Background Paper 6.6
Ischaemic and Haemorrhagic Stroke

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Update on 2004 Background Paper, BP 6.6 Stroke

Table of Contents

Abbreviations .......................................................................................................................... 4

Summary .................................................................................................................................. 5

1. Introduction ........................................................................................................................ 6
   1.1 Definition and classification ......................................................................................... 6
   1.2 Ischaemic stroke ........................................................................................................... 6
   1.3 Haemorrhagic stroke ..................................................................................................... 7
   1.4 Investigation of a stroke ............................................................................................... 8
   1.5 Assessment of acute stroke ......................................................................................... 9

2. Burden of stroke .................................................................................................................. 10
   2.1 Epidemiology ............................................................................................................... 10
   2.2 Economic impact ......................................................................................................... 16

3. Control strategy ................................................................................................................... 18
   3.1 Stroke prevention ......................................................................................................... 18
       3.1.1 Risk factors ........................................................................................................... 18
       3.1.2 Secondary Prevention ......................................................................................... 18
   3.2 Acute Therapy ............................................................................................................. 19
       3.2.1 Acute ischaemic stroke ....................................................................................... 19
       3.2.2 Acute haemorrhagic stroke ............................................................................... 22
   3.3 Supportive care ........................................................................................................... 23

4. Major problem and challenges of stroke management: why does the disease burden persist? 26

5. Stroke Research from 2004 Onwards .............................................................................. 28
   5.1 Update on Neuroprotectives ...................................................................................... 28
   5.2 Extending the Treatment Window ............................................................................. 29
   5.3 Specialized Stroke Units ............................................................................................. 30
   5.4 Enhancing Post-stroke Recovery ............................................................................... 30
   5.5 Stem Cell Treatment for Ischaemic Stroke ................................................................. 31
   5.6 Reducing Haematoma Growth ................................................................................... 33
       5.6.1 Recombinant Factor VII (rFVIIa) Study ................................................................. 33
       5.6.2 Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT) Study ......................................................................................................................... 33

6. What are the opportunities for research into new pharmaceutical interventions that might fill the current gap and make a substantial difference? ......................................................... 34
   6.1 Strategies for reducing treatment delays ..................................................................... 34
   6.2 Identifying the patients who can benefit the most from a specific product ............... 34
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>COPD</td>
<td>Chronic Obstructive Pulmonary Diseases</td>
</tr>
<tr>
<td>CT</td>
<td>computerized tomography</td>
</tr>
<tr>
<td>CVA</td>
<td>cerebrovascular accident</td>
</tr>
<tr>
<td>DALY</td>
<td>disability-adjusted life years</td>
</tr>
<tr>
<td>DWI</td>
<td>Diffusion-weighted imaging</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>EU10</td>
<td>European Union’s new accession countries.</td>
</tr>
<tr>
<td>EU15</td>
<td>European Union with 15 countries</td>
</tr>
<tr>
<td>EU25</td>
<td>European Union with 25 countries</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>HL</td>
<td>hearing loss, adult onset</td>
</tr>
<tr>
<td>IHD</td>
<td>Ischaemic Heart Disease</td>
</tr>
<tr>
<td>LBW</td>
<td>low birth weight</td>
</tr>
<tr>
<td>LRI</td>
<td>Low Respiratory Infections</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>NIHSS</td>
<td>National Institutes of Health Stroke Scale</td>
</tr>
<tr>
<td>NINDS</td>
<td>National Institute of Neurologic Diseases Study</td>
</tr>
<tr>
<td>ODD</td>
<td>other digestive diseases</td>
</tr>
<tr>
<td>OID</td>
<td>other infectious diseases</td>
</tr>
<tr>
<td>OUI</td>
<td>other unintentional injuries</td>
</tr>
<tr>
<td>QALY</td>
<td>Quality-adjusted Life Years</td>
</tr>
<tr>
<td>rt-PA</td>
<td>recombinant tissue plasminogen activator</td>
</tr>
<tr>
<td>TBLC</td>
<td>trachea, bronchus, lung cancers</td>
</tr>
<tr>
<td>TIA</td>
<td>transient ischaemic attacks</td>
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</table>
Summary

Stroke is an abrupt onset of a focal neurological deficit secondary to a vascular event lasting more than 24 hours. An acute stroke refers to the first 24-hour-period of a stroke event. Stroke is classified as either ischaemic (caused by thrombosis or embolisms) or haemorrhagic (caused mainly by rupture of blood vessel or aneurysm).

The occlusion of the cerebral artery causes decreased blood flow and ischaemia. Depending on the severity of the ischemia, infarction (cellular death) will occur within minutes, causing irreversible damage even after blood flow is restored. This is called the “core” of the infarct. Surrounding the core is tissue that is affected but functionally that may recover if blood flow is restored. This is called the “ischaemic penumbra”. Most people will have such an ischaemic penumbra amenable to treatment within the first three hours of occlusion of the cerebral artery, but many patients may have it up to 12 hours. This is the so-called “therapeutic window”. Thus proper identification of treatable patients is crucial for the efficacy of the interventions.

Stroke is the second leading cause of death worldwide and in the European region. Ten per cent of the 55 million deaths that occur every year worldwide are due to stroke. The overall mortality from stroke has been declining both worldwide and in Europe. This is mainly due to improved access to appropriate health care, with the consequent rise in health care costs. In Europe, discharges following hospitalization for stroke doubled during the last 15 years of the twentieth century. The United Kingdom spends 6% of its national health budget on stroke care, twice as much spent on ischaemic heart disease (IHD).

The successful management of acute stroke is based on imaging followed by two main strategies: vascular recanalization and supportive care. Differential diagnosis with haemorrhagic stroke is important. Restoration or improvement of perfusion to the ischaemic area is a key therapeutic strategy. However, currently available options, aspirin (1% better than placebo) and recombinant tissue plasminogen activator (rt-PA) (10% better than placebo) are not very effective. Current stroke therapy, therefore, is mainly based on general care and rehabilitation.

In most patients who have had a haemorrhagic stroke, current treatment focuses on evacuation of the haematoma particularly in the cerebellum, and supratentorial larger than 3 cm, despite the fact that trials have failed to show any benefit of this practice. If the haemorrhage is due to rupture of an aneurysm or AVM early surgical or endovascular intervention are important to avoid re-bleeding.

Despite improvements in care, sequelae of stroke remain a major problem. Fifty to seventy per cent of those who survive an ischaemic stroke will recover functional independence three months after onset, but 20% will require institutional care. Stroke is the second leading cause of disability in Europe after ischaemic heart disease (IHD). Worldwide, stroke is the sixth leading cause of disability. It is also the second leading cause of mortality in Europe and worldwide
Update on 2004 Background Paper, BP 6.6 Stroke

The economic impact of stroke care goes beyond the costs of sophisticated acute care, costly secondary prevention (carotid endarterectomy) and its prolonged high dependent institutional chronic care as well as costs of rehabilitation. Neither mortality rate nor hospital discharges accurately reflect the level of disability, which is mainly borne by patients and their families.

There is little progress being made in research and development of drugs for treating acute stroke, particularly in the field of neuroprotection. Surprisingly low levels of resources have been devoted to research and development of drugs for treating stroke during the last 30 years (no more than 10% of those invested in IHD or cancer).

Major improvements are needed in the chain of care for identification of stroke by relatives (education); early treatment (possibly with aspirin); the prompt referral to an accident and emergency facility (mobile units); accurate diagnosis and fast appropriate treatment (protocols and specialized units); improving access to expanded and more efficacious therapeutic options; and prompt referral to rehabilitation services.

As “time is brain”, more efficacious treatments provided early in the chain of care are needed to minimise disability and avoid future suffering as well as reducing the economic costs in societies with higher ageing populations.

1. Introduction

1.1 Definition and classification

Stroke is defined as abrupt onset of a focal neurological deficit lasting more than 24 hours. It is also called cerebrovascular accident (CVA) or apoplexy. An acute stroke refers to the first 24-hour period of a stroke. Focal neurological deficit lasting less than 24 hours (usually 5–20 minutes) known as transient ischaemic attack (TIA) is relevant but beyond the scope of this discussion paper.

Stroke is classified on the basis of its aetiology as either ischaemic (87%) or haemorrhagic (13%). Ischaemic stroke is produced by occlusion of a cerebral artery [thrombotic or atherosclerotic (50%), embolic (25%) and microartery occlusion, “lacunar stroke”, (25%)]. Haemorrhagic stroke is caused mainly by spontaneous rupture of blood vessels or aneurysms or secondary to trauma. The International Classification of Diseases versions 9 and 10 have codified the different types as 430-438 and 160-169, respectively.

1.2 Ischaemic stroke

Neurological symptoms and signs of an ischaemic stroke usually appear suddenly, but less frequently, they occur in a progressive manner (stroke-in-progress). The typical presentation is the sudden onset of hemiparesis in an older person. Symptoms and signs vary depending on the location of the occlusion and the extent of the collateral flow. Atherosclerotic ischaemic stroke is more common in the elderly, and occurs without warning in more than 80% of cases. A TIA a few months before the stroke is considered an important warning.
The pathophysiology is similar to that of ischaemic heart disease; an atherosclerotic plaque in a cerebral artery ulcerates triggering the aggregation of platelets and coagulation of fibrin to produce the thrombus that occludes the artery. Fewer than 20% of cases do not evolve to ulceration, but progress to cause gradual obstruction of flow and may manifest as TIAs. In hypertension-induced arteriosclerosis, small penetrating arteries of the deep white matter of the brain are affected producing small infarctions known as “lacunar infarcts”. In around 40% of elderly stroke patients no clear origin of the infarction can be found. Embolic ischaemic stroke is more frequent in patients with atrial fibrillation (80%), myocardial infarction, prosthetic valves, rheumatic heart disease and larger artery atheroma (artery-artery embolus). Most emboli are of atherosclerotic origin, and may partially or temporally obstruct cerebral arteries causing TIAs. Embolisms tend to be multifocal and may produce small haemorrhages around the obstruction.

The occlusion of a cerebral artery causes decreased blood flow and ischaemia. If it lasts only few seconds or a minute, recovery is immediate and complete. Depending on the severity of the ischaemia, infarction (cellular death) will occur within minutes, causing irreversible damage even after blood flow is restored. This is called the “core” of the infarct. Surrounding the core is tissue that is affected functionally due to diminished circulation but may recover if blood flow is restored. This is called the “ischaemic penumbra” of a stroke. Most people will have an ischaemic penumbra amenable to treatment for 3 hours, but many patients may have it up to 12 hours. This is known as the ‘therapeutic window’ available for thrombolysis. Thus proper identification of treatable patients is crucial for the efficacy of the interventions.

