroke each year.⁴

Stroke is uncommon in people <40 years of age; therefore, although the incidence of stroke has been declining in developed countries such as Ireland, the absolute numbers continue to rise due to the ageing population and reduced mortality.⁵ This represents a huge burden for the family and the state's healthcare system.

This bulletin will discuss the prevention and management of stroke.

CLASSIFICATION AND DIAGNOSIS OF STROKE

The WHO defines stroke as the sudden onset of focal neurological signs of presumed vascular origin, lasting longer than 24 hours or causing death.⁶ A stroke is either ischaemic or haemorrhagic. The clinical distinction between these subtypes is one of the most urgent aspects of acute stroke management. Classification scales, based on clinical presentation of neurological damage (such as the Oxfordshire Community Stroke Project (OCSP) classification) may be useful in determining the stroke subtype and also convey important prognostic information in terms of the presumed degree of damage;^{6,7} radiological imaging (via CT or MRI) usually gives the definitive diagnosis.²

Ischaemic Stroke: It is estimated that 80-90% of all strokes are ischaemic, caused by an interruption to the blood supply.^{6,8}

The underlying cause in most ischaemic strokes is cardio-embolic disease (atrial fibrillation, mural thrombus, valvular heart disease) or atherosclerotic arterial disease (which can cause either thrombosis in situ or distal embolism).⁶ Rarer causes include thrombocythaemia from elevated platelets, giant cell arteritis and infective endocarditis.⁸ Once vessel occlusion has occurred the infarct core contains tissue that is unsalvageable. However, this is surrounded by functionally impaired, but structurally intact tissue which can be salvaged (i.e. undergo neurological improvement and recovery) if thrombolytic therapy is initiated in time.²

Haemorrhagic Stroke: The commonest cause of a haemorrhagic stroke is small-vessel disease, leading to small aneurysms which bleed.^{2,9} About two-thirds of patients with primary haemorrhagic stroke have either pre-existing or newly diagnosed hypertension. The remaining patients may have an intracranial vascular malformation or aneurysm or a cerebral infarct into which secondary haemorrhage has occurred; rarer causes include cerebral amyloid angiopathy.^{2,9}

Transient Ischaemic Attack (TIA): A TIA typically displays symptoms and/or signs similar to those of an ischaemic stroke. However, it lasts less than 24 hours, and initially this was thought to result in no permanent neurological damage.^{2,6} Neuro-imaging techniques now suggest that some TIAs may be associated with permanent tissue damage. Moreover, **studies have shown that TIA sufferers have an increased risk of developing a stroke in the short-term.** A prospective study, which followed 1,707 patients presenting to the emergency department with a TIA noted that 428 patients (25%) suffered either a stroke (n=180) or other adverse event (including 216 recurrent TIAs and 45 deaths) during the 90-day post-TIA period; approximately 50% (n=91) of the strokes occurred in the first 2 days.¹¹ These findings have been repeated in other studies and several predictive features ("risk factors" including age, clinical features of the TIA and concomitant hypertension or diabetes mellitus) have been identified; in patients with these risk factors, the risk of stroke may be as high as 30% in the 30 days post-TIA.^{6,10,12}

Diagnosis: The commonest historical feature of a stroke is its **acute onset** and the commonest clinical presentations are **focal weakness** (hemiparesis, eye movement / visual field defect) and **speech disturbance**.¹³ **Differential diagnoses** include non-cerebrovascular events such as post-ictal seizure, migraine, dementia, hypoglycaemia and vasovagal syncope.¹³⁻¹⁵ Because of the short time window available for administration of thrombolytic therapy, it is recommended **that urgent transfer to hospital be arranged for all patients with ongoing symptoms suggestive of a cerebrovascular event.**⁶ Where symptoms have already resolved, hospital admission may not be required but the patient requires rapid assessment to determine if a TIA has occurred, to ensure appropriate management.⁶

RISK FACTORS FOR THE DEVELOPMENT OF STROKE

Risk factors for stroke can be broadly divided into modifiable and non-modifiable (fixed).

Modifiable Risk Factors: The major modifiable risk factors for stroke are listed in Table 1. It is important to note that these are also major risk factors for cardiovascular disease (CVD) in general.

