3 *Patients with stroke*

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The burden of stroke

Stroke is one of the leading causes of acute medical admissions to hospitals. It is among the most common causes of death and is a major cause of disability and poor health outcomes (Box 3.1). Worldwide, 17 million people suffer a stroke each year and stroke is the third most common cause of death around the globe, accounting for 12% of all deaths, and exceeded only by heart disease and cancer (Feigin et al., 2009; Thrift et al., 2014; GBD 2013 Mortality and Causes of Death Collaborators, 2015). While its management involves a series of specific responses by the hospital, the principles underlying them – including the importance of coordinated multispeciality and multiprofessional care, speed of response in the acute episode, the importance of prevention (of both the initial episode and any recurrence), and a model of care that follows the patient along the entire pathway, from the onset of illness to recovery and rehabilitation – apply equally to many other common medical conditions, such as acute myocardial infarction, gastrointestinal haemorrhage, or the acute and chronic complications of diabetes.

Age-adjusted incidence and mortality rates for stroke have fallen significantly over recent decades, thought to be due to improvements in stroke prevention through improved management of risk factors for stroke, especially hypertension and tobacco control, and, in some places, improved acute care. Between 1990 and 2013 the age-adjusted mortality rate for stroke in developed countries fell from 113 to 67 per 100 000 (Feigin et al., 2015). However, because of increasing longevity and the strong association between stroke risk and age, the absolute numbers of people having stroke are rising year on year, from an estimated 4.3 million globally in 1990 to 6.9 million by 2013 (Feigin et al., 2015). This is leading to increasing numbers of people dying from stroke (2.1 million in 1990 to 3.3 million deaths in 2013 from ischaemic stroke), increasing disability adjusted life years and an almost doubling in the prevalence of stroke between 1990 and 2013, from 14 million

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Box 3.1 What is stroke?

A stroke is an episode of neurological dysfunction caused by disruption of blood circulation (ischaemic stroke) or bleeding (haemorrhagic stroke) in an area of the central nervous system: the brain, spinal cord or retina. Approximately 90% of strokes are ischaemic and 10% are due to haemorrhage, although there is variation between populations in the relative proportions of ischaemic and haemorrhagic stroke. There are two main types of haemorrhagic stroke: primary intracerebral haemorrhage and subarachnoid haemorrhage. This chapter will address the health care needs of patients with the most frequent types of stroke: ischaemic stroke and primary intracerebral haemorrhage. Subarachnoid haemorrhage, although important in its own right, is less common and patients typically follow different patient pathways than those with ischaemic stroke or primary intracerebral haemorrhage – subarachnoid haemorrhage will therefore not be covered in this chapter.

A transient ischaemic attack (TIA) is caused by a temporary disruption of blood supply to the central nervous system – the symptoms are short-lived but it is a warning sign that an ischaemic stroke may be about to occur. The symptoms of stroke and TIA depend on the area of the nervous system affected, but commonly include muscular paralysis, loss of sensation, loss of vision and speech and language problems. The main risk factors for stroke and TIA are hypertension, physical inactivity, tobacco smoking, other cardiovascular disease (such as diabetes or ischaemic heart disease), atrial fibrillation (AF) and increasing age.

to 26 million (Feigin et al., 2015). Essentially, changes in population demographics are outpacing improvements in stroke prevention, resulting in an increasing burden of stroke on populations and health systems, particularly in lower and middle income countries.

In addition to mortality, stroke causes a wide range of disabilities and impairments and has long-term implications for the health and well-being of survivors. These include neurological impairments such as muscle weakness or paralysis, impaired vision and impairments of speech and language skills. Up to 50% of patients will develop major depression

in the years after stroke (Ayerbe et al., 2013). Cognitive impairment is common and cerebrovascular disease is a major risk factor for dementia. More subtle cognitive problems, such as perceptual impairments, a change in personality, and profound fatigue are common, often lasting for years after the stroke (Wolfe et al., 2011). These problems are often referred to as "hidden deficits" but they account for a significant proportion of the suffering and costs that stroke causes. Effective risk reduction and high quality treatment should not only result in improvements in physical health but also reduce the future burden of dementia and mental health problems.

The financial costs of stroke are large and diverse: to the individual and their family in terms of health care and time off work; to governments in terms of medical and social care; and to wider society in terms of lost productivity. Other non-monetary costs are harder to calculate but are equally important – such as the emotional cost to family and friends of caring for a loved one who can no longer live independently.

Stroke accounts for between 2% and 4% of the total health care expenditure in developed countries. Moreover, stroke incurs substantial costs outside the health care system, reflecting survivors' high rates of disability and dependence. In 2008 the total direct and indirect costs associated with stroke were approximately £8.9 (€9.7) billion per year in the United Kingdom (Saka et al., 2009). Most costs are incurred in the initial months and years after the patient has been discharged from hospital (Saka et al., 2009). Studies from Italy (Bottachi et al., 2012), Denmark (Jennum et al., 2015) and France (Schmidt et al., 2015) have produced similar estimates of the costs of stroke in Europe, at €7000–20 000 per stroke. Almost any intervention that reduces the incidence of stroke or reduces the likelihood of long-term disability will be cost-effective in countries with expensive health and social care systems.

Evidence-based stroke care

Historically, stroke was considered a condition for which little could be done, but there is now an extensive evidence base for interventions that are effective in improving outcomes after stroke: reducing disability, improving survival and reducing the risk of stroke recurrence. Some of these interventions (such as stroke unit based care) are applicable to almost all patients with stroke, while others are limited to selected patient groups (Figure 3.1).

	Proportion of patients with ischaemic stroke applicable	Outcome	Number needed to treat to benefit	Estimated number with improved outcomes per 1000 patients with ischaemic stroke if intervention was given to all applicable patients
Stroke unit care	90–100%	Death or long-term institutionalization	19	50
Antiplatelet therapy	85–95%	Death or dependency	79	11
Early supported discharge	Up to 50%	Death or dependency	20	25
Thrombolysis	Up to 20%	Death or dependency	25	8
Thrombectomy	Up to 10%	Dependency	3	33

Figure 3.1 Number needed to treat for the main evidence-based interventions in acute ischaemic stroke

Source: Authors' compilation

Organized multidisciplinary stroke care

In the past 25 years the medical care of patients with stroke has changed enormously in high income countries. The central change has been the development of organized systems of stroke care, characterized by a move away from general medicine towards specialized multidisciplinary models of care based on the stroke unit model. Randomized controlled trials have shown that being admitted to a stroke unit improves survival and reduces long-term dependency: in the most recently updated Cochrane review of organized stroke care summarizing the results of 31 trials, the odds of death or death or dependency at one year were reduced by 14% and 18% respectively (Stroke Unit Triallists' Collaboration, 2007). Stroke units have been evaluated in many different countries and settings, and found to be effective in all types of stroke patient and in both high and middle/low income countries (Langhorne, de Villiers & Pandian, 2012). Organized models of rehabilitation care after stroke have also been found to improve outcomes. In particular, early

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supported discharge (ESD) services, where multidisciplinary care and therapy are provided in the patient's own home at a similar intensity to inpatient rehabilitation, improve long-term recovery and shorten length of hospital stay (discussed in detail later in this chapter) (Langhorne & Baylan, 2017).

