Stroke care—a work in progress

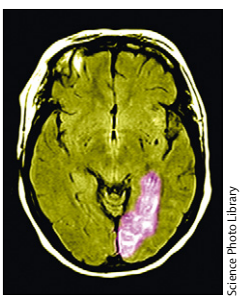
Stroke is an important cause of death and disability in all countries. According to The Stroke Association, some 150 000 people in the UK have a stroke each year, culminating in about 5300 deaths. In the USA, almost 136 000 people died after a stroke in 2007; substantial inequalities were apparent, with an age-adjusted death rate for black men of 67·1 per 100 000 compared with 40·2 for white men. Despite increases in life expectancy, rates of stroke death in developed countries have fallen by 40% or so over the past four decades owing to successive incremental improvements in clinical care. Yet estimates for developing regions, including south Asia, are that corresponding rates have increased by perhaps 100% in the same timeframe. This alarming increase reflects several underlying factors, including genetic predisposition in some populations and a breakneck westernisation of lifestyles. Perceived clinical needs in the developing world seem likely both to increase and to expand geographically in coming decades.

In *The Lancet*, Peter Rothwell, Ale Algra, and Pierre Amarenco discuss one of the important themes that has contributed to improved stroke outcomes in developed countries—a targeted and multifaceted approach to secondary prevention. It has been recognised that in many cases a fatal or disabling stroke is presaged by a transient ischaemic attack or minor stroke. Therefore, guidelines advise precipitate treatment within 7 days of an initial event—typically antiplatelet treatment, such as low-dose aspirin, or anticoagulation in patients with atrial fibrillation. In the longer term, blood-pressure reduction, for example a combination of a thiazide diuretic and angiotensin-converting-enzyme inhibitor, is expected. Statin treatment, too, is now widespread in secondary and primary prevention of stroke. As in primary prevention, advice on lifestyle factors that affect risk of stroke—avoidance of smoking and alcohol consumption, as well as improvements in diet and exercise—is a priority in people at elevated risk of stroke.

It is estimated that stroke patients occupy 20% of the acute hospital beds available in the UK, and about 25% of long-term beds; the costs to the health system are therefore substantial. Deficits in physical and cognitive function as a consequence of stroke are often profound, and can be expected to affect the quality of life of patients and their families dramatically. Heterogeneity in patients' age, neurological deficit, and prospects of recovery means that protracted care and rehabilitation are often necessary, and outcomes uncertain. Also in *The Lancet*, Peter Langhorne, Julie Bernhardt, and Gert Kwakkel review approaches to rehabilitation after stroke, both in hospital and after patients have returned home. The benefits of multidisciplinary management in the context of a stroke unit are well recognised, where a cyclical algorithm comprises assessment and definition of outcome goals, followed by intervention towards achievement of the goals set and subsequent reassessment. In general, rehabilitation will be started as soon after a stroke as practicable, with intensive approaches favoured. Rehabilitative modalities that have been tested in randomised trials range from specific interventions, such as gait training for restoration of walking, to complex interventions (including occupational therapy) to assist in recovery of activities of daily living. In an accompanying piece, Kelly Morris reports on a collaborative project aimed at improving rehabilitation after stroke in Accra, Ghana, illustrating some of the challenges in translating multidisciplinary practice to an African setting.

Imaginative new approaches to stroke rehabilitation are in evidence—in a recent article in *Stroke*, Gustavo Saposnik and colleagues reported a meta-analysis on the benefits of virtual reality activities in people burdened with motor deficits of the arm after a stroke. Along with observational evidence, five small randomised trials yielded an odds ratio of 4·89 (95% CI 1·31–18·3) for comparison of a programme of daily virtual reality activities with physical therapy, on a recognised scale for assessment of motor recovery. Time will tell whether such interventions, which have been tested so far in selected groups of patients, find widespread use in management of recovery after stroke.