Due to changes in the vessels and parenchyma caused by ischaemia, the flow may not be restored even after the original cause of the obstruction has been removed (“no-reflow phenomenon”). Oedema is present in all necrotic tissue. In large areas of necrosis, massive oedema compresses adjacent tissue, which increases intracranial pressure and may cause herniation of the brain, leading to death within a few days in 80% of cases. Surgical decompression has been suggested for these cases. The extent of functional disability will depend on the extent and the localization of ischaemia and complications experienced by the patient.

Seizures at the time of stroke occur in 3–5% of infarctions, more often after embolism than thrombosis. The same proportion of patients will develop epilepsy from 6 to 18 months after a stroke. Idiopathic epilepsy in the elderly, therefore, may be the result of silent cortical infarction.

1.3 Haemorrhagic stroke

There are two types: one resulting from intracerebral haemorrhage secondary to hypertension, cerebral amyloid angiopathy, or degenerative arterial disease; and the other secondary to subarachnoid haemorrhages caused by rupture of an aneurysm. In the United States, 8–10 million people (3% prevalence) might have an aneurysm, and bleeding occurs in only 30 000 people per year. Other causes are uncommon, and sometimes, no source for the haemorrhage can be found. The main risk factors are advanced age, heavy alcohol consumption and hypertension. Cocaine abuse is an important cause of cerebral haemorrhage in young people.
Most intracerebral haemorrhagic strokes develop over 30–90 min. Symptoms will depend on the location and extent of the haemorrhage. Focal neurological symptoms, vomiting and drowsiness are common. Headache may be present, but stiff neck and seizures are uncommon. Large haemorrhages may cause stupor or coma. Most sub-arachnoid haemorrhages appear suddenly with intense headache, vomiting and neurological deficit and altered consciousness may occur in about 50% of patients. Occasionally, prodromal neurological symptoms, such as paralysis of a limb, difficulty in speaking, visual impairment or sudden unexplained headache, appear before a haemorrhage from an enlarging aneurysm causing pressure on the surrounding tissue or as a result of a leak of blood into the subarachnoid space ("warning leaks").

Cerebral vasospasm is an early complication and re-bleeding or hydrocephalus may be complications of SAH in 30% of cases during the first month, resulting in an extra 60% mortality. Of those who survive, more than half will have significant disabilities. The annual risk of recurrence of bleeding of an aneurysm is 3%. Thus, early surgical or intravascular treatment of aneurysm in these patients improves their long term outcome. The effectiveness of evacuation of a supratentorial haematoma due to other causes has not been evaluated. However, surgical removal of a large cerebellar haematoma is the current practice.

### Acute Stroke Basics:

A stroke results from sudden decrease of blood flow to the brain which causes rapid loss of function. Its symptoms, including hemiparesis, vomiting, drowsiness, and loss of consciousness, often go unrecognized as a stroke until after the acute treatment window has passed. Stroke causes a high burden of death and disability, both in Europe and around the world.

### 1.4 Investigation of a stroke

Outcome of investigations are crucial for effective management of acute stroke. Computerised tomography (CT) is the most immediately useful imaging method in identifying/differentiating cerebral haemorrhage from infarction. However, during the first few hours following ischaemic stroke, a CT may show only subtle changes or often nothing at all. A stroke assessment scale used in conjunction with a CT may help resolve uncertainties resulting from an inconclusive scan. On the other hand, magnetic resonance imaging (MRI) is the preferred method of investigation for ischaemic stroke and TIA. The disadvantages of MRI include its lack of wide spread availability and the time required to process the images, especially due to the fact that treatment within the presently available acute therapeutic window is critical to good patient outcomes.

MR or CT angiography demonstrates the cerebral vasculature and may add further information such as aneurisms, segmental narrowing or complete blockage of blood vessels. Doppler ultrasonography of carotid and vertebral vessels in the neck add further information – and is particularly useful in recommending patients for endarterectomy endovascular procedures or intravascular thrombolysis treatment. One analysis found that the immediate and long term success of thrombolysis is correlated with the site of occlusion as determined by Doppler ultrasonography.
None of these procedures is capable of accurately identifying the ‘ischaemic penumbra’ the most important area of brain that is amenable to treatment in a patient with acute stroke. The best method available for detecting this area is called the diffusion-perfusion mismatch. This technique involves comparing the discrepancy between the area of the brain with reduced perfusion (visualized with perfusion-weighted imaging) and the area with cellular swelling, the ischaemic core (visualized with diffusion weighted imaging). The ischaemic penumbra can also be seen up to 48 hours after acute stroke through the use of positron emission tomography (PET). Even though there are a few techniques available, future research in procedures that allow the identification of the penumbra are essential for improving stroke outcomes.²

1.5 Assessment of acute stroke

The evaluation and treatment of patients with acute ischaemic stroke should be performed without delay. The general and neurological history, together with brain imaging, provides the necessary information about the aetiology and potential contraindications to treatment with thrombolytic agents. Brain imaging is currently mandatory to guide acute interventions. The intervention protocols for haemorrhagic stroke are different from ischaemic stroke, and fatal complications may result from misdiagnosis. Other clinical and para-clinical tests required are not discussed here.⁶

The National Institutes of Health Stroke Scale (NIHSS) has come into widespread use in the United States for assessment of the severity of stroke and as an indicator of its prognosis (see Table 6.6.1). The initial NIHSS score provides important prognostic information. Approximately 60–70% of patients with an acute ischaemic stroke with a baseline NIHSS score under 10 will have a favourable outcome after one year as compared with only 4–16% of those with a score above 20.² Two other scales are often used to measure long term disability following acute stroke. The Barthel Index measures patients’ performance in 10 daily activities and the possible scores range from 0-100. The Modified Rankin Scale scores patients on their independence and ranges from 0-5.¹⁴ The National Institutes of Health has also developed a “toolbox” (available at nihtoolbox.org) that is a multidimensional set of brief measures to assess cognitive, emotional, motor, and sensory function on a common scale. These results can then be used across diverse study designs and settings, and may provide value in measuring and understanding recovery from stroke.
Update on 2004 Background Paper, BP 6.6 Stroke

Table 6.6.1: National Institutes of Health Stroke Scale (NIH-SS) (2012)

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
<th>Points available</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Level of consciousness - general</td>
<td>3</td>
</tr>
<tr>
<td>1b</td>
<td>Level of consciousness – questions</td>
<td>2</td>
</tr>
<tr>
<td>1c</td>
<td>Level of consciousness – commands</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>Gaze</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>Visual fields</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>Facial palsy</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>Motor – arms</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>Motor – legs</td>
<td>8</td>
</tr>
<tr>
<td>7</td>
<td>Ataxia</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>Sensory</td>
<td>2</td>
</tr>
<tr>
<td>9</td>
<td>Language (dysphasia)</td>
<td>3</td>
</tr>
<tr>
<td>10</td>
<td>Dysarthria</td>
<td>2</td>
</tr>
<tr>
<td>11</td>
<td>Inattention (neglect)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td><strong>Total</strong></td>
<td><strong>42</strong></td>
</tr>
</tbody>
</table>


Principal 2012 updates to the Introduction:
- Proportion of ischaemic to haemorrhagic stroke has increased slightly (Now 87% of strokes are ischaemic and 13% are haemorrhagic)
- Perfusion-diffusion mismatch, a new technique for identifying the ischaemic penumbra, has been identified and is now in use

2. **Burden of stroke**

2.1 **Epidemiology**

Stroke remains the second leading cause of death at the global level and in the European region. Of the 56 million deaths that occur every year worldwide, 10.8% are due to stroke (see Table 6.6.2). Eighty-five per cent of these stroke deaths among all ages occur in developing countries. Women have a higher lifetime risk of stroke than men: roughly one in five women (20% - 21%) and one in six men (14% - 17%) will suffer a stroke in their lifetime, according to a 2006 study.
Table 6.6.2: Ten Leading Causes of Death by Income Group (2008)

<table>
<thead>
<tr>
<th>Global</th>
<th>Low-income countries</th>
<th>Middle-income countries</th>
<th>High-income countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Ischaemic heart disease (12.8%)</td>
<td>1) Lower respiratory infections (11.3%)</td>
<td>1) Ischaemic heart disease (13.7%)</td>
<td>1) Ischaemic heart disease (15.6%)</td>
</tr>
<tr>
<td>2) Stroke and other cerebrovascular disease (10.8%)</td>
<td>2) Diarrhoeal diseases (8.2%)</td>
<td>2) Stroke and other cerebrovascular disease (12.8%)</td>
<td>2) Stroke and other cerebrovascular disease (8.7%)</td>
</tr>
<tr>
<td>3) Lower respiratory infections (6.1%)</td>
<td>3) HIV/AIDS (7.8%)</td>
<td>3) Chronic Obstructive pulmonary disease (7.2%)</td>
<td>3) Trachea, bronchus, lung cancers (5.9%)</td>
</tr>
<tr>
<td>4) Chronic Obstructive pulmonary disease (5.8%)</td>
<td>4) Ischaemic heart disease (6.1%)</td>
<td>4) Lower respiratory infections (5.4%)</td>
<td>4) Alzheimer and other dementias (4.1%)</td>
</tr>
<tr>
<td>5) Diarrhoeal diseases (4.3%)</td>
<td>5) Malaria (5.2%)</td>
<td>5) Diarrhoeal diseases (4.4%)</td>
<td>5) Lower respiratory infections (3.8%)</td>
</tr>
<tr>
<td>6) HIV/AIDS (3.1%)</td>
<td>6) Stroke and other cerebrovascular disease (4.9%)</td>
<td>6) HIV/AIDS (2.7%)</td>
<td>6) Chronic Obstructive pulmonary disease (3.5%)</td>
</tr>
<tr>
<td>7) Trachea, bronchus, lung cancers (2.4%)</td>
<td>7) Tuberculosis (4.3%)</td>
<td>7) Road traffic accidents (2.4%)</td>
<td>7) Colon and rectum cancers (3.3%)</td>
</tr>
<tr>
<td>8) Tuberculosis (2.4%)</td>
<td>8) Prematurity and low birth weight (3.2%)</td>
<td>8) Tuberculosis (2.4%)</td>
<td>8) Diabetes mellitus (2.6%)</td>
</tr>
<tr>
<td>9) Diabetes mellitus (2.2%)</td>
<td>9) Birth asphyxia and birth trauma (2.9%)</td>
<td>9) Diabetes mellitus (2.3%)</td>
<td>9) Hypertensive heart disease (2.3%)</td>
</tr>
<tr>
<td>10) Road traffic accidents (2.1%)</td>
<td>10) Neonatal infections (2.6%)</td>
<td>10) Hypertensive heart disease (2.2%)</td>
<td>10) Breast cancer (1.9%)</td>
</tr>
</tbody>
</table>


Overall stroke mortality has been declining worldwide despite the increased percentage of people aged over 65 years (75% of stroke victims are above 65 years old). This is mainly due to decreased exposure to risk factors, mainly hypertension and smoking, and to improved access to better healthcare. Figure 6.6.3 illustrates the projected trends for stroke death through the year 2030.