Acute re-perfusion

For patients with ischaemic stroke, early treatment to restore blood flow to the affected area of the brain can limit the extent of damage and increase the patient's chance of making a recovery. Re-perfusion can be achieved either through administration of a clot-busting drug or through a procedure. The first landmark trial to demonstrate the effectiveness of thrombolysis was the National Institute of Neurological Disorders (NINDs) trial in 1995 (National Institute of Neurological Disorders, 1995), which found that the drug alteplase significantly reduced the rate of disability if given within 3 hours of stroke onset. As well as demonstrating the effectiveness of the therapy, the results also had the effect of highlighting the very poor quality of existing health care systems for patients with acute stroke, since the effectiveness of the drug was entirely dependent on very rapid recognition, triage and diagnosis. In the United States the results of this trial prompted in 1995 the first national effort to define standards about how to organize acute stroke care (National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, 1995) and the subsequent development of the Joint Commission's Comprehensive Stroke Centre hospital certification scheme. Thrombolysis has since been evaluated in a number of trials, and has been shown to improve recovery if provided to suitable patients within 4.5 hours of stroke onset (Emberson, 2014).

More recently, evidence has emerged that early physical removal of the blood clot causing ischaemic stroke (a procedure called mechanical thrombectomy) improves outcomes. If provided within 6 hours to suitable patients, thrombectomy is very effective in increasing the chance of patients regaining functional independence after stroke (Goyal, 2016).

The impact of both these approaches is, however, limited by being suitable only for a minority of patients: up to 20% of patients with ischaemic stroke may be eligible for thrombolysis and approximately 10% (McMeekin, 2017) for thrombectomy.

Prevention of complications and stroke recurrence

Evidence-based secondary prevention for stroke includes antiplatelet therapy (Sandercock et al., 2008), anticoagulation in people with AF, blood pressure-lowering therapy, and treatment with statins to lower cholesterol (American Heart Association/American Stroke Association, 2014; Intercollegiate Stroke Working Party, 2016). The risk of recurrent stroke can also be reduced in some patients by early vascular surgery (carotid endarterectomy) to the carotid arteries (North American Symptomatic Carotid Endarterectomy Trial Collaborators, 1991). Early initiation of these therapies is also effective in reducing the risk of stroke in patients with TIA (Rothwell et al., 2007). Identifying the specific cause of the stroke for each patient is an important part of stroke care so that appropriate secondary prevention can be initiated, such as long-term treatment with anticoagulation in patients with AF. As discussed later in this chapter, this involves an increasingly sophisticated array of diagnostic tests and technologies.

Most patients dying of acute stroke do not die directly from brain injury, but from the complications of immobility and impairment. Preventing complications through, for example, screening patients for swallowing problems after stroke to reduce the risk of pneumonia, and using intermittent pneumatic compression (IPC) devices (CLOTS Trials Collaboration et al., 2013) to prevent venous thromboembolism, contribute to preventing the complications of acute stroke and improving survival after stroke.

The great majority of patients with stroke do not require any surgical intervention, but early neurosurgery can improve outcomes in selected patients with very extensive ischaemic strokes (Cruz-Flores, Berge & Whittle, 2012) and in patients with certain types of intracerebral haemorrhage (Mendelow et al., 2013).

Rehabilitation

Helping people to recover, regain function and return to doing the activities and work they were doing before their stroke is an essential component of stroke care. Compared to other areas of stroke care, however, there have been very few large clinical trials of stroke rehabilitation and a relatively weak evidence base exists. There is evidence

that very early mobilization with high intensity therapy after stroke may actually lead to poorer outcomes (AVERT Trial Collaboration Group et al., 2015) than physiotherapy protocols that use more frequent but less intense spells of activity.

The stroke care pathway

Hospitals are central to stroke care but exist as components of a pathway of care that spans pre-hospital emergency medical services, acute hospital care, rehabilitation and primary care (Figure 3.2). For many of the elements of the patient pathway, there is now good quality evidence about how to organize health services to optimize patient outcomes. At the same time, we also know that in the real world there are wide variations both across Europe and within individual health economies in how stroke care is delivered.

Pre-hospital

Most people develop acute stroke out of hospital, although hospital inpatients are at high risk of stroke (particularly people undergoing cardiothoracic surgery or angioplasty) and approximately 5% of strokes

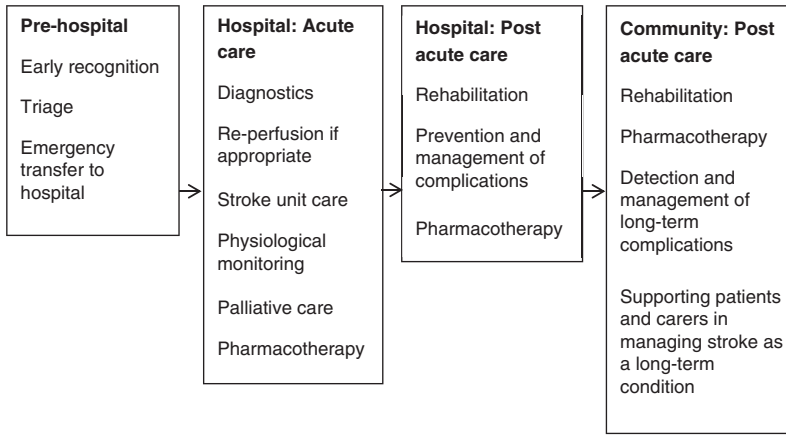

Figure 3.2 An example of a typical stroke care pathway in high income settings

Source: Authors' own

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occur in people who are already in hospital for another reason. Both stroke and TIA are medical emergencies, and delays in presentation to hospital are associated with worse outcomes. Delays in the assessment and treatment of patients presenting with TIA increase the risk of their going on to have a stroke (Rothwell et al., 2007), while pre-hospital delays in patients with ischaemic stroke reduce the chance that they will benefit from re-perfusion therapy. Patients with acute stroke should be admitted directly to hospital and patients with TIA may be managed as outpatients provided that clinics provide urgent (e.g. within 24 hours) assessment, diagnostics (brain and vascular imaging, blood tests, cardiac tests) and treatment (Luengo-Fernandez, Gray & Rothwell, 2009).

Public awareness of stroke symptoms is poor (Reeves et al., 2008) and contributes to the significant number of people presenting late after stroke onset. The FAST (Face Arm Speech Time) test was developed to improve recognition of stroke by the general public and has now been adopted worldwide into public campaigns as part of efforts to inform the general population about how to respond to a stroke (Public Health England, 2015). Promotion of this test as part of a mass media campaign in the United Kingdom appeared to be successful in increasing the proportion of people attending hospital rather than primary care with stroke symptoms (Flynn et al., 2014), but evidence of effectiveness in other countries has been variable (Mellon et al., 2013).

Pre-hospital delays in care can also be reduced by having effective systems to triage patients with possible stroke and alert the receiving hospital that a patient with stroke is on their way to hospital (Fassbender et al., 2013). Tools have been developed (e.g. the ROSIER tool) that allow for the rapid triage of patients with probable stroke pre-hospital or in the emergency department (Nor, 2005).

Acute hospital care

Upon arrival at hospital, the key diagnostic test is brain imaging with CT and/or MRI. Most patients receive a CT scan acutely in order to distinguish between ischaemic stroke and primary intracerebral haemorrhage, and the main role of MRI is in follow-up imaging, in the assessment of patients with TIA or in cases of diagnostic uncertainty (Intercollegiate Stroke Working Party, 2016). For patients who are potentially eligible for thrombolysis or thrombectomy, more advanced types of imaging

(such as CT angiography) may be used to identify appropriate patients and reducing the time from admission to brain imaging is critical in achieving delivery of these treatments quickly: co-location of scanning suites in or adjacent to the "front door" can help in reducing delays in scanning (Meretoja et al., 2013). With the development of thrombectomy as an established therapy, it is essential to rapidly develop robust stroke imaging protocols that include CT or MR angiography as well as CT (or MRI).

