

## EDUCATION ARTICLES

### 21st Century Stroke - A Medical Emergency

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Stroke is the single biggest cause of major disability in the United Kingdom<sup>1,2</sup> and is the third leading cause of death in most Western countries. The condition has a profound effect on patients and relatives and is associated with a vast economic burden.<sup>2,3</sup> In the UK and other countries, these costs are on the rise and consistently consume around 5% of health care resources.<sup>2,4,5</sup> Recognition of this has raised the profile of stroke care but stroke research remains depressingly underfunded<sup>6</sup> and proven effective treatments have been difficult to introduce.

This review is based around a case vignette, which provides the framework for discussion around optimal management of patients with suspected stroke and the recent developments in stroke care.

*A 66 year old retired male was seen by the emergency general practitioner 35 minutes after onset of symptoms. The patient was fully conscious, had a left facial droop and grade 3/5 power in the left arm and leg. Blood pressure was 185/105 mmHg and the patient complained of mild headache. An ambulance was ordered. When referred to the stroke team, some 1.5 hours after onset, the weakness was confirmed and a left homonymous hemianopia and sensory inattention were noted. An urgent CT scan of the brain was performed (at three hours after onset) which revealed change consistent with early infarction in the right middle cerebral artery territory.*

#### **The Importance of Rapid Assessment and Specialist Care in Suspected Acute Stroke (and TIA)**

Acute ischaemic stroke is a treatable condition. When given promptly to an appropriately selected group of patients, recombinant tissue plasminogen activator improves outcome and reduces disability.<sup>7,8</sup> The number needed to treat (NNT) to reduce disability is only 3, and to achieve excellent outcome it is only 7.<sup>8,9</sup> Despite conditional regulatory approval throughout Europe the impact of this powerful therapy has been limited, largely because of logistical rather than medical barriers. Treatment must be delivered within 3 hours of stroke onset. As many as two thirds of otherwise eligible patients miss out on treatment because of delay in presentation

and/or early misdiagnosis.<sup>10</sup> Low uptake of acute treatment is particularly apparent in the UK, which currently holds 15th place in the European league table of thrombolysis use: 238 patients (around 0.2% of stroke incidence) were treated in the UK in 2005. More widespread implementation of acute stroke treatment is arguably the most important challenge facing stroke clinicians today and there is an urgent need for new strategies to increase the proportion of stroke patients receiving treatment. The European aim is to achieve 5% of patients thrombolysed by 2009.

Patients with a recent transient ischaemic attack (TIA) or minor stroke also require rapid investigation and treatment to minimise their risk of stroke recurrence. Fifteen to 30% of patients with stroke give a history of preceding TIA.<sup>11</sup> In some groups the risk of stroke within 7 days following TIA is as high as 31%.<sup>12</sup> Consensus guidelines which are themselves inadequate and opt for politically acceptable targets suggest only that patients with suspected TIA are assessed and investigated within 1 week.<sup>13,14</sup> In common practice, delays of several weeks can occur. In order to tackle this problem, it is recommended that fast track or rapid access neurovascular clinics are established<sup>15</sup> but even these fail to tackle the high risk of stroke in the early days after TIA. Preventative treatment must be initiated as soon as possible and if this cannot be performed in the out-patient setting - which it cannot in most centres - admission should be considered to expedite investigation and treatment. The resource implications of such an approach are minimal in comparison to the accepted practice of hospital admission for patients with atypical and low risk chest pain<sup>16</sup> but would have a considerable impact on costly and important outcomes such as recurrent strokes and long term disability.

#### **Sources of Delay**

Some of the delay to treatment in suspected stroke and TIA is beyond our control but improvements can be made. In-hospital delays to initial and specialist assessment of suspected stroke patients and their transfer to specialist

centres must be reduced. The number of rapid access outpatient clinics and access to imaging services must also be improved. Stroke services could be supported to develop their own imaging services and strategies to reduce the number of non-cerebrovascular referrals could be developed to reduce waiting times and maximise the diagnostic utility of CT scanning (discussed later).

### **Making the Diagnosis of Acute Stroke (and TIA)**

A systematic review of the predictive value of various symptoms and clinical signs encountered when evaluating suspected stroke patients has recently been published.<sup>17</sup> This and the data generated during development and validation of the stroke assessment tools (outlined below) confirm that the presence of unilateral weakness, in particular weakness of the arm and face, and a language disorder strongly suggest that a stroke or TIA has occurred. The absence of such signs and the presence of loss of consciousness or seizure activity point towards an alternative diagnosis. Diplopia, vertigo and sensory loss, while consistent with stroke or TIA, are of less value in making a clear clinical diagnosis.