The prevalence of stroke events is expected to increase significantly across the globe as the global population older than 65 years of age (the age segment which suffers the most strokes, see Table 6.6.4) continues to increase by approximately nine million people per year. In Europe, the proportion of the population over 65 years of age is expected to increase from 20% in 2000 to 35% in 2050. The number of stroke events in Europe is predicted to rise from 1.1 million in 2000 to 1.5 million per year by 2025, largely due to the ageing population.
Figure 6.6.3: projected trends for stroke deaths, by income group.


Table 6.6.4: Estimates of stroke incidence (a) per 100 000 men and (b) per 100 000 women at selected ages in the European Union. The number of individuals experiencing stroke increases substantially with age.

Update on 2004 Background Paper, BP 6.6 Stroke

As the epidemiological and demographic transition extends through developing countries around the globe, stroke prevalence is increasing at an ever-growing rate and, in the period from 2000 to 2008, estimated stroke incidence in low- and middle-income countries surpassed stroke incidence in high-income countries for the first time, by 20%.22

But mortality figures alone do not give an adequate description of the overall burden of stroke. Despite improvement in stroke care and survival, sequelae of stroke remain a major problem.

In 2005, the global prevalence of stroke survivors was estimated to be 62 million, with projections to reach 77 million by 2030.23 However, with the increasing prevalence of stroke survivors comes a consequent increase of people who suffer from stroke-related disabilities. Stroke is associated with 43.7 million lost DALYs (disability-adjusted life years) annually around the world (see Figure 6.6.5), which accounts for about 3.2% of all annually lost DALYs.22 Figure 6.6.6 illustrates the death and disease burden attributable to stroke.

Figure 6.6.5: Global DALYs lost attributable to stroke:

Figure 6.6.6: Burden of disease and death attributable to stroke in selected countries in the WHO European region:

Source: WHO 2009.


Eight to twelve per cent of ischaemic strokes and 37–38% of haemorrhagic strokes result in death within 30 days.24,25 Fifty to seventy per cent of patients who survive an ischaemic stroke will recover functional independence three months after onset, but 20% will require institutional care. Among patients above the age of 65 years, the severity of the attack and permanent disabilities are greater. It has been reported that six months after the attack, 50% of stroke patients had some hemiparesis, 30% were unable to walk without assistance, 26% were dependent on others for help with activities of daily living, 19% had aphasia, 35% had depressive symptoms and 26% were being cared for in a nursing home.26 Table 6.6.7 shows the disability component of diseases in terms of DALYs, ranking stroke second in Europe after IHD (as of 2004).

Due to ageing populations, especially in those countries currently undergoing rapid economic growth, projections to 2020 suggest that stroke will account for 6.3% of the total burden of illness.27 In addition, 2004 estimates predict that stroke will be among the five most important causes of disability in both developing and developed countries (Figure 6.6.8).28

It is clear that the burden of stroke is on track to increase dramatically both in Europe and across the entire globe in the coming decades. Thus, without more effective strategies for the prevention, treatment, and rehabilitation of stroke, the cost of this disease will also increase dramatically.
Table 6.6.7: Leading Causes of Disability- Globally and in Europe (as per cent of total DALYs)

<table>
<thead>
<tr>
<th>Global</th>
<th>European Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Lower respiratory infections (6.2%)</td>
<td>1) Ischaemic heart disease (11.1%)</td>
</tr>
<tr>
<td>2) Diarrhoeal diseases (4.8%)</td>
<td>2) Stroke and other cerebrovascular disease (6.3%)</td>
</tr>
<tr>
<td>3) Unipolar depressive disorders (4.3%)</td>
<td>3) Unipolar depressive disorders (5.6%)</td>
</tr>
<tr>
<td>4) Ischaemic heart disease (4.1%)</td>
<td>4) Alcohol use disorders (3.3%)</td>
</tr>
<tr>
<td>5) HIV/AIDS (3.8%)</td>
<td>5) Hearing loss, adult onset (2.6%)</td>
</tr>
<tr>
<td>6) Stroke and other cerebrovascular disease (3.1%)</td>
<td>6) Road traffic accidents (2.4%)</td>
</tr>
<tr>
<td>7) Prematurity and low birth weight (2.9%)</td>
<td>7) Trachea, bronchus, and lung cancers (2.2%)</td>
</tr>
<tr>
<td>8) Birth asphyxia and birth trauma (2.7%)</td>
<td>8) Osteoarthritis (2.1%)</td>
</tr>
<tr>
<td>9) Road traffic accidents (2.7%)</td>
<td>9) Cirrhosis of the liver (2.0%)</td>
</tr>
<tr>
<td>10) Neonatal infections (2.7%)</td>
<td>10) Self-inflicted injuries (2.0%)</td>
</tr>
</tbody>
</table>


Figure 6.6.8: Leading causes of disability in 2004, and projections for 2030.

2.2 Economic impact

The economic impact of stroke goes beyond the cost of acute care to include sophisticated and costly secondary prevention such as carotid endarterectomy and its prolonged, highly dependent chronic care. The estimated mean lifetime cost per ischaemic stroke patient in the United States was US$ 140,048 in 1999. This includes inpatient care, rehabilitation and follow-up care necessary for lasting disabilities.29

In 2008, the estimated total direct and indirect cost for stroke in the U.S. was US$ 65.5 billion,30 which is higher than the 2004 estimation of US$ 53.6 billion.31 In the UK alone, the cost of stroke care is estimated to be around £9 billion each year (see table 6.6.8).32 This total is comprised of direct care costs (49%), informal care costs (27%), and indirect costs (24%).30 In 27 EU countries, total estimated cost for stroke is €27 billion: €18.5 billion (68.5%) for direct and €8.5 billion (31.5%) for indirect costs. A further sum of €11.1 billion is calculated for the value of informal care.33

Table 6.6.9: Costs of Stroke Care in the United Kingdom (as of 2009)

<table>
<thead>
<tr>
<th>Cost Item</th>
<th>Cost in £</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis costs</td>
<td>45.604 m</td>
<td>0.51</td>
</tr>
<tr>
<td>Inpatient care costs</td>
<td>865.862 m</td>
<td>9.64</td>
</tr>
<tr>
<td>Outpatient costs</td>
<td>109.679 m</td>
<td>1.22</td>
</tr>
<tr>
<td>Outpatient drug costs</td>
<td>505.588 m</td>
<td>5.63</td>
</tr>
<tr>
<td>Community care costs</td>
<td>2,857.113 m</td>
<td>31.82</td>
</tr>
<tr>
<td>Annual care cost total</td>
<td>4,383.858 m</td>
<td>48.82</td>
</tr>
<tr>
<td>Informal care costs total</td>
<td>2,420.921 m</td>
<td>26.96</td>
</tr>
<tr>
<td>Income lost due to mortality</td>
<td>592.733 m</td>
<td>6.6</td>
</tr>
<tr>
<td>Income lost due to morbidity</td>
<td>740.158 m</td>
<td>8.24</td>
</tr>
<tr>
<td>Productivity loss total</td>
<td>1,332.892 m</td>
<td>14.85</td>
</tr>
<tr>
<td>Benefit payments</td>
<td>841.254 m</td>
<td>9.37</td>
</tr>
<tr>
<td>Total</td>
<td>8,978.926 m</td>
<td></td>
</tr>
</tbody>
</table>


The total cost of stroke in the United States from 2005 to 2050, in 2005 US$, is projected to be $1.52 trillion for non-Hispanic whites, $313 billion for Hispanics, and $379 billion for blacks. The per capita cost of stroke estimates is highest in blacks ($25,782), followed by Hispanics ($17,201) and non-Hispanic whites ($15,597). Loss of earnings is expected to be the highest cost contributor in each race/ethnic group.25

In the European Union, hospital discharges for cerebrovascular diseases almost doubled during the last 15 years of the twentieth century. In the United States, the same pattern has been reported for the same period. Specialized stroke care has been shown to improve health and economic outcomes.34,35 Similar trends are observed for mortality and case fatality rate could be lowered by improved stroke services.
In the period between 1989 and 1999, the rate of hospitalization from acute stroke in the United States increased from 32.4 to 34.9 per 10,000. This rate subsequently fell to an average of 31.8 per 10,000 in 2009. Average length of hospital stay in the United States fell from 11.1 to 5.3 days between 1988 and 2009 (see Figure 6.6.10).

But, neither mortality rate nor discharge data from hospitals accurately reflect the level of disability, which is mainly borne by patients and their families. Stroke has been associated with greater use of informal care (family and friends). Health care costs are increasing despite the decrease in stroke incidence and mortality, and will continue to increase as our societies age.

These figures imply that the long-term chronic care that results from stroke is the most costly aspect of the disease, and treatments to reduce its large health and economic impacts are needed.

Priorities, therefore, should be placed on primary prevention of stroke, effective treatment of acute stroke, and effective treatment of recovery from stroke to minimise unfavourable sequelae and extend stroke management outside the hospital to improve accessibility and reduce hospital costs.
3. Control strategy

3.1 Stroke prevention

3.1.1 Risk factors

Stroke prevention is still very important. High blood pressure is one of the leading primary and secondary modifiable risk factors for stroke. While effective and widely available medicines exist for the treatment of hypertension, these are often not used. One study found that only 60% of patients used antihypertension medication as prescribed, due to a variety of factors such as misinformation about the condition and negative attitudes about medication. Lipid reduction with statins for patients with high cholesterol can reduce the risk of stroke—one meta-analysis found a relative risk reduction of 21%. Atherosclerosis may be surgically addressed with endarterectomy but the procedure is often impractical because of its costs and risks. Atrial fibrillation is a major cause of ischaemic stroke (one in six for those over 60) and can be managed with aspirin, warfarin, or a pace maker. Risk of stroke in populations can be reduced by controlling other risk factors such as diabetes, smoking, and heavy alcohol use. The occurrence of fatal and nonfatal stroke also increases with decreasing socioeconomic status, even when all other factors are controlled (stroke incidence per 100 000 per year, European adjusted, 45-84 years): least disadvantaged, 200 (95% CI, 173 to 228); less disadvantaged, 251 (95% CI, 220 to 282); disadvantaged, 309 (95% CI, 274 to 343); most disadvantaged, 366 (95% CI, 329 to 403; 2 for ranks; p < 0.0001, see Annex 1 for non-adjusted data). It has been suggested that prevention strategies to target specific geographical areas may be a cost effective intervention. Prevention is especially important in middle and low income countries where effective interventions such as stroke care units are either not feasible, unaffordable, or otherwise unavailable.