The brain remains a daunting terrain for scientific study, and a limited understanding of its function in health and disease hampers research on stroke and other neurological diseases. In the future, whether in investigating the therapeutic potential of selective serotonin reuptake inhibitors or the use of neuroimaging to target rehabilitation to specific patients after stroke, the multidisciplinary approach that has been of such benefit in patient care should be translated more strongly into the culture of research on this devastating neurological condition. ■ *The Lancet*



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For the **meta-analysis on virtual reality in stroke rehabilitation** see *Stroke* 2011; **42:** 1380–86

Fighting fake drugs: the role of WHO and pharma

Reuters

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Counterfeit medicines pose a serious threat to public health. Up to 15% of all drugs sold worldwide are estimated to be fake. Last year, WHO, at the request of member states at the 2010 World Health Assembly (WHA), convened an intergovernmental working group on counterfeit medicines tasked with deciding the agency's role in tackling this global scourge. The intergovernmental group was required to make specific recommendations to this year's 64th WHA (May 16–24). They will, however, fail in this mission. Although mandated in May, 2010, the group met only once at the end of February this year and decided on one definite thing: they needed more time.

How can the group be more productive this year? At the February meeting, some member states expressed their desire to draw up a legally binding international instrument designed to criminalise the manufacture, export, import, and trade of counterfeit medicines, effectively a global treaty against fake drugs. A treaty would make counterfeit medicines illegal and it should be pursued with vigour by this year's WHA, following the model of another successful WHO treaty, the Framework Convention on Tobacco Control.

The drug industry has expressed support for such an agreement, but it could contribute much more to the fight against fake drugs. At present, all major drug companies notify the Pharmaceutical Security Institute about any counterfeiting that their surveillance operations detect, and it pools the information. The Institute's database, therefore, holds vital information about the global extent of counterfeiting, the categories of drugs being falsified, and the locations where fake drugs are being marketed. But the database is confidential. Evidence of a dangerous iatrogenic epidemic is thus being hidden by industry and this situation must change. The case for open data sharing in science is made in a Comment in today's issue; the Institute should take note.

This year's WHA and the drug industry have a chance to take concrete steps within the coming months to combat the deadly trade in fake medicines. These opportunities should not be squandered. ■ *The Lancet*

Salt and cardiovascular disease mortality

Corbis

The debate over salt, blood pressure, and health has been ongoing since the US Government recommended salt reduction to treat hypertension in the 1970s. A May 4 study in the *Journal of the American Medical Association*, has rekindled controversy. Jan Staessen and colleagues found that systolic blood pressure positively correlated with 24-h urinary sodium excretion. Surprisingly, lower sodium excretion predicted higher cardiovascular disease (CVD) mortality. The researchers concluded that their findings did "not support the current recommendations of a generalized and indiscriminate reduction of salt intake at the population level".

These findings have made sensational news. Some media have reported the study as showing that a low-salt diet is ineffective. However, many experts on salt and its health effects are much more critical. Peter Briss, a medical director of the US Centers for Disease Control and Prevention, criticised the study as being small with low event rates and relatively young participants. Walter Willett, Chair of the Department of Nutrition at Harvard School of Public Health, also pointed out other weaknesses—unreliable measurement of sodium intake, failure to account for key factors that influence sodium intake and heart disease risk, and missing or incomplete urine data from large numbers of participants. In fact, the study measured participants' salt intake by just one calculation of urinary sodium excretion at the start.

This study is disappointingly weak and contributes little to our understanding of salt and disease. It is likely to confuse public perceptions of the importance of salt as a risk factor for high blood pressure, heart disease, and stroke. Questions of intervention and outcome, such as sodium intake and CVD events, cannot be answered by small observational studies. It is dangerous to jump to conclusions on the basis of single studies and ignore the totality of evidence. At a time when CVD is the world's leading cause of death and excess dietary sodium has convincingly been shown to be a serious public health hazard, the results of this work should neither change thinking nor practice. ■ *The Lancet*

For the ***JAMA* study** see http://jama.ama-assn.org/gca?gca=jama%3B305%2F17%2F1777&allch=&submit=Go

For **Peter Briss's comment** see http://www.nytimes.com/2011/05/04/health/research/04salt.html?_r=2&ref=health