Table 1: Major Modifiable Risk Factors for Stroke^{3,14,16}

Risk factor	Comment	Management Strategy
High blood pressure	Most important risk factor for stroke	Treat if $\geq 140/90$ mmHg*
Atrial Fibrillation	Overall 4-5% annual risk of stroke; 5-fold \uparrow risk with certain risk factors	Prescribe anti-thrombotics according to risk score
Abnormal blood lipids	Major risk factor for CVD** in general	Statin therapy \downarrow stroke risk
Tobacco	Risk may be double that of non-smokers	Smoking cessation causes rapid \downarrow in stroke risk
Diabetes Mellitus (DM)	Major risk factor for CVD	Treat early with secondary CVD preventive therapy
Physical inactivity	Increases risk by up to 50%	Studies have shown that a healthy lifestyle can \downarrow stroke risk by up to 55%
Obesity	Major risk factor for CVD + DM	
Unhealthy diet	Estimated by WHO to cause 11% strokes worldwide	

*treat if $>130/80$ mmHg in diabetic patients; **CVD = cardiovascular disease

Active management of modifiable risk factors is associated with an overall reduction in risk of stroke in the individual. **Hypertension** is the single most important and prevalent risk factor for stroke. The higher the blood pressure (BP), the greater is the risk of stroke.¹⁷ **Atrial fibrillation** is a common cardiac arrhythmia occurring in 1% of the general population.⁴ Its prevalence increases with age: estimated prevalence is 4-7% in those aged 65-74 years rising to 14-19% in those aged ≥ 85 years. It is a potent risk factor for stroke, increasing the risk up to 5-fold in certain patients. In addition, studies suggest that stroke due to atrial fibrillation is more severe and leads to greater mortality and disability compared to stroke without atrial fibrillation.⁴ Although there are conflicting results regarding a possible association between **total cholesterol** and risk of stroke, there is clear evidence of the beneficial effect of statins as a primary prevention in reducing stroke risk in susceptible individuals.^{16,18} **Other factors**, such as lifestyle choices (diet, weight, physical activity), low socioeconomic status, mental ill-health, psychosocial stress, heavy alcohol use are also associated with an increased risk of CVD and stroke and studies have suggested a possible role for homocysteine.^{3,17,19}

Non-modifiable (fixed) risk factors: **Age** is a powerful independent risk factor; it is reported that the risk of stroke doubles every decade after the age of 55 years.³ Heredity/family history is also important; the risk increases if a first-degree blood relative has had a stroke before the age of 55 years (for male relatives) or 65 years (for female relatives). **Certain ethnic groups** (Chinese, Japanese and Black populations, some Hispanic Americans) have increased rates of stroke compared with other world populations. However, the rates of stroke are similar for men and women.^{2,3}

MANAGEMENT OF STROKE

Management of stroke includes primary prevention, active management of the acute stroke phase, secondary prevention and rehabilitation.

PRIMARY PREVENTION

The recently published "Changing Cardiovascular Health: National Cardiovascular Health (NCVH) Policy 2010-2019" has recommended (1) the promotion of health awareness and a healthy lifestyle via population education campaigns, and (2) the proactive identification and treatment of high-risk subjects.⁴

Promotion of Health Awareness: It is reported that many Irish people are either **overweight** (36%) or obese (14%).²⁰ In addition, the national **salt intake** is 50% higher than recommended levels, **alcohol consumption** is $>40\%$ higher than the EU average, 29% of the population **smoke cigarettes** and there is an overall **low level of physical activity in the country**.^{4,20} It is estimated that around **60% of middle-aged and older adults in Ireland have at least 2 of the key risk factors for CVD and stroke**.²⁰ A positive physician-patient interaction is known to be a powerful tool to enable shared decision making and enhance adherence to medical advice, including lifestyle change.²¹ However, in the 2008 national audit of stroke care, 86% of GPs reported barriers to implementing primary prevention strategies for stroke in their practices, including staffing, time, funding and lack of screening and risk-factor management protocols.¹

The NCVH policy has recommended the development of media and education campaigns to promote risk awareness with the reinforcement of these messages in primary care settings.⁴

Management of high-risk subjects: Hypertension The risk of stroke increases with increasing BP; however, even those with moderately elevated BP may have one or more other risk factor (such as smoking, obesity, low physical activity level etc) which will increase their risk of stroke even further.⁴ Pharmacological management of BP levels $\geq 140/90$ mmHg is recommended, with regular review to ensure optimal pharmacological control and continued adherence to therapy.^{21,22} Pharmacotherapy may need to be instituted at a lower BP level in those with additional risk factors (e.g. $>130/80$ mmHg in diabetic patients). In addition, non-pharmacological management (e.g. lifestyle changes etc) is an important part of the overall management of hypertensive patients to ensure optimal reduction of stroke risk.⁴

Since **atrial fibrillation** increases with age, the potential stroke risk may be reduced by early detection and management (e.g. opportunistic case finding in patients aged ≥ 65 years). Once diagnosed, the risk of stroke can be dramatically reduced by use of anti-thrombotic therapy (ATT).²³ The European Cardiology Society (ESC) guidelines for the management of atrial fibrillation promote the use of a risk factor-based approach to evaluate stroke risk in individuals with atrial fibrillation.²³

Table 2 outlines the CHA₂DS₂-VASc scoring system which is based on the presence or absence of risk factors for stroke and thrombo-embolism with non-valvular atrial fibrillation.