3.1.2 Secondary Prevention

A wide array of secondary prevention strategies now exist that reduce the rate of stroke reoccurrence.

Aspirin may be one of the most useful and cost effective methods of secondary stroke prevention. Long term aspirin monotherapy leads to an 18.1% risk reduction of recurrent stroke when compared to placebo (p = 0.013). Treatment with dipyridamole also shows a significant risk reduction (16.3%, p = 0.039). Furthermore, the greatest reduction in reoccurrence of stroke was seen with the combination treatment of aspirin plus extended-release dipyridamole, and it has been suggested that this should be the standard in secondary stroke prevention (37.0% risk reduction (p < 0.001)). For patients who cannot use aspirin because of allergy or other side effects, clopidogrel had been shown to be equally as effective at reducing reoccurrence of ischaemic stroke and does not show any greater safety risks than aspirin. Aspirin plus clopidogrel combination treatment does not show greater benefits than either therapy alone and carries an increased risk of bleeding (absolute risk increase 1.3% [95% CI, 0.6 to 1.9]). One study found aspirin and aspirin plus dipyridamole to be of equal cost-effectiveness because while combination treatment improved outcomes but it also increased costs. Treatment with clopidogrel was found to be the least cost-effective of the three.
For patients with atrial fibrillation, warfarin can reduce the relative risk of recurrent stroke by about 70% (hazard ratio 0.34 [95% CI, 0.20 to 0.57]) but a large meta-analysis of trials showed no significant difference between the effects of warfarin and aspirin (OR 0.79 [95% CI, 0.61 to 1.02]). Furthermore, any possible added advantage of warfarin is offset by an increased risk of bleeding (0.3–0.6% per year).

Carotid endarterectomy is an effective secondary prevention strategy in patients who have at least 70% stenosis of the symptomatic carotid artery. The relative risk reduction of recurrent stroke is approximately 60% over three years (as shown in Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis, 1991). The current recommendation is for carotid endarterectomies to be performed within 12 weeks following acute stroke for maximum benefit.

Evidence suggests that treatment with blood pressure medications also serves as a secondary prevention. The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) demonstrated a reduction in recurrent stroke of approximately 30% during five years. This reduction was observed independently of the patient’s baseline blood pressure.

The incidence of reoccurrence of stroke can also be reduced with the administration of statins. This benefit is not correlated with the baseline cholesterol concentration of the patient and may be due to alternative properties of statins, such as anti-inflammation or neuroprotection.

3.2 Acute Therapy
3.2.1 Acute ischaemic stroke

The successful management of acute ischaemic stroke is currently based on two vascular recanalization strategies: anti-platelet agents and thrombolysis.

Because most strokes are due to thromboembolic occlusion of an intracranial artery, restoration or improvement of perfusion to the ischaemic area is the key therapeutic strategy. The concept of an “ischaemic penumbra”, a potentially recoverable brain tissue, allows early intervention to improve the neurological symptoms, and decrease the functional disability after the attack.

There are many strategies suggested for treatment of acute stroke, but oral aspirin and intravenous rt-PA are the only two pharmaceuticals currently recommended for acute stroke treatment.

Anti-platelet Agents

The effectiveness of acute treatment of stroke with aspirin is still unclear. Two large studies have tested the effect of aspirin given once within 48 hours of stroke onset compared to a placebo. 300 mg of aspirin was associated with significantly fewer recurrent ischaemic strokes and did not increase the risk of haemorrhagic strokes, as reported by The International Stroke Trial. Chinese Acute Stroke Trial found that 160 mg of aspirin per day showed a similar decrease in incidence of ischaemic stroke in the aspirin group but was associated with an increase of haemorrhagic strokes. The combined results of the two trials...
showed an overall decreased risk of further stroke or death in the hospital in 9 per 1000 patients treated and showed no net increase in hazard with aspirin treatment.\textsuperscript{53} The combination of aspirin and thrombolytics may increase bleeding, and thus aspirin is currently recommended for those whose strokes are unable to be treated with thrombolysis.\textsuperscript{54} The advantages of acute aspirin treatment are its low cost, easy administration and low risk of toxic effects.\textsuperscript{2} However, it does carry some side-effects, such as abdominal pain, peptic ulcerations and allergy to aspirin, which may limit its wider use.\textsuperscript{55} Clopidogrel is an alternative when aspirin cannot be used. The rate of reoccurrence of stroke was 9.0% in patients who received aspirin plus extended-release dipyridamole and 8.8% in patients who received clopidogrel (hazard ratio 1.01 [95\% CI, 0.92 to 1.11]).\textsuperscript{56} Anticoagulants, such as Warfarin, have not been shown to produce better outcomes than aspirin alone.\textsuperscript{57} No other antiplatelet agent has yet been reported as effective.\textsuperscript{58-59} The administration of acute aspirin can help salvage the ischaemic penumbra, but most of its potential benefits come from early secondary prevention.\textsuperscript{2}

**Thrombolysis**

In 1995, a clinical trial showed that the intravenous administration of rt-PA (0.9 mg/kg; maximum dose 90 mg) within three hours of onset of ischaemic stroke improved outcomes at three months when compared to a placebo (global odds ratio for a favourable outcome, 1.7 [ 95\% CI, 1.2 to 2.6]) (see Figure 6.6.10).\textsuperscript{60} Largely due to the results of this trial, US Food and Drug Administration (FDA) approved rt-PA within the three hours after presentation of symptoms for the treatment of acute ischaemic stroke in 1996.\textsuperscript{61} Treatment with rt-PA is associated with potentially fatal intracranial haemorrhage in 6.3\% of cases compared to 0.6\% of cases treated with placebo. The safety and efficacy of rt-PA for the treatment of children has not been established. Common side-effects include bleeding from cuts, gums, wounds, injection sites, fever and low blood pressure.\textsuperscript{62} Because of potential fatal complications thrombolytic treatment should be carried out according to a strict pre-determined protocol. Rt-PA is only used in approximately 5\% of patients due to factors such as lack of stoke experts and reimbursement issues.\textsuperscript{2}

To date, no other thrombolytic agent has been established as a safe and effective alternative to intravenous rt-PA. Currently available data do not support the clinical use of either streptokinase or ancod.\textsuperscript{24,63} The PROACT II study (1999) reported promising results in a trial testing treatment with prourokinase but the risk of intracranial haemorrhage during the first 24 hours following treatment was high (10\% vs. 2\% of control, p = 0.06).\textsuperscript{64} No recent clinical trials have been completed using prourokinase.
As the ischaemic process progresses very fast, the time at which treatment starts has been shown to be critical if there are to be significant benefits. Treatment within the first three hours has been defined as the ‘therapeutic window’ for acute stroke, but evidence suggests that earlier treatment brings a better outcome (adjusted odds ratio for favourable three-month outcome: 0-90 min, 2.11 [95% CI 1.33 to 3.35]; 91-180 min, 1.69 [95% CI 1.09 to 2.62] (see figure 6.6.12). However, recent studies have shown that treatment up to four and a half hours after onset is still effective and does not carry an increased risk of haemorrhage.
As intracranial haemorrhage is difficult to treat it must be avoided at all costs. The National Institute of Neurologic Diseases Study (NINDS) of rt-PA showed the NIHSS score to be useful in identifying patients with higher haemorrhagic risk. Patients with a score of 20 or more on the NIHSS had a 17% chance of intracranial haemorrhage, whereas the risk of bleeding was only 3% among those with a score less than 10.67

The size of the infarct, based on computed tomography scan (CT scan), is also a predictor of haemorrhage and poor outcomes, but no study has yet determined whether treatment of severe cases with rt-PA might have higher risks than benefits. As a result, it has been suggested that the performance of these tests should not delay treatment with intravenous rt-PA. Other investigations, including imaging of cerebral vessels, carotid Doppler studies, cardiac echo can be delayed until after the thrombolytic treatment.67

### 3.2.2 Acute haemorrhagic stroke

Haemorrhagic stroke is the most difficult form of stroke to treat and few effective strategies exist to reduce disability and mortality. Mayer et al. reported promising results with the use of Recombinant Activated Factor VII, a drug that is FDA approved for the treatment of excessive bleeding in patients with haemophilia68,69. Because Factor VII is not currently in use for the treatment of acute haemorrhagic stroke, it is discussed further in section 6.6.5
The assessment should be done in consultation with a neurosurgeon and the use of a CT scanner. The size and location of the haematoma determine the prognosis. Current treatment focuses on evacuation of the haematoma particularly in the cerebellum, and supratentorial region which is larger than 3 cm, despite the fact that trials have yet to show any benefit of this practice. Surgical evacuation of moderate-volume intracerebral haemorrhage was examined in the STICH trial, completed in 2007. The trial did not produce significant results—at 6 months, 26% of patients given the treatment had a favourable outcome compared with 24% of the patients given initial conservative treatment (OR 0.89 [95% CI 0.66 to1.19], p = 0.414). However, a second study, STICH-2, is currently underway investigating the same issue.

Haemorrhagic stroke patients are at a risk for re-bleeding during the time in which surgery is delayed, antifibrinolytic agents which may reduce this risk are seen as an attractive option. A meta-analysis found that they are associated with a reduced incidence of aneurysmal re-rupture (OR 0.55 [95% CI 0.42 to 0.71]). However, treatment with antifibrinolytics did not improve poor patient outcome (death, vegetative state, or severe disability) (OR 1.12 [95% CI 0.88 to 1.43]) and was also associated with an increased risk of cerebral ischemia (OR 1.39 [95% CI 1.07 to 1.82]).

3.3 Supportive care

When cerebral infarction occurs, the immediate goal is to optimize cerebral perfusion of the ischaemic area, monitor potential stroke-related complications (cerebral oedema, seizures, haemorrhagic transformation, cardiovascular and pulmonary problems, fever and malignant hypertension) and to prevent the common complications of bedridden patients, such as malnutrition, infections, pressure sores, aspiration pneumonia, deep venous thrombosis and pulmonary embolism. Early mobilisation is very useful in preventing these complications. Early involvement of physical therapists may reduce the rate of long term stroke complications and may speed up the recovery process.