For **Walter Willett's comment** see http://www.hsph.harvard.edu/nutritionsource/salt/jama-sodium-study-flawed/index.html

Endovascular coils for cerebral aneurysm: HELPS has arrived

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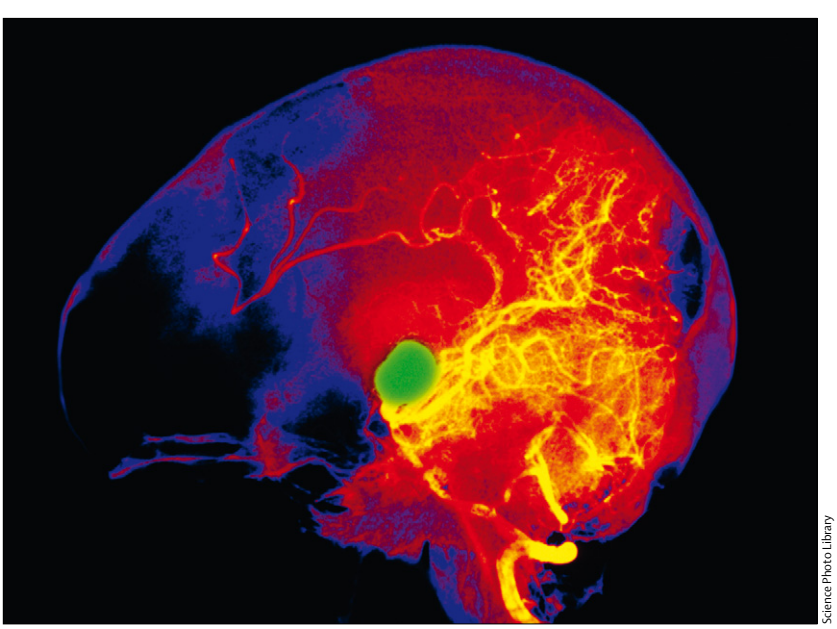
The publication of a randomised trial comparing two types of endovascular coils for cerebral aneurysm treatment in *The Lancet*[1] shows again that high-quality research can, and indeed should, be done in the field of endovascular treatment of cerebrovascular diseases. HELPS randomised 499 patients to one of two different coil types: a standard platinum coil or a hydrogel-coated coil that expands to fill the aneurysm. The primary outcome, angiographic recurrence of the aneurysm combined with procedure-related morbidity or death, was not significantly different between the groups (odds ratio 0·73, 95% CI 0·49–1·1, p=0·13). We agree with the conclusions of the investigators that randomised trials of complex interventional neuroradiological procedures are feasible and essential to quantify any associated risks and benefits.

One difficulty in the design and interpretation of endovascular trials is deciding what outcome to measure. Bioactive coils were first introduced a decade ago, in an attempt to improve angiographic outcomes through the generation of a healing response in the blood-vessel wall. It was hoped that such a response would lead to fewer recurrences and, ultimately, a reduction in the risk of late bleeding. However, with the early generations of platinum coils,[2] the re-bleeding risk is (fortunately) exceptionally low. Nonetheless, we are left with angiographic outcome as an important endpoint in HELPS, because it is generally assumed to be a reasonable surrogate measure of risk of future aneurysm rupture.

Apparently in an effort to reconcile some of the ambiguity of angiographic versus clinical outcome, HELPS used a composite endpoint, which leads to several questions.[3] Are the component endpoints of similar importance to patients? Patients would probably not weight being dead or disabled (one part of the composite endpoint) equally to suffering from a major angiographic recurrence (the other part of the composite endpoint). For example, 30% of patients had a major recurrence, defined as one that could theoretically be re-treated, yet only 3% of patients were actually re-treated; this disparity suggests that these recurrences were not so major after all. Did endpoints with high and low importance occur with similar frequency? Recurrence occurred about twice as frequently as death or dependency; because these frequencies are on the same order of magnitude, this criterion seems well satisfied. Are the component endpoints likely to have similar relative risk reductions? The frequency of angiographic recurrence was lower in the hydrogel coil group than in the control group, but death and disability were much the same between the two groups. Use of angiographic findings alone as the primary outcome would have allowed the investigators to conclude specific benefits of hydrogel-coated over platinum coils, potentially streamlining and clarifying the take-home message of the trial.