For patients suitable for thrombolysis, the sooner it is administered ("door to needle time"), the greater is the likely benefit. Some single centres routinely achieve extraordinarily fast times for treatment, with thrombolysis being administered in just 20 minutes after arrival at hospital (Meretoja et al., 2013), and there is evidence from the United Kingdom that treatment is fastest in larger/higher volume centres (Bray et al., 2013b). Typical door to needle times in Europe are approximately 1 hour, although there is significant international variation in times between countries (for example, a median door to needle time of 56 minutes in England and Wales compared to 45 minutes in Sweden (RiksStroke, 2018; Sentinel Stroke National Audit Programme, 2018).

Inpatient care for stroke patients should be on a specialist stroke unit (Intercollegiate Stroke Working Party, 2016). A stroke unit consists of a discrete area of a hospital ward that exclusively or nearly exclusively takes care of stroke patients and is staffed by a specialist MDT (Cochrane Stroke Group, 2013). A small proportion (less than 5%) of patients will require ICU care or surgical interventions as part of their stroke management – such as neurosurgical management of very large ischaemic strokes and intracerebral haemorrhages, or vascular surgery. However, most patients should spend the majority of their inpatient stay on either an acute stroke unit or a rehabilitation stroke unit.

Acute care in the stroke unit involves (Langhorne, Pollock & Stroke Unit Triallists' Collaboration, 2002):

- medical assessment and diagnosis
- early assessment of nursing and therapy needs
- monitoring of physiological and neurological status
- screening and prevention of complications
- mobilization
- rehabilitation therapy (physiotherapy, occupational therapy, speech and language therapy).

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Priorities in the first few hours after admission are physiological monitoring, correction of problems such as dehydration, fever and high blood sugar, and managing the complications of stroke. For patients with primary intracerebral haemorrhage, there is some evidence that rapid blood pressure lowering may improve functional outcomes (Anderson et al., 2013). Swallowing problems are common after stroke and place patients at increased risk of pneumonia if they eat or drink; patients need to be screened for swallowing problems and may be temporarily fed through a feeding tube during this time to reduce the risk of pneumonia. Delivering these interventions as a care bundle has been shown to improve patient outcomes (Middleton et al., 2011) and delays in carrying out swallow screening are associated with higher rates of stroke-associated pneumonia (Bray et al., 2017). Careful nursing care in this early period is especially important in preventing complications of stroke (Middleton, Grimley & Alexandrov, 2015), since most of the early deaths after stroke are caused not directly by the stroke itself, but by complications such as pneumonia, sepsis or venous thromboembolism.

Many patients with stroke are immobile and so are at high risk of pressure ulcers and venous thromboembolism (VTE). Managing VTE risk is complicated in patients with stroke because the risk of intracranial bleeding is increased by the anticoagulants typically used for VTE prevention. VTE risk can, however, be reduced by the use of IPC devices in patients who are unable to mobilize (CLOTS Trial Collaboration et al., 2013).

End of life care

Approximately one in six patients admitted to hospital with stroke will die in the next 30 days, and the risk of death is particularly high in older people, those with more severe stroke and patients with intracerebral haemorrhage. Providing good quality palliative and end of life care is therefore an essential component of all stroke services. This requires health care professionals on stroke units to have the relevant knowledge and skills to provide palliative care, and the availability of specialist palliative care services for patients with complex or hard to manage symptoms. Palliative care for patients with stroke is complex, and requires not only the provision of symptom control and compassionate and dignified end of life care, but also complicated decision-making

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about treatment withdrawal, artificial nutrition and feeding, and goal setting (Holloway et al., 2014).

Rehabilitation

Most patients with stroke will require a period of rehabilitation and assessment of their impairments and needs. This usually involves physiotherapy, occupational therapy, and speech and language therapy. Care models for this vary considerably between health economies. In some settings the stroke unit will provide both acute care and rehabilitation, whereas in other settings these functions are separated, with patients being transferred to a dedicated rehabilitation ward. Models commonly used in Europe include:

- inpatient rehabilitation on a stroke unit which also provides acute care
- inpatient rehabilitation on a stroke unit dedicated to providing rehabilitation
- inpatient rehabilitation in a generic rehabilitation ward or facility
- discharge home, with community-based rehabilitation provided in outpatient facilities
- discharge home, with community-based rehabilitation provided in the patient's place of residence.

In contrast to the strong evidence base concerning the organization of acute stroke care (see Figure 3.2), there is relatively scant evidence about the clinical cost and cost-effectiveness of the later stages of the stroke care pathway. One of the models of care that has been well studied is ESD. In this model, stroke patients are discharged home when medically stable, and continue to receive rehabilitation in their own home at the same intensity as they would do as an inpatient. This has several potential advantages: patients recover and learn to adapt to impairments in their own environment, leave hospital sooner and may be less exposed to hospital-related harms.

A strong body of research has shown that ESD provides better outcomes in terms of mortality, disability, institutionalization, patient satisfaction, and length of hospital stay (Langhorne & Baylan, 2017). These improved outcomes are achieved at a reasonable additional cost. The incremental cost-effectiveness ratio of stroke unit care followed by early community rehabilitation is £10 661, compared with the general medical ward without such care, and £17 721 compared with the stroke

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unit without early community rehabilitation (Saka et al., 2009). Despite this evidence, there has been limited uptake of this model of care. For example, although the service is applicable to up to 40% of stroke discharges in the United Kingdom, 25% of the regions of the country have not commissioned an ESD service and overall only 20% of patients receive the services of a dedicated team (Sentinel Stroke National Audit Programme, 2018). ESD has also been slower to develop in other high income countries in Europe, which have traditionally focused more on inpatient or clinic-based models of rehabilitation (Douw, Nielsen & Pedersen, 2015).

Recovery and long-term management

The final stage of the pathway is long-term care, management and support. This includes maintaining and monitoring secondary prevention therapy, identifying and managing the longer-term consequences of stroke, and providing support and information provision to patients and their families. In contrast with the acute phase of this pathway, it is arguable that this is an area of stroke care that has been relatively neglected by health care systems. Certainly, many stroke survivors express dissatisfaction about the quality of this longer-term support and many patients have a high burden of unmet needs after stroke (McKevitt et al., 2011). An additional challenge comes from managing multimorbidity, which is common in people with stroke (Gallacher et al., 2014) and adds to disease burden, increases the complexity of treatment decisions, and places patients at risk of the harmful effects of polypharmacy.

Workforce

Optimal stroke care is highly multidisciplinary, with a core stroke service requiring specialist doctors, nurses, physiotherapists, occupational therapists, speech and language therapists, dieticians and psychologists. Coordinating the work of the team is essential and formal MDT working (such as regular MDT meetings to discuss individual cases) is one of the components of stroke unit care (Langhorne, Pollock & Stroke Unit Triallists Collaboration, 2002).

Stroke medicine has traditionally not existed as a medical speciality in its own right, and as a result there is variation between countries in

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the specialty background of the lead physician. In most countries acute stroke care is largely provided by neurologists, but in some countries (such as the United Kingdom) stroke care is mainly led by stroke specialist physicians with a background in geriatric medicine.

Other medical specialties with important roles in the stroke pathway include neuroradiology (both diagnostic and interventional), neurosurgery, vascular surgery, intensive care, emergency medicine, rehabilitation medicine, and primary care.