Good nutrition, support of paralyzed limbs, and general positioning of the patient may also minimize complications immediately following stroke. There are also on going trials evaluating the effectiveness of active cooling in the period following a stroke.

The provision of airway support and ventilatory assistance for patients with acute stroke who have depressed levels of consciousness or airway obstruction may be necessary. A further recommendation is to provide supplementary oxygen only to hypoxic patients. Fever is associated with poor outcomes and should be treated with antipyretics with no antiplatelet effect. There is general agreement to recommend control of hypoglycaemia or hyperglycaemia following stroke. A reasonable goal would be to lower markedly elevated glucose levels to <300 mg/dL (<16.63 mmol/L). Swallowing function should also be monitored and treated if necessary with dietary modifications or a nasogastric feeding tube. These strategies were found to be effective in a trial that implemented protocols for monitoring for hyperglycaemia, fever and swallowing dysfunction. These patients showed reduced death and dependency at 90 days following the incidence of a stroke.

As cardiovascular diseases (mainly myocardial infarction and arrhythmias) are risk factors and complications of an acute stroke, they should be carefully evaluated and treated using established protocols in stroke patients. Use of anticoagulants during the first 14 days should
be avoided. Controversy exists within the research community regarding whether or not hypertension should be actively treated during the acute phase of the stroke. Studies have been done confirming both arguments, thus more research is urgently needed in this area. Hypotension may also be a complication and should be carefully monitored.¹¹

Once the patient has been stabilized, patient and family education, screening and treatment of depression, and physical and functional rehabilitation should be started as soon as possible. Finally, the patient should have further evaluation to determine the cause of the stroke, and medical or surgical therapies should be administered to prevent recurrent ischaemic events.¹¹

In patients with malignant middle-cerebral-artery-territory infarction and space-occupying brain oedema, hemispheric decompression preformed within 48 hours of infarction has been shown to be beneficial. A combined analysis of three clinical trials found that 75% of patients who received the surgery had an mRS≤4 at 12 months compared to 24% of controls (pooled absolute risk reduction 51% [95% CI 34 to 69]). Though only a small group of patients will benefit from this surgery, it has been shown to be effective and should become part of protocol for patients who qualify for it.⁷²
Table 6.6.13: Summary of stroke therapies that are proven or under investigation

### Acute Stroke

<table>
<thead>
<tr>
<th>Study, year</th>
<th>RRR (95% CI)</th>
<th>ARR</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proven</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke unit</td>
<td>Langhorne and colleagues, 1993</td>
<td>6.5%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Thrombolysis (tPA)</td>
<td>NINDS, 1995</td>
<td>9.8%</td>
<td>5.5%</td>
</tr>
<tr>
<td>Aspirin</td>
<td>IST, 1997</td>
<td>2.6%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Decompressive surgery for IS</td>
<td>Vahedi and colleagues, 2007</td>
<td>48.8%</td>
<td>23.0%</td>
</tr>
<tr>
<td><strong>Under investigation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recombinant factor VII</td>
<td>Mayer and colleagues, 2005</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Surgery for ICH</td>
<td>Mendelow and colleagues, 2005</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Extending time widow for thrombolysis</td>
<td>DIAS, 2005</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Sonothrombolysis</td>
<td>Alexandrov, 2004</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Thrombectomy</td>
<td>MERCI, 2005</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Blood pressure lowering</td>
<td>ENOS, 2007</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Neuroprotection</td>
<td>SAINT, 2006</td>
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### Secondary prevention

<table>
<thead>
<tr>
<th>Study, year</th>
<th>RRR (95% CI)</th>
<th>ARR</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proven</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>Canadian Co-op Study Group, 1978</td>
<td>13.0%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Aspirin plus dipyridamole</td>
<td>Deiner, 1996</td>
<td>15.0%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Clopidrogel</td>
<td>CAPRIE, 1996</td>
<td>10.0%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>EAFT, 1993</td>
<td>66.0%</td>
<td>8.0%</td>
</tr>
<tr>
<td>Carotid endarterectomy</td>
<td>NASCET, 1991; ECST, 1991</td>
<td>44.0%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Blood pressure lowering</td>
<td>PROGRESS, 2001</td>
<td>28.0%</td>
<td>4.0%</td>
</tr>
<tr>
<td>Cholesterol lowering</td>
<td>SPARCL, 2006</td>
<td>16.0%</td>
<td>2.2%</td>
</tr>
<tr>
<td><strong>Under investigation</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Angioplasty</td>
<td>Yadav and colleagues, 2004</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Thrombin inhibitors</td>
<td>SPORTIF, 2003</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>


Note: NNT: number needed to treat to prevent one stroke patient dying or becoming dependent (acute stroke) or to prevent one fatal or non-fatal stroke (secondary prevention) per year. RRR: relative risk reduction. ARR: absolute risk reduction.
4. **Major problem and challenges of stroke management: why does the disease burden persist?**

The process of care begins with calling an ambulance or upon arriving in an accident and emergency facility. In one study in an urban area in the United States, only 17% of patients were admitted to hospital within the three-hour therapeutic window\(^ {73}\) and in an international trial, only 4% of patients were admitted within three hours of symptoms onset.\(^ {74}\) In a 2012 Japanese trial of 712 stroke patients, pre-hospital delays were significantly associated with decreased levels of consciousness at the time of patient admission to the hospital, measured by Glasgow Coma Scale score at admission. After adjusting for age and sex, a longer time between call and arrival at the hospital was associated with poorer GSC score (OR 1.020 [95% CI 1.002 to 1.038]).\(^ {75}\) Though the results of the trial showed statistically significant outcomes, the improvement was not large and may be impractical to implement if the costs outweigh the patient benefits.

Lack of access to general health services might be an important factor in delayed treatment in developing countries. A 2012 study estimated the cost burden of post-stroke conditions in Nigeria, and on average the costs were N 95,000 (US$ 600) in a government hospital and N 767,900 (US$ 4860) in a private hospital. The researchers concluded that managing stroke care is too high of a cost burden to be afforded by an average Nigerian stroke sufferer. This, in turn, results in increased death and disability, and consequent burdens on both the patient and their caretakers.\(^ {76}\)

In developed countries, a cause of delay in getting acute stroke care is the lag time between the stroke onset and when emergency services are actually called. A 2012 qualitative interview study in the United Kingdom revealed that the underlying reasons for this delay are quite complex. Factors influencing who called emergency services and when include: lack of knowledge of stroke symptoms, severity of the stroke symptoms, fear of hospitals and the consequences of stroke, and unwillingness to impose on medical staff, family, or friends. There remains a clear need for stroke-related education to ensure the general public understands when a stroke is occurring and the proper course of action to take when the situation arises.\(^ {77}\)

Several educational studies using diverse formats, especially mass media, have been shown to increase public knowledge of stroke symptoms. Often these efforts focus on recognizing the symptoms of stroke and emphasizing the need to call emergency services. Some of these studies have demonstrated higher likelihood that patients or by-standers who have been exposed to these mass-media campaigns will call an emergency number,\(^ {78}\) but many trials were brief and thus the large-scale and long-term benefits of such mass media campaigns are still uncertain. More research is needed in this area to increase the number of stroke victims who arrive at the hospital within the treatment window.

Once the patient is in contact with the health system a number of major barriers to treatment within the therapeutic window have been identified. Lack of specific protocols and training, delay in obtaining a diagnostic imaging test, delay in referring the patient to a specialized stroke unit and the low efficacy of available treatments (aspirin 1% and rt-PA 10% superior than placebo) are some of these factors in developed and developing countries. Lack of access to rt-PA might be an important factor in developing countries.
The majority of stroke research trials have not included patients with comorbidities, despite the fact that most stroke patients are over the age of 65 years, and often present comorbidities that add complexity to the management of the condition. Stroke is highly unstable during the acute phase and requires close monitoring and prompt attention to complications. Access to highly skilled professionals and the availability of costly resources have been shown to improve overall outcomes. The integration of rehabilitation services with acute hospital care has also been shown to be effective in improving health outcomes.

Though there have been intensive research efforts aimed at finding new acute stroke therapies, the vast majority of trials end in failure. The SAINT II (Stroke-Acute Ischaemic-NXY Treatment) and DIAS-2 (Desmoteplase in Acute Stroke) trials were designed on the basis of extensive promising preclinical data, as well as phase IIb and early phase III data. Yet, these two trials showed no efficacy. There have been multiple strategies proposed to address the continual lack of success in translating research from the bench to the bedside, as described in a 2008 review:

“1) vascular occlusion: current recanalization strategies have limited effectiveness and may have serious side effects;

2) complexity of stroke pathobiology: therapy must acknowledge the ‘Janus-faced’ nature of many stroke targets and must identify endogenous neuroprotective and repair mechanisms;

3) inflammation and brain-immune system interaction: inflammation contributes to lesion expansion, but is also instrumental in lesion containment and repair; stroke outcome is modulated by the interaction of the injured brain with the immune system;

4) regeneration: the potential of the brain for reorganization, plasticity and repair after injury is much greater than previously thought;

5) confounding factors, long-term outcome and predictive modeling

These five areas are linked on all levels and therefore need to be tackled by an integrative approach and innovative therapeutic strategies.”

Thus, the primary challenges of stroke care that face the world are: the lack of timely and affordable care (especially care involving specialized stroke units), the low efficacy of available interventions, and the continual failure of translating therapies from the laboratory to the bedside.

An additional yet extremely important challenge is the insufficient funding for stroke-related research, especially when compared to the funding of other prevalent chronic diseases. A government review in the United Kingdom compared the amount of research funding to the impact of the disease on the population and the economy for four of the most prevalent chronic diseases: dementia, cancer, coronary heart disease (CHD) and stroke. The results are summarized below in Table 6.6.14.