Various stroke assessment tools have been developed in an attempt to tackle these issues. These were primarily developed for paramedic<sup>18,19,20</sup> and emergency room staff<sup>21</sup> to expedite transfer and hasten identification of acute stroke patients. They typically involve a screen for components of the history which make stroke less likely and for clinical signs commonly seen in stroke. These scales are simple to use and typically yield diagnostic accuracy in the range of 80-90%<sup>18,19,20,22</sup> but results can be improved further by training.<sup>23</sup> Assessment algorithms also exist for suspected TIA and increase diagnostic accuracy<sup>24,25</sup> but have not been widely used in clinical practice.

Accurate identification of stroke and TIA patients therefore appears simple but reported experience suggests otherwise. Even when patients are assessed by a stroke specialist as many as one fifth initially thought to have a stroke transpire to have an alternative diagnosis.<sup>26</sup> While in reality this figure may be slightly lower,<sup>27,28</sup> with suspected TIA, where reliance on the history is greater, misdiagnosis rates by non-specialists are high. Between 31% and 62% of patients referred with suspected TIA are found to have a non-cerebrovascular diagnosis when assessed by a stroke specialist<sup>29,30,31</sup> The majority of "stroke mimic" diagnoses are seizure, systemic infection, tumour, metabolic disturbance, including hypoglycaemia

or complicated migraine. Paraesthesiae of unknown origin, peripheral neuropathy or psychogenic and conversion disorders can also be confused.

Further refinement and the introduction of validated assessment scales into emergency rooms and general practice should be encouraged as they allow rapid identification of stroke patients and may reduce unnecessary referrals which will reduce waiting times and presumably improve outcomes.

### **Investigation of Suspected Acute Stroke**

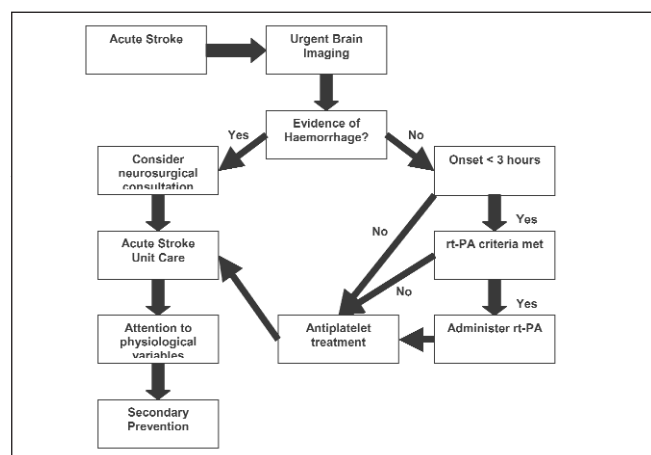
We investigate stroke patients in an attempt to confirm or refute the diagnosis, differentiate haemorrhagic stroke from infarction, inform acute treatment strategies such as thrombolysis, provide prognostic information and to identify potentially remediable risk factors. Patients should have blood glucose, urea and electrolytes and full blood count testing, an electrocardiogram and a chest x-ray. An emergency brain scan is however the crucial diagnostic test. Thereafter, and if appropriate, evidence of an underlying embolic source or significant carotid artery disease must be sought.

The choice of brain imaging modality lies between CT and MRI. All patients with suspected stroke should have an urgent brain scan. This must be performed as an emergency in those presenting within three hours of onset to rapidly differentiate ischaemic from haemorrhagic stroke. Other indications for emergency scanning include severe headache, fever, exposure to, or expected use of, anticoagulants and abnormal clotting function. There is no rationale for waiting to image patients – it delays treatment initiation and is the least cost effective approach.<sup>32</sup> A non-contrast CT brain is the most widely available test and has excellent sensitivity for identification of haemorrhage early after onset. Its sensitivity is considerably less than MRI for the identification of ischaemic change within the first 24 hours, but a normal scan in the presence of clinical evidence of stroke is accepted as consistent with ischaemia. The sensitivity of CT for detection of haemorrhage falls dramatically after 7 days, whereafter MRI becomes the investigation of choice.<sup>33</sup> Developments in technology have rendered MRI as sensitive as CT for the detection of haemorrhage in the acute phase<sup>34,35</sup> and make it the investigation of choice for all stroke patients, although at present its use is hindered by reduced availability and longer scanning times. Delays to assessment of patients with minor stroke or TIA who are referred to outpatient services mean that MRI is

often required to ensure to differentiate haemorrhage from infarction. If these delays were reduced, reliance on the more readily available CT scan would be increased and the long waiting times for MRI scanning avoided. However, a priority should be to ensure that MRI scanning is more widely available for the majority of stroke patients.