Nursing care is an essential aspect of acute stroke care and it is likely that good quality nursing is one of the key mechanisms for the beneficial effect of stroke units (Middleton, Grimley & Alexandrov, 2015). In addition to general nursing skills, nurses need specific skills and knowledge in managing patients with stroke, such as screening and managing dysphagia, the positioning and mobilization of patients with muscle weakness or paralysis, prevention of pressure sores, and communicating with patients with language impairment after stroke (aphasia). Because many patients with stroke die as inpatients, nurses also need skills in providing end of life and palliative care. In some countries (such as the United Kingdom) nurses have taken on extended roles in prescribing, diagnostics, and assessing patients for thrombolysis.

In addition to the general evidence concerning nurse staffing levels and patient outcome (Needleman et al., 2011), there is specific evidence in stroke care that nursing-to-patient staffing ratios are associated with patient outcomes, with higher mortality rates for patients admitted at weekends to units with lower numbers of trained nursing staff (Bray et al., 2014).

Rehabilitation is typically carried out by physiotherapists, occupational therapists, and speech and language therapists (speech pathologists). This includes carrying out assessments of the extent of a patient's impairments and the impact of these on functioning, and planning treatment goals. Describing the full range of assessments and therapies provided by stroke therapists is beyond the scope of this chapter, but a wide range of methods may be used, from relatively simple mobilization techniques to more sophisticated interventions requiring the use of specialized equipment and aids. Therapists may also carry out additional diagnostic tests requiring additional skills and equipment. Therapists are central in planning patients' discharge from hospital and implementing adaptations or the installation of equipment in patients' homes, and have a key role in communicating with and providing psychological support for patients and their families and carers.

Stroke services also involve a variety of other allied health professionals. Dietetics is a core component of an acute stroke service, since many patients require nutritional support or assisted feeding. Problems with cognition, memory, mood or executive functioning are common after stroke and access to a clinical psychologist enables more detailed neuropsychological assessments to be carried out and appropriate information, support and therapy to be provided. Some patients with persistent physical or visual impairments may also require the provision of support aids from prosthetics and orthoptics specialists. As most patients will be discharged home on new or changed medications, pharmacists have an important role in ensuring safe prescribing, medicines reconciliation and in providing information to patients and family members about medications and side effects.

Networks of stroke care

In parallel with the development of organized stroke care in individual hospitals, many health systems have developed regional and network models of stroke care. In much of Europe and the USA a distinction is made between primary stroke centres and comprehensive stroke centres. Primary stroke centres are those with the necessary staffing, infrastructure and expertise to provide treatment for most stroke patients, but which may not have the capability to manage patients with more complex problems. Comprehensive stroke centres provide the same core stroke service but also the high technology and resource-intensive elements of care, such as interventional neuroradiology or neurosurgery, and play a greater role as centres for research and education. The European Stroke Organisation has produced guidelines setting out in detail the facilities and staffing required by comprehensive stroke centres ("ESO Stroke Centre") in Europe (Ringelstein et al., 2013), which includes 24/7 provision of advanced imaging and interventional neuroradiology. In many countries these levels of care are formally accredited through certification schemes (for example, in the USA and Germany) or through quality registers (for example, in the United Kingdom and Sweden). There is evidence from the USA (Xian et al., 2011), Japan (Iihara et al., 2014), Finland (Meretoja et al., 2013) and the United Kingdom (Bray et al., 2013a) that hospitals with higher levels of organized stroke care provide better outcomes for patients, suggesting that formal mechanisms to ensure stroke quality standards are important.

Networks of hospitals are frequently used in stroke care to provide access to the higher technology care offered in comprehensive stroke centres. These may act as the central referral centre for "hub and spoke" networks of hospitals, taking referrals from a number of primary stroke centres. Such networks have become increasingly important with the advent of more sophisticated diagnostic and interventional innovations, such as advanced brain imaging and thrombectomy, which would not be feasible or cost-effective to provide in smaller hospitals. In the United Kingdom the concept of the comprehensive stroke centre and primary stroke centre is more frequently defined in terms of hyperacute stroke units (HASUs) (providing acute care for the first 72 hours after stroke) and stroke units (for post-72 hour care).

There is evidence that these types of network can lead to better patient outcomes. In 2010 health care providers in London carried out a major reorganization of stroke services, reducing the number of acute admitting hospitals from 28 to 8 centres, each serving a population of approximately 1–1.5 million people. These eight hospitals were designated as HASUs and formal pre-hospital protocols were established so that all patients with suspected stroke would be transferred to a HASU. These HASUs provide acute care for up to 72 hours, and patients requiring ongoing inpatient treatment and rehabilitation are then transferred to a stroke unit closer to their home. The network is supported by agreed protocols for patient transfers, minimum standards for training, facilities and staffing, a common framework for payment and reimbursement from funders, and regular audit of quality and performance. Since these changes were established, there have been large improvements in the quality of stroke care in London, with stroke case fatality rates falling faster in London than in other urban areas in England (Morris et al., 2014). One of the key aspects of stroke care in London that is different from many other "hub and spoke" models of care is the concept of providing higher level acute care to all patients and not just to selected patients; the majority of patients therefore have the opportunity to benefit from early intensive acute stroke care in an HASU.

Some models of care have emerged to help tackle the issue of providing specialist stroke care at scale by providing regional systems for transferring patients to specialist centres or providing specialist input remotely. Telemedicine is widely used in stroke care and many areas have implemented telemedicine systems to transmit video, audio and imaging data so that stroke specialists at home or working in another

hospital can help in assessing patients presenting with acute stroke (Hess & Audebert, 2013). This has particular uses in delivering thrombolysis in rural areas where it may not be feasible to provide specialist stroke services in areas of low population density.

Telemedicine models may also be augmented by pathways that provide initial triage and assessment of patients in local hospitals, initiate thrombolysis if appropriate, and then transfer the patient to a hospital with specialist stroke care provision. These "drip and ship" models have been used particularly in the USA, where one in four patients treated with thrombolysis is now managed this way (Sheth et al., 2015).

Variation in quality

Within Europe there is wide variation in the organization of stroke services and in the use of policies aimed at increasing care quality, such as clinical audit, financial incentives, clinical guidelines, accreditation and regulations (Di Carlo et al., 2015). The quality of care delivery across Europe is hard to measure consistently, since even when data are available, differences in the choice and definition of quality indicators make comparisons difficult (Wiedmann et al., 2012). Nonetheless, wide variation exists even for aspects of stroke care with the strongest evidence base and most consistent inclusion in guidelines and audits, such as admission to a stroke unit or treatment with thrombolysis (Ayis et al., 2013). For example, in 2011 only 33% of stroke patients in France were admitted to a stroke unit (Schmidt et al., 2015), compared with 62% in Scotland (Turner et al., 2016). A survey of 25 European countries in 2005 found evidence of extremely wide variation in the provision of acute stroke care, with particularly poor provision of stroke unit care in Estonia, France, Greece and Portugal (Leys et al., 2007). Only 49% of the 886 hospitals included in the survey provided the minimum level of care to be considered a primary or comprehensive stroke centre. Stroke outcomes also vary significantly across Europe. For example, one comparative study of stroke outcomes between six European cities (in France, Italy, Lithuania, the United Kingdom, Spain and Poland) found three-fold variation in the risk of death after stroke (Heuschmann et al., 2011).

Poor provision of acute stroke care occurs even in higher income European countries. For example, a survey of neurology services in

Italian hospitals found that only 28% provided stroke unit based care, and large numbers of patients with stroke were admitted to hospitals without stroke units (de Falco, Leone & Beghi, 2009). Organized stroke care was also relatively slow to develop in France, with only two hospitals out of 121 surveyed in 2005 providing stroke unit care (Leys et al., 2009). Policy-makers in France have subsequently prioritized stroke care and developed a national strategy for improvements, with a particular focus on developing stroke care networks (Lebrun et al., 2011).