This study demonstrates that funding for stroke research is quite disproportional to its relative burden. There is an evident mismatch between the funds allocated to research and development and the burden of stroke, whether measured in terms of mortality or disability. Lack of funding undermines the capacity to do valuable research to an extent that stroke scientists are no longer able to apply for further required funding. This disparity should be addressed to ensure advancements in stroke therapies are not smaller than the disease’s burden on society, both in terms of health and economics.
Table 6.6.14: United Kingdom Research funding for four prominent chronic diseases

<table>
<thead>
<tr>
<th>Total Research Funding (£833 million = 100%)</th>
<th>Funding per Lost</th>
<th>1000 DALYs</th>
<th>Funding per £1 million of health and social costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer (£590 million = 71%)</td>
<td>Cancer (£482)</td>
<td></td>
<td>Cancer (£129 269)</td>
</tr>
<tr>
<td>CHD (£169 million = 20%)</td>
<td>CHD (£266)</td>
<td></td>
<td>CHD (£73 153)</td>
</tr>
<tr>
<td>Dementia (£50 million = 6%)</td>
<td>Dementia (£166)</td>
<td></td>
<td>Stroke (£8745)</td>
</tr>
<tr>
<td>Stroke (£23 million = 4%)</td>
<td>Stroke (£71)</td>
<td></td>
<td>Dementia (£48 82)</td>
</tr>
</tbody>
</table>


5. Stroke Research from 2004 Onwards

As was the status of stroke care in 2004, there have been no substantial breakthroughs in stroke therapy or management, though some promising research has been done. Investigation of neuroprotective therapies and methods of extending the treatment window still continues, and new directions of research have begun as well. These new areas of research include specialized stroke units, enhancing recovery, stem cell therapies, and methods to reduce haematoma growth.

5.1 Update on Neuroprotectives

There continues to be no substantial breakthrough in neuroprotective therapies for stroke, though some progress has been made since 2004. One 2005 study in particular demonstrated that edaravone, a free radical scavenger, significantly reduced the infarct volume (68.10 cm³ +/- 6.24%; p < 0.05) and provides a neuroprotective effect through the early free radicals scavenging pathway and a late anti-inflammatory effect (edaravone 05). This study suggests that edaravone may be important for expansion of the therapeutic time window in stroke patients but larger samples and higher quality trials are needed to confirm this trend.82

The 2006 Stroke-Acute Ischaemic-NXY Treatment (SAINT I) trial of about 1700 patients was one of the first successful translations of neuroprotectives into clinical practice,83 but the larger (about 3200 patients) and more comprehensive SAINT II study in 2007 showed no efficacy, suggesting the first study was a false positive [See Table 6.6.15].84 Though NXY was a failure in its primary outcome, it provides insight into the design faults of stroke trials, which could be the root cause of the repeated failure of neuroprotectives in clinical trials. There are multiple gaps in translating therapies from the lab to the bedside that need to be addressed, especially in the relevancy of animal trials, before neuroprotective research should be fully abandoned.
There is a growing body of research on the effects of induced hypothermia immediately following acute ischaemic stroke. Promising results have been seen in animal studies but questions still remain about the safety and efficacy of the treatment. It is probable that hypothermia works through multiple sites of action, including reducing the size of the infarction, reducing intracerebral pressure, and reducing cerebral oedema formation. However, a 2011 clinical trial showed no difference in NIHSS scores at six months following acute stroke between patients given the hypothermia treatment and control subjects, though the trial had flaws including small sample size and single-blind study design. It is recommended that a larger, double blind study be conducted in the future to determine the efficacy of the treatment.

Consistent failures in trials for neuroprotective stroke therapies may indicate that the next logical step is to demonstrate proof-of-principle, perhaps with a preloaded dose of neuroprotectant in high-risk patients, which would provide reassurance that the strategy is effective in humans.

### 5.2 Extending the Treatment Window

As identified in the 2004 Stroke Background report, prolonging the treatment window for thrombolysis continues to be an important area of research for stroke therapy. Various approaches currently undergoing investigation include (1) standard tPA therapy with expanded entry criteria with therapeutic time windows of up to six hours; (2) imaging techniques to assess the presence of a penumbra with time windows of six hours or even nine hours; (3) combined approach with intravenous therapy followed by intra-arterial therapy; (4) combination therapies using, for example, glycoprotein (GP) IIb/IIIa antagonists with tPA, tested with time windows of up to 24 h (ReoPro Retavase Reperfusion of Stroke Safety Study—Imaging Evaluation [ROSIE]); and (5) use of alternative thrombolytic agents such as desmoteplase. Desmoteplase is the only thrombolytic agent in late-stage development for acute ischemic stroke that is now tested in patients with proven stroke pathology.

Ultrasound-enhanced thrombolysis is another promising therapy that may enhance thrombolysis. By mobilizing endogenous tPA, it increases the treatable surface area available...
to exogenous tPA, as well as mechanically disrupting the clot. In a phase II trial, patients showed improved recanalization rates, with a nonsignificant trend toward an increased rate of recovery from stroke, as compared with placebo. A phase III trial is currently under way.\textsuperscript{56}

5.3 Specialized Stroke Units

Organized stroke unit care is provided in hospitals by doctors, nurses, and therapists who work as a coordinated team to provide specialized care to stroke patients. The results of a 2009 Cochrane systematic review indicate that patients receiving inpatient care in a stroke unit are more likely to survive, regain independence, and return home than those receiving less organized service. There are many forms of specialized stroke care that have evolved, including specialized wards and mobile stroke teams, but benefits were most apparent in units based in a dedicated ward.\textsuperscript{84} Compared with conventional-ward care, stroke-unit care was associated with a reduced probability of death or disability at the end of follow-up (OR 0.81 [95% CI 0.72 to 0.91]; \(p = 0.0001\)) [see figure 6.6.16]. However, there is delay in implementing these specialized stroke units in Europe, and in North America there is still disagreement on the need to have such specialized teams.\textsuperscript{90} Further research may be necessary to identify which patients benefit from such units.

Table 6.6.16: Health Outcomes of Stroke Unit vs. Control Care

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Stroke unit (n=4936)</th>
<th>Control (n=6636)</th>
<th>Odds Ratio (95% CI)*</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital case fatality</td>
<td>542 (11%)</td>
<td>1034 (15%)</td>
<td>0.78 (0.64-0.95)</td>
<td>0.016</td>
</tr>
<tr>
<td>Long-term mortality</td>
<td>1363 (28%)</td>
<td>2382 (36%)</td>
<td>0.79 (0.68-0.91)</td>
<td>0.001</td>
</tr>
<tr>
<td>Death or disability</td>
<td>2611 (53%)</td>
<td>4112 (62%)</td>
<td>0.81 (0.72-0.91)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Not living at home</td>
<td>1743 (35%)</td>
<td>2829 (43%)</td>
<td>0.85 (0.74-0.97)</td>
<td>0.019</td>
</tr>
</tbody>
</table>


Note: *Adjusted by age, sex, time from stroke onset, intracranial haemorrhages, atrial fibrillation, and unconsciousness, and clustered at the hospital level

5.4 Enhancing Post-stroke Recovery

The 2011 “Fluoxetine for motor recovery after acute ischaemic stroke (FLAME)” study demonstrated that the early prescription of fluoxetine with physiotherapy enhanced motor recovery after three months in ischaemic stroke patients with moderate to severe motor deficit. Table 6.6.17 below outlines the outcomes in fluoxetine and placebo patient groups. Fluoxetine is a well-tolerated drug that no longer has a patent, allowing the cost to be more affordable.
Table 6.6.17: Fugl-Meyer motor scale (FMMS) scores.

<table>
<thead>
<tr>
<th></th>
<th>Fluoxetine (n=57)</th>
<th>Placebo (n=56)</th>
<th>Difference between groups (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Total Score</td>
<td>53.7</td>
<td>35.1</td>
<td>18.6 (9.2-27.9)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Mean Upper Limb Score</td>
<td>29.7</td>
<td>16.2</td>
<td>13.5 (6.2-20.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean Lower Limb Score</td>
<td>24</td>
<td>18.9</td>
<td>5.1 (2.1-8.1)</td>
<td>0.001</td>
</tr>
</tbody>
</table>


*note: Mean was adjusted for age, history of stroke, and FMMS score at inclusion*

5.5 Stem Cell Treatment for Ischaemic Stroke

Stem cells are an emerging therapeutic modality in treatment of stroke. Stem cells are an emerging therapeutic modality in treatment of stroke. This new arena is based on the relatively recent discovery that certain parts of the adult brain are capable of recovery. A 2006 study of patients with ischaemic stroke demonstrated the presence of a natural neurogenesis process in the ischaemic penumbra, but this endogenous regeneration is not effective enough to fully repair severe brain damage, such as that caused by a stroke. Targets for developing stem cell therapies include the promotion of these endogenous repair processes, as well as protecting at-risk tissue during the acute phase of the stroke, and direct replacement of already-damaged brain tissue.

Though the few existing experiments show promising results, there are many challenges that remain to be addressed in using stem cells for stroke therapy, including:

**Which type of stem cells should be used?**

There are multiple types of stem cells that can potentially be used in stroke therapy, and they all come from two main sources: embryonic stem cells (which are quite controversial) or adult stem cells (which are less controversial, but also have less differentiation potential). One of the more promising studies involved adult hematopoietic stem cells (HSCs), which have shown significant benefits in rodent stroke models, including evidence of functional improvement and reduced infarct volume. Furthermore, as HSCs are derived from bone marrow, peripheral blood, or umbilical cord blood, they are not associated with the bioethical controversy that surrounds embryonic or fetally derived stem cells. A further study investigating direct intracerebral implantation of HSCs one week after induced stroke in an animal model showed evidence of neurogenesis and angiogenesis, with differentiation of transplanted cells into cells expressing markers for neurons, glial cells, and vascular endothelial cells.

**What is the best mechanism of action?**

There are several potential paths of action that stem cells could take in order to treat stroke. Following an ischaemic stroke, neurons and glia die by a mixture of necrosis and apoptosis. Stem cell transplantation may elicit a neuroprotective response by rescuing the apoptic cells, particularly in the penumbral tissue, which in experimental models has led to improved neurological recovery. Another strategy under investigation is the use of stem cells to promote angiogenesis to aid in the regeneration of blood vessels and similar structures that are also damaged during acute stroke. A third potential mechanism of action is to promote
endogenous repair processes that occur naturally. When the patient has an ischaemic stroke, certain types of stem cells are mobilized from the bone marrow into the bloodstream. There is evidence that increased mobilization of these cells in stroke patients is correlated with increased neurological recovery. More research is needed to evaluate these various mechanisms.

Which patients will benefit from stem cell therapy?

The type and anatomical location of the stroke are important issues to consider when selecting the appropriate therapy for a patient. Additionally, demographic differences such as age and gender are likely to affect how patients respond to treatment. Most preclinical studies that have been conducted focus on young, healthy, male animals. The benefits that these studies demonstrate may not translate to elderly patients—the demographic in which the majority of strokes occur. The majority of preclinical studies have focused on ischaemic rather than haemorrhagic strokes, which make up one fifth of stroke cases. Finally, the current and completed studies do not include patients who suffer from comorbidities and other complications, an issue which must be addressed in future research efforts.

What is the optimum timing and method of delivery for treatment?