### Management of Acute Stroke

Management of acute stroke (and TIA) serves a dual purpose; to reduce the high risk of recurrent stroke and to reduce the burden of disability in established stroke. Secondary preventative measures include antiplatelet treatment, blood pressure lowering, HMG CoA reductase inhibitors, smoking cessation, carotid revascularisation and treatment of cardioembolic sources and have been reviewed elsewhere.<sup>36</sup> Acute treatment of stroke involves control of physiological variables, strategies to reperfuse the ischaemic area (thrombolytic therapy and perhaps reperfusion devices), measures to reduce growth of primary intracerebral haemorrhage (haemostatic therapy) and protection of the vulnerable, yet salvageable, ischaemic penumbra (neuroprotectant therapy). See Figure 1.



**Fig 1 Summary algorithm for management of patients with suspected acute stroke.**

Patients with acute stroke are at risk of airway compromise and often have a poor swallow – only recognised after formal testing. Basic measures to maintain the airway and early swallow assessment are required in all patients. In those with reduced conscious level and airway compromise, airway support and ventilation should be considered. Hypoxia must be avoided, although there is no evidence that patients with normal oxygenation benefit from supplemental oxygen.<sup>39</sup> Venous thrombosis rates have dropped dramatically since full-length anti-embolism stockings were routinely applied to all of our patients. Nursing care to protect against pressure sores and vigilant monitoring for the early signs of circulatory or respiratory complications such as arrhythmia or pneumonia are required.

Arterial hypertension is common following acute stroke, affecting as many as 80% of patients<sup>40</sup> and is associated with a poor outcome.<sup>41</sup> However, cerebrovascular autoregulation is impaired following acute stroke.<sup>42</sup> Perfusion becomes more directly dependent upon systemic arterial pressure such that falls in blood pressure may lead to infarct extension. This also applies following intracerebral haemorrhage but on the other hand hypertension may contribute to haemorrhage growth. These difficulties are reflected in uncertainty regarding the optimal treatment of hypertension in the early period after stroke: it is unclear whether antihypertensives should be discontinued in the acute phase, at what level of hypertension to intervene and for which targets treatment should aim. We have no adequate randomised controlled trials to guide us, although several trials are now underway (Controlling Hypertension and Hypotension Immediately Post-Stroke Trial [CHHIPS trial], Continue or Stop post-Stroke Antihypertensives Collaborative Study [COSSACS] and Efficacy of Nitric Oxide in Stroke Trial [ENOS trial]). Current guidelines suggest lowering blood pressure in the presence of encephalopathy or of aortic aneurysm with renal involvement, and withholding antihypertensive treatment unless systolic blood pressure is >220 mmHg or diastolic blood pressure is >120 mmHg. More aggressive treatment is probably required in those with intracerebral haemorrhage and in those who have received thrombolytic therapy, since the latter is contraindicated if blood pressure exceeds 185/110 mmHg.

Elevated blood glucose in the acute phase following ischaemic stroke is associated with a poor outcome,<sup>43</sup> regardless of the presence of diabetes. In a recent systematic review, blood glucose of greater than 8 mmol/l was strongly predictive of increased hospital mortality (RR 3.28, 95% CI 2.32-4.64) and poor functional outcome (RR 1.41, 95% CI 1.16-1.73).<sup>44</sup> Elevated blood glucose increases brain lactate production, which is associated with increased infarct size<sup>45</sup> and may reduce the efficacy of thrombolytic therapy.<sup>46</sup> It may also increase the risk of suffering haemorrhagic conversion of infarction. Whether lowering of elevated blood glucose after stroke actually improves outcomes remains the subject of randomised controlled trials but current guidelines suggest that glucose containing fluids should be avoided after acute stroke and either that “markedly elevated” levels should be lowered or that levels should be maintained within normal limits.<sup>47,48</sup> Either glucose-potassium-insulin or sliding scale regimens are suitable. Fever has also been associated with a poor outcome

following acute stroke.<sup>49</sup> This may be related to a detrimental effect on intracerebral metabolism, increased free radical production<sup>50</sup> or changes in blood brain barrier function.<sup>51</sup> Guidelines suggest the maintenance of temperature within normal limits, using antipyretic agents if required but it is still unclear whether this improves clinical outcomes. The role of therapeutic hypothermia is being examined and while safety and efficacy data are only beginning to emerge, induced hypothermia may represent a new treatment strategy in acute stroke.<sup>52</sup>