Table 2: CHA₂DS₂-VASc scoring system

Risk factor	Score*
Congestive heart failure (left ventricular dysfunction)	1
Hypertension	1
Age ≥ 75 years	2
Age 65-74 years	1
Diabetes mellitus	1
Stroke / TIA / thrombo-embolism	2
Vascular (including prior MI, PAD, aortic plaque)	1
Female sex	1
Total possible score	9

*Score of 2 = major risk factor; score of 1 = clinically relevant non-major risk factor

The CHA₂DS₂-VASc scoring system has been evaluated against a cohort of 7,329 subjects with atrial fibrillation.²⁴ During a follow-up of 11,233 patient-years, results showed a stepwise increase in thromboembolism risk with increasing score. The score correctly identified 98% (n=181) of those who suffered an event as being at high risk, with a negative predictive value (i.e. the percentage categorised as “not high risk” being free from risk) of 99.5%.²⁴

The current ESC recommendations for choice of ATT for patients with atrial fibrillation, based on the CHA₂DS₂-VASc score are outlined in Table 3.

Table 3: Recommended anti-thrombotic therapy (ATT) in patients with atrial fibrillation²³

Risk category	CHA ₂ DS ₂ -VASc score	Recommended ATT
One major or ≥2 “clinically relevant” non-major risk factors	≥2	Oral anticoagulants (OAC) e.g. warfarin to intensity range of 2.0-3.5 INR
One “clinically relevant” non-major risk factor	1	Either OAC as above or aspirin 75-325mg/d [OAC is preferred to aspirin]
No risk factors	0	Either aspirin as above or no therapy [no ATT is preferred to aspirin]

The benefits of ATT, and warfarin in particular, must be balanced with the risk of bleeding in the individual patient. Studies have shown sub-optimal prescribing of warfarin in patients with known atrial fibrillation both prior to a stroke onset in those who have suffered a stroke and in community dwellers designated as high-risk atrial fibrillation patients.^{1,4,25,26} **Patient characteristics reported to be associated with a risk of bleeding with warfarin include: hypertension, abnormal renal / liver function, concomitant use of certain drugs or alcohol (especially misuse), age, history of labile INRs, stroke or bleeding.**²³ The fear of falls may be overstated; it has been estimated that a patient may need to fall about 300 times per year for the risk of intracranial haemorrhage to outweigh the benefit of OAC in stroke prevention. A simple score has been developed (**HAS-BLED**) to assist clinicians in deciding whether to use warfarin for an individual patient (guideline available at: <http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-afib-FT.pdf>). Newer OAC drug classes (e.g. direct thrombin inhibitors and factor Xa inhibitors) are currently undergoing development for stroke prevention in atrial fibrillation.^{23,27}

The NCVH strategy has recommended the development of formalised structures for the detection and management of BP and atrial fibrillation (including use of IT resource systems) at primary care level.⁴

Transient Ischaemic Attack: The risk of early stroke may be as high as 30% in TIA patients with certain risk factors.^{10,12} The ABCD² score of risk factors predictive of early stroke after TIA (see Table 4) is a tool that has been devised to help identify those at particular risk of early stroke, who may require urgent implementation of intensive stroke prevention measures to improve outcome.²⁸

Table 4: ABCD² score: Risk factors after TIA^{14,28}

Feature (risk factor)	Points
Age (≥60 years)	1
Blood Pressure (first assessment after TIA) • SBP ≥140mmHg; DBP ≥90mmHg	1
Clinical features of TIA • Unilateral weakness	2
• Speech impairment without weakness	1
Duration of TIA • ≥60 minutes	2
• 10-59 minutes	1
Diabetes (treated)	1

An ABCD² score of ≥4 points may justify admission to hospital and/or urgent evaluation, observation and appropriate treatment (anti-thrombotic, anti-hypertensive, lipid lowering therapies etc), within the first few days of the index event.² Studies undertaken in the Irish setting have shown that the ABCD² score can be useful in helping non-specialist physicians (who may be the first to assess the patient) to differentiate between transient cerebrovascular and non-cerebrovascular events.^{14,15} However, the score should not be used in isolation; the results of a recent study suggested that the ABCD² score may underestimate the risk associated with certain TIA symptoms (visual or sensory symptoms); therefore the overall individual clinical profile must be taken into account as well.¹⁵ Other tools such as the web-based **recurrence risk estimator** may also be useful (www.nmr.mgh.harvard.edu/RRE/)¹⁰