Preclinical trials have shown benefits in both acute and chronic stroke cases, thus future studies need to evaluate the optimal timing of treatments and their comparative effectiveness. The best method of delivery for stem cell treatments remains unclear. Positive results have been seen with intracerebral implantation (which is effective, but highly invasive) as well as intravenous and intra-arterial routes (which are less risky, but also less reliable because only a small proportion of injected cells reach the brain). Further studies are needed to compare these three methods, keeping in mind practicability and safety, and not solely the therapy’s effectiveness.

How can transplanted cells be tracked?

Tracking the stem cells once they are inside the patient’s body is essential to improving our understanding of cell migration and mechanisms of action. However, there is currently no ideal method of accomplishing this, so it is likely in the future that a combination of imaging and tracking methods will be used to give an overall assessment. More research is needed to determine the best process for tracking stem cell distribution.

Currently, the routine use of stem cells at the bedside for stroke patients is an exciting prospect, though realistically it remains a long way off. Stem cell transplantation in animal models of ischaemic stroke has shown encouraging results, but evidence in human patients is lacking and the current clinical trials are still in their infancy. There have been a number of recent phase I and II studies investigating ischaemic stroke therapy, but these trials have not yet addressed the best cell type, route of delivery, or timing of therapy. Large, well-designed trials are urgently needed in the arena of stem cell research.
5.6 Reducing Haematoma Growth

In stroke management, the development of a haematoma is a key indicator of a poor patient outcome. Consequently, there has been research investigating ways to reduce these haematoma, including two notable studies involving: (1) Recombinant Factor VII, and (2) early reduction of blood pressure.

5.6.1 Recombinant Factor VII (rFVIIa) Study

A 2005 study involving 399 patients investigated the potential stroke-related applications of recombinant factor VII (rFVIIa), which is usually given to patients to reduce haemorrhagic complications of major surgical procedures. Hematoma volume increased more in the placebo group than in the rFVIIa groups.

The mean increase was 29% in the placebo group, as compared with 16%, 14%, and 11% in the groups given 40 µg, 80 µg, and 160 µg of rFVIIa per kilogram, respectively (p = 0.01 for the comparison of the three rFVIIa groups with the placebo group). Growth in the volume of intracerebral haemorrhage was reduced by 3.3 ml, 4.5 ml, and 5.8 ml in the three treatment groups, as compared with that in the placebo group (p = 0.01). Sixty-nine percent of placebo-treated patients died or were severely disabled (as defined by a modified Rankin Scale score of four to six), as compared with 55%, 49%, and 54% of the patients who were given 40, 80, and 160 µg of rFVIIa, respectively (p = 0.004 for the comparison of the three rFVIIa groups with the placebo group). Mortality at 90 days was 29% for patients who received placebo, as compared with 18% in the three rFVIIa groups combined (p = 0.02).

But though treatment with rFVIIa within four hours after the onset of intracerebral haemorrhage limited the growth of the hematoma, reduced mortality, and improved functional outcomes at 90 days, there was a small increase in the frequency of thromboembolic adverse events. These events, mainly myocardial or cerebral infarction, occurred in 7% of rFVIIa-treated patients, as compared with 2% of those given placebo (p = 0.12). Furthermore, a follow up study completed by the same researchers in 2008 did not produce the same results in rFVIIa’s reduction of long term disability. They found that it was not associated with improved outcomes at 90 days. More research is needed to reduce the complications associated with this therapy, determine its efficacy, and to identify which patients would benefit from such therapy.

5.6.2 Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT) Study

Early elevation of blood pressure (BP) is very common after intracerebral haemorrhage, and a number of observational studies have demonstrated strong associations between increasing levels of BP and poor patient outcomes. The 2010 INTERACT study aimed to examine the effects of BP-lowering treatment on haematoma and perihaematomal oedema over 72 hours. The results of the study confirmed the reduction of haematoma growth in intracerebral haemorrhage over 72 hours, though there were no recognizable effects on perihaematomal oedema. Because haematoma growth is a strong predictor of poor outcomes in intracerebral haemorrhage, these results reaffirm potential benefits of rapid physiological control of elevated BP and support the hypothesis that early intensive BP lowering may promote recovery from intracerebral haemorrhage. Further research is needed to fully translate these
practices to the bedside and confirm the improved patient outcomes of haematoma reduction.

6. What are the opportunities for research into new pharmaceutical interventions that might fill the current gap and make a substantial difference?

Opportunities for research can be divided into four categories:
   a) reducing treatment delays;
   b) identifying those patients who can benefit the most from a product;
   c) prolonging the treatment window; and
   d) therapies that work outside the treatment window.

6.1 Strategies for reducing treatment delays

Specialized stroke wards in hospitals have been shown to be very effective in reducing rates of death and disability in stroke patients. Though a 2007 study on the effectiveness of specialized stroke wards showed improved patient outcomes irrespective of the patient’s age,90 more research is needed in determining the effectiveness of these special units in terms of the type of stroke and the presence of comorbidities. Additionally, the benefits of mobile stroke units, especially in terms of cost-effectiveness, have yet to be proven but may have benefits for certain demographics of patients, such as those living far away from a well-equipped hospital. More research should be done in this area as well.

The use of rt-PA in mobile stroke units at the first contact with the patient and prompt referral to specialized centres, has been effective in improving health outcomes. As rt-PA is contraindicated in patients with haemorrhagic stroke or those likely to have it as a consequence of the treatment, research is required to develop and test diagnostic protocols to be used by the paramedics in these units. In order to avoid duplication of ambulance systems, the use of rt-PA by paramedics should be considered in normal ambulances rather than in mobile stroke units. The current major drawback is inaccessibility to CT scanning.

Another area of research is the development of safer drugs that could be used earlier in sequence with stronger intervention later in hospital. Aspirin is shown to be effective in improving health outcomes in acute stroke. It is safer for patients with haemorrhagic stroke and is readily available. Further research is required to evaluate the cost-effectiveness of using aspirin at the time of onset of symptoms at home, in the ambulance or on arrival at the hospital in relation to its interaction with rt-PA at different dosages; and the additional risk for patients with haemorrhagic stroke that may have been misdiagnosed as ischaemic stroke.

6.2 Identifying the patients who can benefit the most from a specific product

Drug efficacy may be lower and/or drugs may have a higher profile of side-effects for erroneous reasons, e.g. trials may have included patients who no longer have an ischaemic
penumbra, or who have experienced different physiopathological mechanism, or who were admitted using different concomitant treatment. Such patients should be identified and included in trials designed specifically for them.

Diagnosis using perfusion–diffusion MRI and CT may delineate the existence and extent of the ischaemic core, the extent and severity of perfusion impairments, occlusion of large vessels, and the ischaemic penumbra. It has also shown promising results in predicting health outcomes and identifying patients with treatable ischaemic penumbra beyond the standard three-hour therapeutic window. Several studies are currently evaluating some of these issues (the DWI Evaluation for Understanding Stroke Evolution (DEFUSE), the Echo Planar Imaging Thrombolytic Evaluation Trial (EPHITHET), the Desmoteplase in Acute Stroke (DIAS) and the Stroke Evaluation for Late Endovascular Cerebral Thrombolysis). Further research is needed to evaluate feasibility of these techniques to be used clinically in resource-poor settings and also to be able to match specific treatments to specific patients using more advanced techniques.

In each therapy that is proven to be effective, research is necessary to determine which subset of patients will benefit most from the treatment, especially in minority subgroups such as women, disabled patients, and patients with comorbidities. This guidance will aid health professionals in determining the optimal course of treatment for their specific patients. Analyses of cost-effectiveness for each intervention will also be useful in reducing the economic burden of stroke.

6.3 Prolonging the treatment window

Therapies with neuroprotectives that are aimed at slowing down the cascade of events leading to cell death have been tested, but the results have been disappointing. These unfavourable results might have been the product of many methodological errors. If neuroprotectors are to be effective in slowing down cell death this may be very useful in prolonging the therapeutic window, and therefore the management of acute stroke. Some publications have suggested that it would be beneficial to begin the use of neuroprotector earlier in the chain of care, before treatment with fibrinolytic agents. More funding is urgently needed in this specific area of research.

Currently there are multiple ongoing trials for various therapies to expand the treatment window. Desmoteplase is the only thrombolytic agent in late-stage development for acute ischemic stroke that is now tested in patients with proven stroke pathology. Further research is needed in this area to translate these practices to the bedside.

Ultrasound-enhanced thrombolysis is another promising therapy that may enhance thrombolysis. A Phase III trial is currently under way, and its results will provide guidance on further approaches to apply this therapy to patients.

Treatments for late intervention

Many therapies that are not indicated in the early stages of care because of serious complications such as cerebral haemorrhage, but they may be useful at later stages when haemorrhages are less likely to occur. Some other therapies target mechanisms that appear several hours after the onset of the symptoms. Exploitation of such therapies will
significantly increase the number of patients that could be treated leading to major improvements in healthcare provision.

One of the fast-growing areas of research for stroke therapies outside (and in some cases, inside) the acute treatment window is applications of stem cells. Though no trials have been performed on patients to date, animal studies have been producing very promising results. Many questions remain to be answered, including which type of stem cells should be used, what the best mechanism of action is, which patients will benefit most, when the optimal timing to apply the stem cells is, and what the best way is to deliver and track the cells. More research and funding are urgently needed in this emerging area of research.

7. Where does Europe have an advantage?

The European Commission (EC) has a unique research advantage because it has the power to unite scientists, patients, policymakers, health care workers, and other actors across the continent towards a common goal. Through these partnerships, the EC can foster substantial advances in the arena of stroke-related research and management. Framework Programme 7 (FP7) works towards the creation of a European research area that contributes to the development of a knowledge-based economy and society in Europe via its goals of: supporting transnational cooperation across the EU, strengthening human potential in research and technology in Europe, and enhancing the excellence of European research institutions and universities. Several large-scale, EU-funded projects established under the Health theme (six-year budget of EUR 6100 million) of the FP7 are currently under way, and will provide further insight into the future of stroke care.

The EUSTROKE initiative, with funding of nearly EUR 10 million, focuses on the “neurovascular unit” (NVU) - the complex system of neurons, microvessels, and supportive cells – as a target of ischaemic injury. This research will expand upon our understanding of this dynamic unit by looking beyond a single-cell approach towards a more integrated answer to ischaemic brain damage. The project will aim at developing new methods for targeting the NVU, in order to potentially evolve multi-targeted or combination therapeutic approaches. Past investigations into neuroprotectives focused more narrowly on neurons, and EUSTROKE researchers will expand this focus to include the entire neurovascular unit in hopes of increased translational success of these therapies.