### Thrombolytic Therapy

Thrombolytic therapy with tissue plasminogen activator is the only licensed treatment for acute ischaemic stroke in most countries. Despite the first evidence of efficacy being published in 1995, and licence being granted for use in the USA in 1997, its uptake has been depressingly slow and is a particular problem in the UK. A conditional European licence for intravenous use within 3 hours of onset of stroke was finally granted in 2002. The number of patients receiving treatment is now increasing, as are referrals for potential thrombolysis. Thrombolytic therapy can be delivered either intravenously or via direct intra-arterial administration.

The benefits from intravenous thrombolytic therapy have been clearly shown in a recent pooled meta-analysis of the major thrombolysis studies.<sup>8</sup> The analysis considered 2775 patients treated within six hours of ictus. The odds of favourable outcome were 2.8 (95% CI 1.8-9.5) for treatment within 90 minutes and 1.6 (95% CI 1.1-2.2) for treatment between 91 and 180 minutes. Benefit was still apparent for patients treated between 181 and 270 minutes (odds ratio 1.4, 95% CI 1.1-1.9). The rate of significant intracerebral haemorrhage was 5.9% in those treated with tPA compared to 1.1% in those treated with placebo. It is important to note that this risk of haemorrhage is already accounted for in the calculation of odds of favourable outcome. These results tell us that the chances of being free of handicap after stroke are increased nearly 3 fold by thrombolytic treatment provided it is administered within 90 minutes of onset, with smaller but still significant benefits seen up to 4.5 hours. The number needed to treat (NNT) and number needed to harm provide the most readily digestible information; the NNT to avert one case of death or dependency following treatment is approximately 7, while the NNT to achieve a reduction in disability is much lower, at approximately 3, with a number needed to harm of 30.<sup>8,9</sup> Thus, for every 100 patients treated with t-PA within 3 hours, 32 will

achieve a better outcome despite approximately 3 who will suffer significant haemorrhagic change. Trials to confirm efficacy beyond the current three hour licence are in progress. One fear that held back widespread introduction of stroke thrombolysis has concerned the risk of haemorrhage if rt-PA was used outwith research settings. In practice, a rigorous audit of outcomes in several thousand European patients has confirmed that safety is at least as good as in trials, though experienced centres achieve the best results (unpublished data).

While the risk of haemorrhage should not be a deterrent to use of thrombolytic therapy, precautions must be taken to minimise its risk. Factors associated with an increased risk of haemorrhage are increasing age, extensive early infarct change on brain imaging, diabetes mellitus, elevated blood glucose and a low platelet count.<sup>53</sup> High baseline stroke severity may also be associated though these patients may derive greater benefit from treatment. Mild systemic bleeding can also occur and there is a risk of angio-oedema of approximately 1.3%, which is typically mild.<sup>54</sup> In practice, inexperienced stroke specialists usually err on the side of excessive caution, and as a result many patients with milder strokes are deprived of the opportunity of cure. Treatment rates in UK presently run at well under 0.2% of stroke patients and yet several isolated UK centres already exceed the arbitrary 5% initial target recently set for Europe (unpublished data).

Intra-arterial thrombolysis involves direct catheterisation of an occluded artery and local administration of thrombolytic agents. The advantages include a higher recanalisation rate of MCA and basilar artery occlusions, which may translate into improved outcomes,<sup>55,56</sup> the potential to use lower systemic doses of thrombolytic agents and the use of mechanical clot disruption in those with a significant haemorrhage risk. The disadvantages are limited availability and the need for specialist neuro-radiology staff: if iv thrombolysis is difficult in UK, then acute invasive intervention may be a more distant hope.