Information on stroke care quality is collected systematically in some European countries (Wiedmann et al., 2012), but most countries in Europe lack or have only fragmentary systems of data collection for quality improvement (Di Carlo et al., 2015). Where data are available, there is evidence of widespread variation in care quality within countries, not just between countries. For example, stroke care quality is measured in England and Wales by the Sentinel Stroke National Audit Programme (SSNAP) (Sentinel Stroke National Audit Programme, 2018) and there are wide geographical variations in a variety of care quality indicators (Figure 3.3). National clinical audits and registries in other countries show similar variation in stroke care quality, including Scotland (Scottish Stroke Care Audit; SSCA), Sweden (RiksStroke) and Germany (Wiedmann et al., 2014). Some of these variations reflect broader geographical inequalities in the provision of health care services, such as the relative under-provision of stroke units in southern Italy compared to northern Italy (Guidetti et al., 2013).

Specialist resources

The main essential component of a stroke service is a stroke unit (Figure 3.4), and stroke unit beds should be available 24 hours a day for new admissions. Stroke units are more defined by staffing than by physical infrastructure, but stroke units do have a few specialist environmental and equipment considerations. Acute stroke units need to have the equipment to provide continuous (or regular) physiological monitoring. There is evidence that care bundles of nursing interventions that focus on physiological monitoring and detecting complications are effective in improving outcomes after stroke (Middleton, Grimley & Alexandrov, 2015). Appropriate facilities and space need to be available to mobilize patients and provide rehabilitation. This might include a gym for physiotherapy and areas (such as a therapy kitchen) for occupational therapy assessments.

Figure 3.3 Geographical variation in admission to a stroke unit within four hours of admission in England and Wales

Source: January–March 2015, SSNAP

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Specialist resources required for a core stroke service	Specialist resources required for subgroups of patients
Brain imaging	Specialist diagnostics
Stroke unit	Neuroradiology/thrombectomy
Diagnostics (blood tests, ECG)	Neurosurgery
Rehabilitation	Vascular surgery
Pharmacotherapy for secondary prevention & thrombolysis	Critical care
Long-term care (follow-up, primary care)	

Figure 3.4 Specialist resources for a stroke service

Source: Authors' compilation

Brain imaging is the core diagnostic requirement of a stroke service. CT imaging needs to be available 24 hours a day for the assessment of new patients and in carrying out imaging on patients who develop neurological deterioration after stroke. Although non-contrast CT imaging is adequate for most acute treatment decisions, increasing use is being made of more advanced CT imaging modalities (CT angiography and perfusion) and MRI.

A small proportion (less than 5%) of patients will require neurosurgical intervention (Vahedi et al., 2007). Managing these patients requires access to neurosurgical infrastructure (theatres, specialist surgical, anaesthetic and nurse staffing, critical care facilities) either on site or after transfer to a referral centre. Similarly, some patients with stroke or TIA require vascular surgery for carotid endarterectomy. Patients with strokes that result in reduced consciousness may need to be managed in an intensive care unit as part of their admission. As thrombectomy services become more widely available, stroke care in high income countries will increasingly require access to neurointerventional facilities and the staffing required to provide them for patients suitable for this treatment.

Vascular ultrasound and echocardiography are also recommended as part of the diagnostic work-up for many patients (European Stroke Organisation Guidelines). All of these investigations require appropriate equipment and staff skilled in carrying out and interpreting these tests.

The requirements from stroke services of laboratory and pathology services are limited largely to common blood tests and in the

diagnostic work-up of rarer causes of stroke. POCT is widely used in the emergency room for patients being assessed for thrombolysis, where rapid results are important in achieving fast door to needle times (Rizos et al., 2009).

Stroke is not an area with a high use of specialist pharmaceuticals. The main pharmaceuticals that are required for an acute stroke service are alteplase (the only agent licensed for stroke thrombolysis in Europe) and secondary prevention agents (anticoagulants, antiplatelets, statins, anti-hypertensives).

Barriers to delivering optimal care

Training sufficient numbers of specialist staff has been a challenge in many countries. In the United Kingdom, for example, despite training pathways for physicians developing a specialty interest in stroke and the existence of stroke-specific professional organizations to support trainees and specialists, there is a shortage of physicians specialized in stroke medicine, with 25% of consultant posts remaining unfilled (Sentinel Stroke National Audit Programme, 2018). The reasons for this are unclear but might include the increasing requirement for out-of-office-hours working as stroke care has become higher in intensity. There are also fewer options for private practice for stroke specialist physicians than many other procedure-based or office-based specialties, which may affect its perceived attractiveness as a specialty. Lack of staffing resources, particularly of therapists and nursing home staff, was also identified as being one of the main barriers to improving stroke care in France (Gache et al., 2014). There is potential for tackling staff shortages by expanding the roles and skills of existing clinical staff, such as empowering nurses to manage thrombolysis calls and take on leadership roles in stroke services.

One of the key barriers to providing optimum care has been the difficulty of closing the gap between evidence and widespread implementation into practice. Here the barriers are not merely lack of financial or other resources, but also contextual and behavioural factors such as culture, organization and leadership. Indeed, implementation gaps in stroke care involve not only the high technology and resource-intensive elements of stroke care, but also the key evidence-based components of care (such as stroke units and secondary prevention): even "getting the basics right" can be difficult. For example, even 20 years after the

publication of the first trial to demonstrate the effectiveness of thrombolysis for ischaemic stroke, rates of use of thrombolysis vary widely even in highly developed health economies. In particular, the uptake of thrombolysis was initially very poor in the United Kingdom: when the National Audit Office reported on the quality of stroke care in England in 2005 it found that fewer than 1% of stroke patients were receiving thrombolysis. By contrast, during the same period 3–4% of stroke patients were treated with thrombolysis in Sweden (Eriksson et al., 2010). The low rate of implementation in the United Kingdom occurred in the context of underdeveloped stroke services and highly variable care between centres, with only 60% of stroke patients being cared for in a stroke unit and many patients waiting more than two days for a brain scan (National Audit Office, 2005). This report prompted the development of a national improvement strategy, financial investment in stroke care, an expansion in training for stroke specialists and new resources allocated to quality improvement and audit. National clinical audits have since demonstrated significant improvements in the quality of stroke care in England and an acceleration in the uptake of thrombolysis, with 11–12% of patients (of all ages) now treated with thrombolysis: rates that are comparable with other high performing health systems in Europe (Sentinel Stroke National Audit Programme, 2018).

Although stroke care has been transformed by evidence-based medicine, there are still many areas of stroke care with little evidence to guide practice. One of the reasons for this may be relative underfunding of stroke research: in the United Kingdom for every £10 of health and social care costs attributable to stroke, it received only £0.19 in funding, compared to £1.08 for cancer and £0.65 for coronary heart disease (Luengo-Fernandez, Leal & Gray, 2015). The areas of stroke care with the poorest evidence base are generally the less acute components of care, such as therapy and rehabilitation. Even fundamental questions about rehabilitation, such as when physiotherapy should commence after stroke, and at what intensity, are only now being addressed in randomized controlled trials (AVERT Trial Collaboration Group et al., 2015). Lack of evidence makes it difficult to define what optimal care in these areas should be, contributing to variations in practice. For example, there are wide variations across Europe in the amount of therapy provided to patients after stroke, which are not explained by differences in patient characteristics and likely reflect variation in access and availability (Wolfe et al., 2004; Wellwood et al., 2009).