Another major EC-funded program investigating new stroke therapies is ARISE (Affording Recovery In Stroke), which has a budget of over EUR 11 million. Its objective is to develop novel approaches to minimize the propagation of brain damage after stroke, and to repair damage if it cannot be prevented. Because of the substantial overlap between the ARISE and EUSTROKE programs, the two initiatives collaborate strongly and have joined to form the European Stroke Network (ESN, europeanstrokenetwork.eu), where researchers from all parties can share results, plan joint trials, and discuss challenges and opportunities, while being advised by a joint advisory board.

One EU-funded study in particular that many experts are hopeful for is EUROHYP-1, a phase III clinical trial that will assess the benefits of therapeutic cooling in adult patients with
acute ischaemic stroke (including efficacy, safety, and economic impact of the therapy). In animal studies, cooling to 35°C reduced the size of the infarct by about one third, and cooling to 34°C reduced it by around 45%. Thus, this study aims to determine whether systemic cooling to a target temperature of 34 to 35°C started within 6 hours of symptom onset and maintained for 24 hours, improves functional outcome at three months in patients with acute ischaemic stroke. According to Dr. Malcolm Macleod, head of experimental neuroscience in the Centre for Clinical Brain Sciences at the University of Edinburgh, “A project of this scale would not be possible without a pan-European approach—no one country or smaller group of Member States has yet managed to organize a clinical trial of therapeutic cooling for stroke, despite widespread acknowledgement that this is an important and promising therapy.” Results of the EUROHYP-1 trial are not yet available.

Another long-awaited initiative being funded by the FP7 is investigation into a “polypill” designed to prevent heart attack and stroke. The project is titled UMPIRE (“Use of a Multidrug Pill In Reducing cardiovascular Events), and is receiving EUR 3 million under the Health theme of the FP7. This low-cost one-a-day pill will contain multiple medicines: a low-dose aspirin, a statin to lower blood cholesterol, and two blood-pressure-lowering medicines. The concept behind the polypill is to make it easier for patients to take all of their needed medicines by combining them into one pill, rather than patients having to take multiple pills a day at different times, which often results in patients discontinuing the use of their medicines. UMPIRE researchers hope to investigate patient preferences regarding a polypill vs. multiple pills, as well as if the single-pill strategy actually reduces blood pressure and lowers cholesterol. The European results will eventually combine with trials carried out in Australia, Brazil, Canada, China, India, New Zealand, and South Africa. Ultimately, the final data will represent 7 000 patients across ten countries. The polypill’s low cost makes it an attractive candidate for use in low- and middle-income countries, where people often do not have frequent access to affordable health services. Its health and economic value in high-income countries will be evaluated in the UMPIRE study as well. Encouraging preliminary results were presented at the American Heart Association conference in 2012. (See Chapter 6.3).

The disease burden of stroke in Europe has not largely changed between 2004 and 2012. This means that, in addition to medicines, other stroke-care issues such as health systems are important to include when assessing the value of current stroke prevention and treatment methods. The EUROHOPE (European Health Outcomes, Performance, and Efficiency) project, with a budget of 3.99 million, will evaluate the performance of health care systems across EU Member States. Researchers will measure performance, quality, use of resources, and health care costs for five key public health issues, one of which is stroke care, which still suffers from gaps in timely access and access to effective thrombolytic treatments. They will also investigate the relationships between patient outcomes and costs of various treatments across European countries and regions, and assess potential causes behind any differences. The study will begin by investigating seven Member States (Finland, Hungary, Italy, the Netherlands, Norway, Sweden, and the United Kingdom), and expanding from there.

Horizon 2020, the programme to follow FP7, will take place from 2014 to 2020 and will be the financial instrument implementing the Innovation Union, a flagship initiative that is aimed at securing Europe’s global competitiveness. It will combine funding currently provided through the Framework Programmes for Research and Technical Development (FP), Competitiveness and Innovation Framework Programme (CIP), and the European Institute
of Innovation and Technology (EIT), and will have a total budget of approximately EUR 80 billion over six years.\textsuperscript{104}

Expanding upon the research that the EUROHOPE study will provide about health systems across Europe, Horizon 2020 is placing an emphasis on personalized health care.\textsuperscript{105} Much remains to be understood and resolved about personalized health care, including its costs, patient benefits, necessary regulatory processes, and whether it is a realistic possibility in the current health budget framework, given the high costs of screening, diagnosis, and treatment (see Chapter 8.4). Additionally, patients with comorbidities, as is often the case with stroke, present challenges. Large-scale research studies are necessary to ensure that patients receive the treatment they will benefit the most from, and the European Commission has the power to initiate such influential trials.

Future research funded by the European Commission should be on carefully chosen topics that can make important contributions to improving care for stroke, but which private sector actors, such as pharmaceutical companies, will not explore themselves. An example of such research is the aforementioned EUROHYP-1 study, which does not necessarily involve a profitable medical device or pharmaceutical that would be developed by a private company. Future areas for public sector research to explore include (a) comparative effectiveness research and (b) development of clear and safe guidelines along the entire chain of stroke care.

The European Union has the advantage of containing a large number of highly skilled professionals in many sectors throughout its diverse Member States. Thus, they are uniquely positioned to implement large-scale projects by coordinating funds and fostering partnerships to increase efficiency and reliability of research that will get necessary stroke treatments developed and implemented. Applications of these studies could potentially have positive impacts on reducing the burden of stroke throughout not only Europe, but the entire world.

8. Conclusions

Ischaemic and haemorrhagic stroke are the second leading cause of death and disability worldwide. Acute stroke accounts for 3.2% of total DALYs globally, the estimated cost of lifetime care for a stroke survivor in the US is $140,048. The mortality, economic costs, disability, and associated with acute stroke are only expected to rise as the world’s population ages.

The natural progression of stroke allows for many possible points of intervention. During ischaemic stroke, the occlusion of blood flow produces irreversible cellular death within a few minutes. Surrounding the ischaemic core is the tissue that is affected by ischaemia, but still functional and recoverable. Any therapeutic measures should be directed in stopping the progression of the ischaemia and achieving functional recovery of tissue as soon as possible. Time is a major factor in treatment of acute stroke due to the nature of the disease.
The management of patients with acute stroke requires multiple interventions, an accurate initial diagnosis, close monitoring of potential complications and skilled highly trained professionals. The evidence suggests that mortality can be reduced further and neurological disability can be avoided or improved with the appropriate treatment of acute stroke.

Major improvements in stroke care have been made since 2004. Many patients around the world are now treated in specialized stroke units which increase patient survival and improve long term positive outcomes. Increasing access to stroke units around the world should be a top priority and is an opportunity to improve stroke outcomes for many. Several recent studies indicate that the therapeutic window for thrombolysis treatment can safely be extended from three hours to four and a half hours. Recent advancements in secondary prevention, such as long term treatment with aspirin or statins, reduce stroke reoccurrence. Lastly, improvements in post stroke supportive care speed recovery and increase patients’ quality of life.

There is still a long way to go. Major improvements are needed in the chain of care, in the identification of an attack by relatives (education), early treatment (aspirin?), the prompt referral to an accident and emergency facility (mobile units), accurate diagnosis and fast and appropriate treatment (protocols and specialized units), improving access to efficacious therapeutic options, and prompt referral to rehabilitation services.

The results of trials of therapies currently in the pipeline have been disappointing, especially in the field of neuroprotectors. Promising advancements have been made in the field of hypothermic treatments and stem cell applications, though they are not yet ready for implementation in the health system. More research is necessary in these areas, especially for patients with comorbidities.

The decrease in mortality is due to the provision of complex and costly general care and not as a result of salvaging the ischaemic brain by specific stroke therapy. Most patients sadly have significant disability when they are discharged from the hospital where the society is expected to support. More efficacious treatments provided earlier in the chain of care are needed to avoid future suffering and the economic cost of increasing disability in rapidly ageing societies.

**Principal messages from the 2012 update:**

- Stroke research remains severely underfunded despite its high burden in both Europe and the world.
- A breakthrough therapy has yet to be approved and there are still no highly effective acute therapies available.
- Promising research is being done in the areas of hypothermia, stem cell therapies, and a polypill for secondary prevention of stroke.
- More clinical trials that focus on patients with comorbidities and the elderly are needed.
- Due to lack of advancement in acute pharmaceutical treatments for stroke, there should be an emphasis on prevention and improving health approaches such as specialized stroke units.
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Update on 2004 Background Paper, BP 6.6 Stroke


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Annex 6.6.1: Demographic Data on Stroke Patients and Base Population for Each Area of Socioeconomic Disadvantage

<table>
<thead>
<tr>
<th>Area of Disadvantage</th>
<th>Strokes n</th>
<th>First-Ever No. (%)</th>
<th>Male (%)*</th>
<th>Mean Age (years)</th>
<th>Current Smoker n (%)**</th>
<th>Hypertension n (%)***</th>
<th>Population Base &gt;65 Years %</th>
<th>% Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Least disadvantaged</td>
<td>346</td>
<td>253 (73.1)</td>
<td>39.1</td>
<td>77.9</td>
<td>18 (7.1)</td>
<td>118 (47)</td>
<td>17.2</td>
<td>38.5</td>
</tr>
<tr>
<td>Less disadvantaged</td>
<td>381</td>
<td>269 (70.6)</td>
<td>39.4</td>
<td>77.2</td>
<td>18 (6.7)</td>
<td>140 (55)</td>
<td>16.0</td>
<td>37.6</td>
</tr>
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<td>Disadvantaged</td>
<td>321</td>
<td>228 (71.0)</td>
<td>47.4</td>
<td>71.8</td>
<td>50 (21.9)</td>
<td>125 (55)</td>
<td>12.9</td>
<td>43.3</td>
</tr>
<tr>
<td>Most disadvantaged</td>
<td>373</td>
<td>285 (76.4)</td>
<td>49.5</td>
<td>71.5</td>
<td>59 (20.7)</td>
<td>167 (59)</td>
<td>13.5</td>
<td>42.5</td>
</tr>
<tr>
<td>Total</td>
<td>1421</td>
<td>1035 (72.8)</td>
<td>43.9</td>
<td>74.6</td>
<td>145 (14.0)</td>
<td>559 (54)</td>
<td>14.9</td>
<td>40.2</td>
</tr>
</tbody>
</table>

*Mean and proportion of first-ever strokes only; **missing values in smoking status are 59 (23%) in the least disadvantaged, 42 (16%) in the less disadvantaged, 20 (3%) in the disadvantaged, and 28 (8%) in the most disadvantaged; ***there are 10 missing values in hypertensive status (<1.0%).