MANAGEMENT OF ACUTE STROKE

The earlier the patient with an acute stroke is evaluated for suitability for, and can receive thrombolytic therapy if appropriate, the lesser the degree of permanent damage around the infarct core with ischaemic stroke.² Current guidelines recommend that any patient with symptoms suggestive of a stroke should seek urgent attention.²⁹ The **FAST media campaign** (**F**ace **A**rm **S**peech **T**ime to act) has been effective in raising the public’s awareness that stroke is a medical emergency and anyone with symptoms suggestive of a stroke should contact the emergency ambulance service immediately.³⁰ A study undertaken in 2 Dublin teaching hospitals, during the first phase of the FAST campaign in 2010, showed an increase of 87% in stroke-related admissions during the 3-month study period; of importance, 59% more stroke patients were in time (3 hours from symptom onset) to receive thrombolytic therapy.³⁰

The great improvements noted in outcome of acute stroke are reported to be due to a number of factors: the (1) development of specialist stroke care units (SCUs), (2) administration of thrombolytic therapy, (3) use of aspirin and (4) availability of specialist decompressive surgery for massive cerebral oedema.^{2,6}

The **availability of a SCU (with a dedicated multidisciplinary team)** enables the early triage of patients with a suspected stroke and rapid access to CT or other imaging procedures to exclude haemorrhagic stroke or other clinical contraindications to use of thrombolytic therapy, integrated management of the acute stroke phase, and implementation of an individualised care plan for secondary prevention and rehabilitation (tertiary prevention).^{2,6} The 2010 NCVH policy has defined the establishment of stroke units as a key priority for the hospital reconfiguration programme within Ireland.⁴

Early **intravenous administration of thrombolytic therapy** (using a tissue plasminogen activator) has been shown to reduce morbidity compared with placebo; current data do not allow a definite conclusion regarding improvement in mortality.³¹⁻³³ However, it must be used within 3 hours of symptom onset.³³ Results are conflicting regarding the benefits of use after the 3-hour window, although some studies recommend an extension of the window to 4.5 hours (unlicensed use).^{2,4} Side effects include a 6-7% rate of intracranial haemorrhage,² therefore thrombolytic therapy should only be used under the direct supervision of a specialist trained physician (either stroke physician or neurologist).³³

A recent review has shown that **aspirin**, started within 48 hours of stroke symptom onset, reduces the risk of early recurrent ischaemic stroke, without a major risk of early haemorrhagic complications, and improves long-term outcome (up to 6 months’ follow-up).³⁴ Oral aspirin 300mg daily (or rectal / via an enteral feeding tube if the patient is dysphagic) should be administered

no sooner than 24 hours after thrombolytic therapy (as there is an increased risk of intracranial bleed in the infarct zone immediately after thrombolysis). For patients, not receiving thrombolysis, aspirin should be started as soon as possible within 48 hours of symptom onset. Treatment should be continued for 14 days, at which time long-term ATT treatment can be initiated. Alternative anti-platelet therapy should be considered for those allergic to, or genuinely intolerant of, aspirin.²⁹

Decompressive surgery to remove haematoma and relieve intracranial pressure has shown consistently improved outcome in small randomised clinical trials and case series, especially for stroke in selected sites (e.g. cerebellum) and/or in younger (<60 years old) patients.^{6,9}

Other aspects of acute management: Stroke patients may present with **hypertension**, which either pre-dates, or is a consequence of, the stroke. There is little evidence for acute lowering of BP following a stroke and indeed rapid lowering may result in reduced cerebral perfusion.^{32,35} Therefore treatment should only be instituted in the event of severe hypertension (>220/120mmHg; >180/100mmHg in proven intracerebral haemorrhage) or if the patient is being considered for thrombolytic therapy. **Failure of homeostatic mechanisms** during the acute stroke phase is common, therefore monitoring (and management, if required) of hydration, electrolytes and blood sugar may be necessary in those patients. In addition **active management of infections** is necessary as the acute phase of stroke carries a high risk of infection, and pyrexia has been associated with a poor outcome.^{6,9,35}

Anticoagulants are not recommended as an alternative to aspirin in acute management of stroke as review of the existing data has reported no short- or long-term benefit.³⁶ Parenteral anticoagulants should only be used if the stroke patient is symptomatic of, or at high risk of developing, venous thrombo-embolism.^{32,36}