One of the biggest challenges for stroke medicine in high income countries in the next few years will be in implementing access to thrombectomy. Current provision is largely concentrated in relatively small numbers of specialist hospitals, and even in these hospitals there may not be round-the-clock access. The main barrier to implementation is insufficient numbers of trained neurointerventionists; increasing capacity will take time and there are likely to be resource challenges in maintaining a 24/7 acute thrombectomy service that may only be used relatively infrequently, with only a minority of acute stroke patients being appropriate for this treatment. Another risk is that a focus on developing thrombectomy services will distract attention and resources away from the wider challenge of implementing good quality stroke unit based care and post-stroke rehabilitation.

The future

The challenge for the future involves the twin tasks of implementing an ever-growing evidence base on new interventions and innovations and in improving the availability and quality of the elements of stroke care that we already know to work. As has already been described, wide variations in care quality exist both across and within European countries and these will not be reduced if the focus of clinicians, funders and managers is solely on implementing the "new". Indeed, it is worth emphasizing that from a global perspective most people with stroke do not even receive the most core elements of stroke care such as stroke unit based care. By far the greatest reduction in the future burden of stroke on populations will come about not through new technologies but as a result of public health efforts to reduce stroke incidence through tobacco control, public health programmes to reduce cardiovascular risk factors (such as hypertension, obesity, alcohol and physical inactivity), increasing access to stroke unit based care and rehabilitation, and effective use of secondary prevention.

There are also examples of interventions that are still in use, despite evidence of ineffectiveness or even harm. One of the most prevalent of these is the use of antiplatelet agents in patients with AF. Historically, antiplatelet agents such as aspirin were often used as an alternative to anticoagulants to reduce the risk of stroke in people with AF (particularly in older people), but it is now known that antiplatelets provide much less benefit and are no safer than oral anticoagulants

(Aguilar, Hart & Pearce, 2007). Current guidelines therefore recommend that antiplatelet agents are not used for stroke prophylaxis in AF. However, many patients with AF are still prescribed antiplatelets, and oral anticoagulants remain underused. In England, for example, 31% of eligible patients known to be in AF in primary care were not prescribed an oral anticoagulant in 2013/2014 (NHS Quality and Outcome Framework, 2015), resulting in many thousands of avoidable strokes per year. Newer oral anticoagulants have become available in recent years that offer similar reductions in stroke risk but may have reduced risks of major complications than treatment with warfarin (Gómez-Outes et al., 2013).

As already discussed, the innovation most likely to change stroke care in the next five years in high income countries is thrombectomy for ischaemic stroke. The challenges of implementing this at scale, though, are significant and it is not certain how quickly this will become widely available experience from thrombolysis suggests that it is likely to be slow and highly variable between settings. There are other emerging areas of research that are still at early stages but may lead to significant impacts in the future. One of the most intriguing ideas is of reducing delays in thrombolysis by installing brain CT scanners in ambulances, allowing pre-hospital diagnosis of stroke type and administration of thrombolysis if appropriate. The concept has been demonstrated in a small number of centres (Walter et al., 2012; Parker et al., 2015), and although the real-world feasibility and cost-effectiveness of this model of care remain unproven, using new diagnostic technologies to facilitate pre-hospital stroke diagnosis could transform stroke care pathways. Imaging is an area of fast-moving innovation and development – for example, it is now possible to non-invasively image areas of unstable atherosclerotic plaque that are the source of the majority of strokes, and identify at an early stage the patients at highest risk of new or recurrent stroke (Tarkin, Joshi & Rudd, 2014). Further off, there is the prospect that stem cell technologies may allow the repair of established brain damage occurring as a result of stroke; early-stage clinical trials in stroke patients are already ongoing (Banerjee et al., 2014). Rehabilitation is also increasingly making use of new advances in robotics to provide therapy and augment motor functioning in patients with limb paralysis after stroke (Burgar et al., 2000).

Although exciting, most of these innovations are likely to be applicable only to a minority of stroke patients. The implementation of

these new resource-intensive interventions therefore needs to be linked to efforts to develop models of delivery that can provide these in the most clinically and cost-effective way: for many aspects of acute stroke care this is likely to mean further development of networks of care and centralization of specialist services into hub hospitals.

Perhaps of greater medium-term significance to population health will be innovations that are applicable to all patients with stroke: the shift towards increased engagement of patients in managing their own health through shared decision-making and self-management, and in the increasingly sophisticated use of data to support research, quality improvement and new models of care. For example, there is good evidence that helping patients to manage their own blood pressure leads to better blood pressure control than the typical model of clinic-based management (McManus et al., 2014); it is likely that health care services will increasingly take the role of supporting stroke survivors (and their carers) in managing stroke as a long-term condition. Similarly, health care in the future will make much more sophisticated use of real-world data such as electronic health records and clinical registries (Krumholz, 2014). For example, use of such data to generate more accurate predictions of prognosis, or to generate patient-specific estimates of the harms and benefits of interventions, can help in making better decisions about treatment and support patients in shared decision-making (Spertus et al., 2015).

Stroke care in the hospital of the mid-21st century

Stroke care has changed dramatically over recent decades, driven by the development of organized multidisciplinary care and an increasing emphasis on acute intervention. The dependency on advanced medical imaging, resource-intensive multidisciplinary care and acute treatments that can only feasibly be administered in large hospitals means than hospitals are likely to remain the cornerstone of acute stroke care with most patients being admitted for inpatient care. The hospital of the future, if it is to provide comprehensive care for patients with stroke, will therefore need to be organized and designed to deliver:

- round-the-clock access to advanced imaging, diagnostics and neurointervention facilities that are geographically located within the hospital to optimize speed of access;

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- stroke units to which patients with acute stroke are admitted without delay and which are the setting for multidisciplinary stroke specialist care;
- the appropriate environment and equipment to enable optimal provision of therapy and to support rehabilitation and recovery; and
- organized pathways of care that reduce treatment delays and support the provision of good quality therapy not just in hospital but also in the community.

In many places this means that some acute hospitals should no longer attempt to treat stroke. Rather, there is a need to find alternative models of care whereby those suffering a stroke will be taken, at least for definitive treatment, to a hospital that can provide a comprehensive care package, including rapid diagnosis and intervention where required. This will often not be the nearest facility. This could have profound implications for the organization of hospitals in a defined area, especially where they have had a high degree of autonomy. It will often be extremely challenging, politically and legally, to tackle this and each solution must be tailored to the particular context.

The critical component of stroke care services will remain not physical assets and medical devices but the MDTs of people that are the core of organized stroke unit care. Maintaining and developing this resource will require long-term investment in the training of the stroke workforce (medical, nursing and allied health professions). Providing ongoing education and training will be of increasing importance in helping clinicians keep up to date with the accelerating pace of new medical knowledge and evidence.

It will be disappointing if the next few decades do not see the development of new, high-impact drugs and devices that improve recovery after stroke, reduce complications, or help survivors manage the long-term consequences of stroke. The development of therapies that facilitate brain repair (for example, through stem cells) could be a real paradigm shift, but the brain is vastly complex and still contains many mysteries; progress in the development of new "brain regeneration" therapies is hard to predict. For patients with permanent impairments after stroke, assistive technologies (such as robotics) are likely to become much more mainstream and sophisticated, and allow more stroke survivors to live independent lives. The challenge for the future will be providing these innovations at scale in a cost-effective way and in speeding up the diffusion of new evidence into widespread clinical practice.