There is preliminary evidence that the use of MRI or CT based diffusion and perfusion techniques will allow safe use of thrombolytic therapy in selected patients up to 9 hours after onset. During perfusion scanning, repeated scanning of an area of brain are made as a bolus of contrast passes through it. This allows estimation of cerebral blood flow and blood volume, which in turn can be used to predict whether areas of ischaemic brain can survive – regions with decreased cerebral blood flow and volume usually infarct where as areas with normal cerebral blood

volume and reduced cerebral blood flow may survive. Thrombolytic therapy may still prove beneficial, regardless of time from onset if such potentially salvageable areas are found. Preliminary evidence to support this approach has already emerged from the MRI-based DIAS trial (Desmoteplase in Acute Ischaemic Stroke Trial).<sup>57</sup> Reperfusion rates following treatment with desmoteplase (at a dose of 125 mg/kg) were significantly higher when compared to placebo (71% vs 19.2%,  $p=0.012$ ) and clinical outcomes were also improved (favourable outcome in 60% vs 22.2%,  $p=0.009$ ). A further phase III study (DIAS II) is now underway and also incorporates a CT based entry criterion.

Our emphasis must be on rapid and safe delivery of intravenous thrombolytic therapy to all suitable patients by experienced centres. Given the treatment effect size and tight time window this should be given at least the same priority as attempts to achieve recommended door to needle times for thrombolytic treatment of ST elevation myocardial infarction.

### **Aspirin Treatment**

Patients with ischaemic stroke should be treated with aspirin. The effect size is modest but important in public health terms; for every 1000 patients treated with aspirin in the acute phase, approximately nine deaths or non-fatal strokes will be prevented.<sup>58,59</sup> If patients receive thrombolytic treatment, aspirin should be deferred for 24 hours.

### **Specific Treatment for Intracerebral Haemorrhage**

Supportive treatment is indicated as for all types of stroke although the thresholds for blood pressure reduction are likely to be lower. Approximately 15% of cases of intracerebral haemorrhage are associated with warfarin use and the risk of death and disability in these patients is higher.<sup>60</sup> Rapid reversal of anticoagulation improves outcomes in these patients.<sup>61</sup> All patients with a suspected stroke whilst taking anticoagulants must have urgent brain imaging performed. We should not delay imaging whilst awaiting an INR result: in the presence of a low INR, a scan is still needed to inform decisions regarding further anticoagulation. If haemorrhage is confirmed, treatment should also be initiated prior to INR results. Vitamin K in combination with fresh frozen plasma or prothrombin concentrates can be used with the latter being the agent of choice due to quicker action and a lesser fluid load.

At present, there is no specific licensed treatment for spontaneous intracerebral haemorrhage but just as in ischaemic stroke, there are exciting developments. Recombinant activated factor VII (rFVIIa) is a licensed treatment for bleeding in haemophiliacs who are resistant to factor VIII replacement. It is a powerful initiator of haemostasis even in patients with normal coagulation. It has been widely used in emergency surgery and trauma with considerable success. We know that haemorrhage growth occurs in the early hours after onset and recent trial data suggest that rFVIIa can limit this with ensuing reductions in mortality and disability, provided treatment is administered within 4 hours of onset.<sup>62</sup> Three month mortality was 18% in the treatment groups compared to 29% in the placebo group – a relative risk reduction of 38% ( $p=0.02$ ). The odds of improved functional outcome were also improved by treatment. Because of its procoagulant effect, treatment may transiently promote thrombosis. Thromboembolic events were more common with treatment (7% vs 2%,  $p=0.12$ ) and arterial thromboembolic events were significantly increased (5% vs 0%,  $p=0.01$ ). However, these risks must be kept in perspective – most of the events were minor and not associated with permanent harm whereas the mortality of untreated intracerebral haemorrhage exceeds 30% and only around 20% regain functional independence.<sup>63</sup> A trial to explore the risk-benefit ratio further should report shortly.

### **Neuroprotectant Strategies**

Neuroprotectant drugs may help us to salvage tissue within the ischaemic penumbra. The penumbra is the region where blood supply is significantly reduced but collateral flow allows energy metabolism to be maintained.<sup>64</sup> Its viability depends on the depth and duration of ischaemia. If blood flow is restored, some of this tissue may be saved. However, during the time lag to restoration of blood flow, a physiological cascade occurs which places penumbral tissue at further risk. Cellular metabolism becomes anaerobic and acidosis ensues. Sodium-potassium transporters become dysfunctional leading to a rise in intracellular osmolarity and cytotoxic oedema develops. Intracellular calcium increases and ultimately the process becomes self-perpetuating with further rises in intracellular calcium, possibly because of release of intracellular glutamate.<sup>65</sup> Rises in intracellular calcium are central to apoptosis and cause lipase, protease and free radical activation. Blood brain barrier integrity is reduced<sup>66</sup> and if breached, blood components can enter the interstitial space causing vasogenic oedema and increasing the risk of haemorrhagic transformation, with