SECONDARY PREVENTION

Patients surviving an initial stroke are known to be at significantly increased risk for further stroke(s) compared to the general population.³⁷ All known modifiable risk factors, including **weight control, smoking cessation and a healthy lifestyle and diet (including salt reduction)** must be proactively managed and appropriate pharmacotherapy prescribed.^{2,8} In addition to the well-known benefits of **optimal BP control**, studies have shown that **statin therapy**, initiated in the early months post-stroke (especially post-ischaemic stroke), significantly reduces the risk of recurrence; effects in addition to lipid lowering (such as anti-inflammatory effects) may be involved.^{38,39} **Anti-platelet therapy is recommended for patients in sinus rhythm post-ischaemic stroke.**^{8,16} Low-dose aspirin is reported to reduce the risk of recurrence by around 23% compared with an estimated reduced risk of >30% for aspirin plus long-acting dipyridamole; the combination is associated with an increased risk of intracranial bleeds and greater rates of discontinuation due to poor tolerability, compared with aspirin alone.⁴⁰ Clopidogrel, which has a similar benefit/risk profile to that of the aspirin / dipyridamole combination, generally is not the treatment of first choice in this patient group, unless the patient has concomitant coronary heart disease or is intolerant of aspirin.^{2,41,42} Studies have shown that **oral anticoagulants (OAC) are significantly more effective than antiplatelet therapy in reducing the risk of recurrent ischaemic stroke in patients with atrial fibrillation**; therefore these patients should be treated with OAC (see Tables 2 and 3).⁴³

Once the patient's management pathway has been implemented **regular follow-up is vital** to reinforce the need for lifestyle changes and to promote compliance with the agreed therapeutic regimen, all of which contribute to a maintained reduction in the risk of recurrent stroke. A UK study⁴⁴ showed that only one third of patients post-stroke were receiving all recommended secondary preventive therapies, while a 3-year follow-up, carried out in the south eastern region of Ireland showed that, of those who had survived a stroke, only 55% were still on ATT and 63% of those with hypertension were still on anti-hypertensive treatment.⁸

REHABILITATION

All stroke patients require multidisciplinary rehabilitation, tailored to their specific needs. The goals are to restore physical and mental well-being and maximise quality of life and potential for independent living.⁴ **Rehabilitation should start within 24 hours post-stroke, with a full needs assessment undertaken within the first 5 days, in order to design an individualised patient care plan.** It is now accepted that most recovery occurs within the first three months following stroke, with the fastest progress occurring in the first few weeks.⁴⁵ In addition, there is evidence to suggest that an unrehabilitated patient costs the health service more than a rehabilitated one over his/her lifetime.¹ However, the national audit on stroke (2008) reported that only 43% of stroke patients had been reviewed by a physiotherapist within 72 hours of the event, with only 22% being assessed by an occupational therapist within 7 days.¹ The NCVH policy recommends a shared / integrated care rehabilitation service, incorporating both primary care teams and multidisciplinary stroke services.⁴

MANAGEMENT STRATEGY FOR STROKE: SUMMARY

- Hypertension, the single most important risk factor for stroke, should be actively managed; patients should be monitored regularly to ensure optimal control and to promote compliance with therapy
- Early detection and management of atrial fibrillation as well as proactive management of modifiable risk factors such as smoking, diet (including salt intake), alcohol intake and exercise has also been shown to greatly reduce the risk of stroke
- Patients with ongoing symptoms suggestive of acute stroke should be advised to seek immediate hospital admission, in order to increase their chance of thrombolytic therapy if warranted
- In addition to thrombolytic therapy, patient outcome in the acute phase is improved by multidisciplinary management in a stroke care unit, use of aspirin (≥ 24 hours after thrombolysis) and early rehabilitation
- Stroke patients are at increased risk of further strokes therefore they need to be actively managed with antihypertensive and lipid lowering therapies, appropriate ATT and management of lifestyle factors; regular follow-up ensures optimal control and improves patient compliance
- Up to 30% of patients who experience a TIA are at risk of developing an acute stroke within 30 days; therefore TIA patients require urgent assessment and aggressive management of risk factors
- Primary prevention, early diagnosis and appropriate management of stroke can be improved by education of the public and healthcare professionals

List of references available on request. Date of preparation: July 2011

Every effort has been made to ensure that this information is correct and is prepared from the best available resources at our disposal at the time of issue. Prescribers are recommended to refer to the individual Summary of Product Characteristics (SmPC) for specific information on a drug.

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