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The evidence of current variation in care quality and outcome points to the importance of prioritizing and developing quality improvement in stroke care. This includes supporting and developing current systems of clinical audit (SSNAP, SSCA, Riks-Stroke, Danish Stroke Register) and increasing the capacity of health care systems to deliver continuous quality improvement. As the sophistication and scope of health care data collection increase, this is likely to lead to a growing emphasis on the development of new ways of using data in stroke care as part of clinical care, research and quality improvement. It is hard to foresee in much detail what this new, data-aware world of health care will look like in practice, but it may have a transformative effect on the delivery and organization of stroke care in the next few decades.

References

Aguilar MI, Hart R, Pearce LA (2007). Oral anticoagulants versus antiplatelet therapy for preventing stroke in patients with non-valvular atrial fibrillation and no history of stroke or transient ischemic attacks. *Cochrane Database Syst Rev* 3:CD006186.

American Heart Association/American Stroke Association (2014). Guidelines for the Prevention of Stroke in Patients with Stroke and Transient Ischaemic Attack. *Stroke*, 45(7):2160–236.

Anderson CS et al. (2013). INTERACT2 Investigators. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. *N Engl J Med*, 368(25):2355–65.

AVERT Trial Collaboration Group et al. (2015). Efficacy and safety of very early mobilisation within 24 h of stroke onset (AVERT): a randomised controlled trial. *Lancet*, 386(9988):46–55. doi: 10.1016/S0140-6736(15)60690-0. Epub 16 April 2015.

Ayerbe L et al. (2013). Natural history, predictors and outcomes of depression after stroke: systematic review and meta-analysis. *Br J Psychiatry*, 202:14–21.

Ayis SA et al. (2013). Variations in acute stroke care and the impact of organised care on survival from a European perspective: the European Registers of Stroke (EROS) investigators. *J Neurol Neurosurg Psychiatry*, 84(6):604–12.

Banerjee S et al. (2014). Intra-Arterial Immunoselected CD34+ Stem Cells for Acute Ischemic Stroke. *Stem Cells Transl Med*, 3(11):1322–30.

Bottacchi E et al. (2012). The cost of first-ever stroke in Valle d'Aosta, Italy: linking clinical registries and administrative data. *BMC Health Serv Res*, 12:372.

Bray BD et al. (2013a). Associations between the organisation of stroke services, process of care, and mortality in England: prospective cohort study. *BMJ*, 346:f2827.

Bray BD et al. (2013b). Bigger, faster? Associations between hospital thrombolysis volume and speed of thrombolysis administration in acute ischemic stroke. *Stroke*, 44(11):3129–35.

Bray BD et al. (2014). Associations between stroke mortality and weekend working by stroke specialist physicians and registered nurses: prospective multicentre cohort study. PLOS Med, 11(8):e1001705.

Bray BD et al. (2017). The association between delays in screening for and assessing dysphagia after acute stroke, and the risk of stroke-associated pneumonia. *J Neurol Neurosurg Psychiatry*, 88(1):25–30.

Burgar CG et al. (2000). Development of robots for rehabilitation therapy: the Palo Alto VA/Stanford experience. *J Rehabil Res Dev*, 37(6):663–73.

CLOTS (Clots in Legs Or sTockings after Stroke) Trials Collaboration et al. (2013). Effectiveness of intermittent pneumatic compression in reduction of risk of deep vein thrombosis in patients who have had a stroke (CLOTS 3): a multicentre randomised controlled trial. *Lancet*, 382(9891):516–24. doi: 10.1016/S0140-6736(13)61050-8. Epub 31 May 2013.

Cochrane Stroke Group (2013). Organised inpatient (stroke unit) care for stroke. *Cochrane Database Syst Rev*, 9: CD000197.

Cruz-Flores S, Berge E, Whittle IR (2012). Surgical decompression for cerebral oedema in acute ischaemic stroke. *Cochrane Database of Syst Rev*, 1:CD003435.

de Falco FA, Leone MA, Beghi E (2009). Stroke in neurological services in Italy. *Neurol Int*, 1(1):e8.

Di Carlo A et al. (2015). European Implementation Score Collaboration Study Group. Methods of Implementation of Evidence-Based Stroke Care in Europe: European Implementation Score Collaboration. *Stroke*, 46(8):2252–9.

Douw K, Nielsen CP, Pedersen CR (2015). Centralising acute stroke care and moving care to the community in a Danish health region: challenges in implementing a stroke care reform. *Health Policy*, 119(8):1005–10.

Emberson et al. (2014). Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *Lancet*, 384(9958):1929–35.

Eriksson M et al. (2010). Dissemination of thrombolysis for acute ischemic stroke across a nation: experiences from the Swedish stroke register, 2003 to 2008. *Stroke*, 41(6):1115–22.

Fassbender K et al. (2013). Streamlining of prehospital stroke management: the golden hour. *Lancet Neurol*, 12(6):585–96.

Feigin VL et al. (2009). Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. *Lancet Neurol*, 8(4):355–69.

Feigin VL et al. (2015). Update on the Global Burden of Ischemic and Hemorrhagic Stroke in 1990–2013: The GBD 2013 Study. *Neuroepidemiology*, 45(3):161–76.

Flynn D et al. (2014). A time series evaluation of the FAST National Stroke Awareness Campaign in England. *PLoS One*, 9(8):e104289.

Gache K et al. (2014). Main barriers to effective implementation of stroke care pathways in France: a qualitative study. *BMC Health Serv Res*, 14:95.

Gallacher KI et al. (2014). Stroke, multimorbidity and polypharmacy in a nationally representative sample of 1,424,378 patients in Scotland: implications for treatment burden. *BMC Med*, 12:151.

GBD 2013 Mortality and Causes of Death Collaborators (2015). Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*, 385(9963):117–71.

Gómez-Outes A et al. (2013). Dabigatran, Rivaroxaban, or Apixaban versus Warfarin in Patients with Nonvalvular Atrial Fibrillation: A Systematic Review and Meta-Analysis of Subgroups. *Thrombosis*, 2013:640723.

Goyal et al. (2016). Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet*, 387(10029):1723–31.

Guidetti D et al. (2013). Monitoring the implementation of the State-Regional Council agreement 03/02/2005 as to the management of acute stroke events: a comparison of the Italian regional legislations. *Neurol Sci*, 34(9):1651–7.

Hess DC, Audebert HJ (2013). The history and future of telestroke. *Nat Rev Neurol*, 9(6):340–50.

Heuschmann PU et al. (2011). Three-month stroke outcome: the European Registers of Stroke (EROS) investigators. *Neurology*, 76(2):159–65.

Holloway RG et al. (2014). Palliative and end-of-life care in stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*, 45(6):1887–916.

Iihara K et al. (2014). Effects of comprehensive stroke care capabilities on in-hospital mortality of patients with ischemic and hemorrhagic stroke: J-ASPECT study. *PLoS One*, 9(5):e96819.

Intercollegiate Stroke Working Party (2016). *National Clinical Guideline for Stroke* (5th edn). London, Royal College of Physicians.

Jennum P et al. (2015). Cost of stroke: a controlled national study evaluating societal effects on patients and their partners. *BMC Health Serv Res*, 15(1):466.

Krumholz HM (2014). Big data and new knowledge in medicine: the thinking, training, and tools needed for a learning health system. *Health Aff (Millwood)*, 33(7):1163–70.

Langhorne P, Baylan S (2017). Early supported discharge services for people with acute stroke. *Cochrane Database Syst Rev* 7:CD000443.

Langhorne P, de Villiers L, Pandian JD (2012). Applicability of stroke-unit care to low-income and middle-income countries. *Lancet Neurol*, 11(4):341–8.