The choice of a composite endpoint approach is not just an academic exercise. Finding clinically meaningful endpoints in trials of coils is problematic. In the ISAT trial,[4] death and disability rates were high enough to allow statistically meaningful comparative measures of outcomes between groups. Patients who are enrolled into trials comparing various endovascular devices tend to have similar (low) rates of short-term death and disability (again, fortunately), making such rates impractical as primary endpoints. Investigators have looked to angiographic endpoints, because angiographic recurrence has historically been perceived as the Achilles heel of these devices, leading to the custom of surveillance imaging to assess for recurrences. However, mounting evidence indicates that angiographic recurrence can be an inadequate surrogate for the health and wellbeing of a patient.



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Angiogram showing cerebral aneurysm (green)

Enough about endpoints. What we really want to know is: should we use hydrogel coils in our patients? For medium-sized ruptured aneurysms, if we want to avoid angiographic recurrence, HELPS offers evidence of benefit of hydrogel over platinum coils. Before extending that conclusion to all ruptured aneurysms, the still unanswered issue of hydrocephalus might need to be taken into account.

What else can HELPS help with? The trialists have kindly provided us with several provocative analyses that can shape future trials. First, hydrogel-coil-associated hydrocephalus remains a victim of the statistics of rare events; even in this trial, the event rate was so low that no statistically significant difference between groups was recorded. Rates provided by HELPS can improve power estimates for future study of hydrocephalus and meningeal reaction.[5] Second, the recorded benefit of hydrogel coils in medium-sized aneurysms suggests that future trials of endovascular aneurysm treatments might benefit from narrowed inclusion criteria. These medium-sized aneurysms seem to represent the statistical sweetspot (not too small, when all coils do well, and not too big, when no coil does well) for comparing coil technologies; investigators should be aware, though, that the feasibility and generalisability of trials with narrow inclusion criteria might be compromised. Finally, treatment targets, including the proportion of hydrogel coils used, could be worth investigating. These findings might provide support for mechanistic and biological theories of why hydrogel-coated coils can be beneficial in the treatment of aneurysms.

HELPS was a successful trial, providing us with some important answers and several questions to consider in the future.

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DFK has applied for grants to support preclinical research from eV3, MicroVention, Sequent, NFocus, Micrus, Cook, AthroCare, CareFusion; and his institution has received payment for development of educational presentations from eV3 and CareFusion. AJM has a consulting agreement with Micrus Endovascular Inc and Covidien Inc.

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Hydroxycarbamide for sickle-cell anaemia in infancy

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The inherited disorders of haemoglobin, sickle-cell anaemia, its variants, and the thalassaemias, are by far the commonest monogenic diseases. An estimated 300 000 babies are born each year with these conditions, mainly in middle-income and low-income countries.[1] Last year, the US National Institutes of Health held a symposium to commemorate 100 years of research on sickle-cell disease since it was first described by the American physician James Herrick in 1910.[2] It was the first disease to be characterised at the molecular level, as reported in Linus Pauling's famous 1949 paper,[3] and much has been learnt about its pathophysiology. However, much less progress has been made in prevention and management. Because of the remarkable phenotypic variability, prenatal diagnosis has been applied less frequently than for the β thalassaemias. Although neonatal screening and the use of prophylactic antibiotics or vaccines has reduced associated mortality due to infection in early life in higher-income countries, and the symptomatic management of various complications, including stroke, has improved for many patients, sickle-cell anaemia remains a crippling disease.

For reasons that are still not absolutely clear, patients with sickle-cell anaemia or β thalassaemia continue to produce variable amounts of fetal haemoglobin (HbF), throughout their lives. Many years ago, we observed that patients with higher concentrations of HbF tend

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