or without thrombolytic treatment. Furthermore, even if reperfusion occurs, the penumbra is vulnerable to the effects of reperfusion injury<sup>67</sup> where, following restoration of blood flow, further free radical formation and release of harmful neurotransmitters can occur. While these processes can be harmful, they provide a further therapeutic target. Damping down these mechanisms could prolong the life of the penumbra - effectively buying time until recanalisation occurs - and could maintain blood brain barrier integrity, reduce oedema and haemorrhagic transformation, and reduce reperfusion injury. Such strategies may also be of benefit in the perihemorrhage region in intracerebral haemorrhage.

Unfortunately, this has been notoriously difficult to achieve. In excess of 11000 patients have participated in more than 65 clinical trials of neuroprotectant strategies and it was increasingly feared that such approaches would never become fruitful. Recently however, the first real evidence that a neuroprotectant has clinical efficacy has emerged.<sup>68</sup> NXY-059 is a novel free radical trapping agent<sup>69</sup> that limits infarct size and preserves brain function in animal models of stroke. It is the first neuroprotectant to be developed following the STAIR criteria.<sup>70</sup> In man, NXY-059 is administered as a 72 hour intravenous infusion. In the recently reported SAINT I trial, 1772 patients within 6 hours of onset of acute ischaemic stroke were randomised to receive NXY-059 or placebo. Treatment significantly improved disability at 3 months after stroke as measured by the modified Rankin scale (mRs, a categorical scale from 0-5, with 0 describing no symptoms and 5 indicating patients who are bed-ridden and require full care). The mRs is the preferred clinical endpoint in acute stroke trials. With NXY-059 compared to placebo, the odds for improvement in disability were 1.2 (95% CI 1.01-1.42). There was no reduction in mortality but 4.4% more became asymptomatic (modified Rankin score of 0) and 3.7% more were able to walk without help (modified Rankin score of < 4). NXY-059 appeared free from adverse events apart from a slight excess of mild hypokalaemia. An intriguing result was a reduction in the rate of haemorrhagic transformation amongst those who had been treated with rt-PA and who received NXY-059 rather than placebo (2.5% vs 6.4%,  $p=0.036$ ). Benefits were also seen on Barthel index and neurological scores soon after stroke (unpublished data). Secondary endpoints comprising other functional and disability scores at 3 months were not improved, but the trial was not powered to study these.

The results of the SAINT I trial are encouraging and while the treatment effect was modest, even limited improvements in functional ability that can be offered to a high proportion of the acute stroke population could reduce dependency and have a significant economic effect. If efficacy is confirmed by the ongoing SAINT II trial, new horizons for treatment and research will have opened.

### Management of Mr X

Mr X suffered an acute stroke. He accordingly underwent emergency brain imaging, which showed subtle early ischaemic change in the right middle cerebral artery territory. There had been unfortunate delays in his transport to hospital, referral to the stroke team and time to imaging. Nevertheless, thrombolytic therapy was administered without complication at 3 hours 5 minutes from onset – beyond the licensed limit but still within a range in which meta-analysis suggests continued benefit. However, because of the delays his odds of an excellent outcome were only half of those achieved by treatment within 90 minutes of onset. His follow up CT scan showed a small infarct in the right MCA territory with no evidence of haemorrhage. He made a good recovery and was discharged home, to live independently, 4 days after admission. His ECG, chest x-ray, carotid imaging and blood tests were all normal. He was established on aspirin treatment, a statin and an ACE inhibitor with a plan for early out-patient clinic review.

### Conclusions

Stroke is a clinical emergency. Despite being a devastating process, rapid triage and treatment deliver improvements in outcome and reductions in death and disability. Safe medical treatment of both ischaemic and haemorrhagic stroke is available but is hindered by limited availability and delays to assessment and investigation. All patients must be managed in centres where they are afforded specialist stroke unit care, immediate brain imaging and the opportunity to receive thrombolytic therapy should haemorrhagic stroke be excluded. Further treatments are likely to be introduced in coming years, not only extended treatment for ischaemic stroke but also effective treatment for intracerebral haemorrhage.

In order to ensure optimal results we must continue to raise the profile of acute stroke care and further develop our services. Twenty-four hour imaging, including perfusion/diffusion techniques, must become readily available and all patients with acute stroke must be managed in experienced centres. Treatment of this condition must become the rule rather than the exception.

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