Langhorne P, Pollock A, Stroke Unit Triallists' Collaboration (2002). What are the components of effective stroke unit care? *Age Ageing*, 31(5):365–71.

Lebrun L et al. (2011). Improving stroke care: a French health-care organiser's perspective. *Int J Stroke*, 6(2):123–4.

Leys D et al. (2007). Facilities available in European hospitals treating stroke patients. *Stroke*, 38(11):2985–91.

Leys D et al. (2009). Facilities available in French hospitals treating acute stroke patients: comparison with 24 other European countries. *J Neurol*, 256(6):867–73.

Luengo-Fernandez R, Gray AM, Rothwell PM (2009). Effect of urgent treatment for transient ischaemic attack and minor stroke on disability and hospital costs (EXPRESS study): a prospective population-based sequential comparison. *Lancet Neurol*, 8(3):235–43.

Luengo-Fernandez R, Leal J, Gray A (2015). UK research spend in 2008 and 2012: comparing stroke, cancer, coronary heart disease and dementia. *BMJ Open*, 5(4):e006648.

McKevitt C et al. (2011). Self-reported long-term needs after stroke. *Stroke*, 42(5):1398–403.

McManus RJ et al. (2014). Effect of self-monitoring and medication self-titration on systolic blood pressure in hypertensive patients at high risk of cardiovascular disease: the TASMIN-SR randomized clinical trial. *JAMA*, 312(8):799–808. doi: 10.1001/jama.2014.1005.

McMeekin P et al. (2017). Estimating the number of UK stroke patients eligible for endovascular thrombectomy. *Eur Stroke J*, 2(4):319–326.

Mellon L et al. (2013). Can a media campaign change health service use in a population with stroke symptoms? Examination of the first Irish stroke awareness campaign. *Emerg Med J*, 31(7):536–40. doi: 10.1136/emermed-2012-202280.

Mendelow AD et al. (2013). Early surgery versus initial conservative treatment in patients with spontaneous supratentorial lobar intracerebral haematomas (STICH II): a randomised trial. *Lancet*, 382:397–408. (Erratum appears in *Lancet*, 382(9890):396.)

Meretoja A et al. (2013). Helsinki model cut stroke thrombolysis delays to 25 minutes in Melbourne in only 4 months. *Neurology*, 81(12):1071–6.

Middleton S, Grimley R, Alexandrov AW (2015). Triage, treatment, and transfer: evidence-based clinical practice recommendations and models of nursing care for the first 72 hours of admission to hospital for acute stroke. *Stroke*, 46(2):e18–25.

Middleton S et al. (2011). Implementation of evidence-based treatment protocols to manage fever, hyperglycaemia, and swallowing dysfunction in acute stroke (QASC): a cluster randomised controlled trial. *Lancet*, 378:1699–706.

Morris S et al. (2014). Impact of centralising acute stroke services in English metropolitan areas on mortality and length of hospital stay: difference-in-differences analysis. *BMJ*, 349:g4757.

National Audit Office (2005). Reducing Brain Damage: faster access to better stroke care.

National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group (1995). Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*, 333(24):1581–7.

Needleman J et al. (2011). Nurse staffing and inpatient hospital mortality. *N Engl J Med*, 364(11):1037–45.

NHS Quality and Outcome Framework (2015). NHS Digital.

Nor AM (2005). The Recognition of Stroke in the Emergency Room (ROSIER) scale: development and validation of a stroke recognition instrument. *Lancet Neurol*, 4(11):727–34.

North American Symptomatic Carotid Endarterectomy Trial Collaborators (1991). Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med*, 325(7):445–53.

Parker SA et al. (2015). Establishing the first mobile stroke unit in the United States. *Stroke*, 46(5):1384–91.

Public Health England (2015). *PHE encourages people to act FAST if they experience stroke symptoms* (Online). Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/400241/Stroke_press_release_020215.pdf.

Reeves MJ et al. (2008). Changes in knowledge of stroke risk factors and warning signs among Michigan adults. *Cerebrovasc Dis*, 25(5):385–91.

RiksStroke (2018). URL: www.riksstroke.org/eng/.

Ringelstein et al. (2013). European Stroke Organisation recommendations to establish a stroke unit and stroke center. *Stroke*, 44(3):828–40.

Rizos T et al. (2009). Point-of-care international normalized ratio testing accelerates thrombolysis in patients with acute ischemic stroke using oral anticoagulants. *Stroke*, 40(11):3547–5.

Rothwell PM et al. (2007). Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. *Lancet*, 370(9596):1432–42.

Saka O et al. (2009). Cost-Effectiveness of Stroke Unit Care Followed by Early Supported Discharge. *Stroke*, 40:24–9.

Sandercock PA et al. (2008). Antiplatelet therapy for acute ischaemic stroke. *Cochrane Database Syst Rev*, 3:CD000029. *Doi: 10.1002/14651858.CD000029.pub2*.

Schmidt A et al. (2015). Acute Ischemic Stroke (AIS) patient management in French stroke units and impact estimation of thrombolysis on care pathways and associated costs. *Cerebrovasc Dis*, 39(2):94–101.

Sentinel Stroke National Audit Programme (2018). *Sentinel Stroke National Audit Programme* (Online). Available at: www.strokeaudit.org.

Sheth KN et al. (2015). Drip and ship thrombolytic therapy for acute ischemic stroke: use, temporal trends, and outcomes. *Stroke*, 46(3):732–9.

Spertus JA et al. (2015). Precision medicine to improve use of bleeding avoidance strategies and reduce bleeding in patients undergoing percutaneous coronary intervention: prospective cohort study before and after implementation of personalized bleeding risks. *BMJ*, 350:h1302.

Stroke Unit Triallists' Collaboration (2007). Organised inpatient (stroke unit) care for stroke. *Cochrane Database Syst Rev*, 4:CD00019.

Tarkin JM, Joshi FR, Rudd JH (2014). PET imaging of inflammation in atherosclerosis. *Nat Rev Cardiol*, 11(8):443–57.

Thrift AG et al. (2014). Global stroke statistics. *Int J Stroke*, 9:6–18.

Turner et al. (2016). Stroke patients admitted within normal working hours are more likely to achieve process standards and to have better outcomes. *J Neurol Neurosurg Psychiatry*, 87:138–43.

Vahedi K et al. (2007). Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials. *Lancet Neurol*, 6(3):215–22.

Walter S et al. (2012). Diagnosis and treatment of patients with stroke in a mobile stroke unit versus in hospital: a randomised controlled trial. *Lancet Neurol*, 11(5):397–404.

Wellwood I et al. (2009). An observational study of acute stroke care in four countries: the European registers of stroke study. *Cerebrovasc Dis*, 28(2):171–6.

Wiedmann S et al. (2012). Variations in quality indicators of acute stroke care in 6 European countries: the European Implementation Score (EIS) Collaboration. *Stroke*, 43(2):458–63.

Wiedmann S et al. (2014). The quality of acute stroke care – an analysis of evidence-based indicators in 260 000 patients. *Dtsch Arztebl Int*, 111(45):759–65.

Wolfe CD et al. (2004). Variations in care and outcome in the first year after stroke: a Western and Central European perspective. *J Neurol Neurosurg Psychiatry*, 75(12):1702–6.

Wolfe CD et al. (2011). Estimates of outcomes up to ten years after stroke: analysis from the prospective South London Stroke Register. *PLoS Med*, 8(5):e1001033.

Xian Y et al. (2011). Association between stroke center hospitalization for acute ischemic stroke and mortality. *JAMA*, 305(4):373–80.