

# A strategy for stroke

**Professor Martin M Brown** describes the circumstances that led him to dedicate his career to stroke research and reveals the ways in which understanding of the condition is changing



## Why did you initially pursue a research interest in stroke?

As a Senior House Officer at the Hammersmith Hospital, UK, in 1976, I worked for Professor Jack Shillingford on the coronary care unit (CCU). This had been one of the first of its kind in the world, with the aim of researching ways to improve the care of patients with myocardial infarction. Patients were rushed by ambulance directly to the CCU, where they were monitored and treated intensively. It struck me at the time how extraordinary it was that patients arriving at the hospital with cerebral thrombosis, a similar problem but in the brain, were virtually ignored. It was then that I resolved to specialise in stroke and decided that what was needed to advance stroke care was acute stroke units and research into stroke treatment. It was more than 30 years before the UK's National Health Service (NHS) finally accepted the need for acute emergency admission of stroke patients to hyperacute stroke units.

## How have treatment strategies for stroke developed in recent years?

In addition to the major advances in service provision, there have been extraordinary changes in the management of acute stroke in the last few years, firstly with the advent of early aspirin therapy, then the introduction of intravenous thrombolysis and, more recently, the development of endovascular techniques for thrombus extraction from cerebral arteries. Prevention therapies have evolved from relying on aspirin and less-than-satisfactory control of

hypertension to current regimes of intensive therapy with dual antiplatelet therapy, targeted blood pressure lowering and statin therapy to lower cholesterol. It is likely that the introduction of statins and their widespread use has had the greatest therapeutic impact on stroke rates, although improved screening for hypertension, reduction in smoking, healthier diets and higher standards of living have had an equally important impact in the community.

## Are there suitable models that can be used to predict a patient's stroke risk?

Although a very large number of risk factors have been identified, very few modelling studies have attempted to predict an individual's future risk of stroke. One exception is the Oxford Stroke Prevention Research Unit tool for predicting the risk of stroke in patients with recently symptomatic carotid artery stenosis, but this uses data from trials of carotid stroke treatments conducted more than 20 years ago, and therefore needs to be updated. Furthermore, existing risk calculation tools such as the Framingham Risk Score take into account too few risk factors to be sufficiently reliable.

## Stroke research receives significantly less funding than other major illnesses, such as cancer and heart disease, despite its high levels of morbidity and mortality. Why is this, and how can this be changed?

The reasons why stroke research has received significantly less funding are complex. One reason may be the outdated perception that there is no treatment for stroke, which of course is no longer true. Another reason may be that it is seen as a disease of the elderly, which again is not true; strokes can occur at any age, and indeed 25 per cent of stroke patients are under the age of 65. A third reason may be the fact that stroke is not seen as a painful condition, and perhaps the fear of pain from heart attack and cancer influences individuals' charitable donations.

There is a lot of ignorance about stroke, which could no doubt be changed by government initiatives and pressure groups; for example, the Stroke Association had considerable success in persuading the UK Government to improve stroke services through the National Stroke Strategy. However,

the Stroke Association still remains vastly underfunded compared to the cancer and heart disease charities, which means its ability to influence external funding and fund research and new posts is very limited, compounding the inequality in provision.

## What would you consider to be your greatest professional achievement to date?

On the clinical side, developing three acute stroke units in three hospitals over 20 years, each of which improved on the previous one. On the educational side, establishing stroke medicine as an officially recognised subspecialty with a specialist training programme and curriculum. On the research side, organising and completing the International Carotid Stenting Study. That said, although I may have had the ideas that led to these initiatives, none of it would have been possible without the support and hard work of many others.



# Treating carotid atherosclerosis

Since the 1990s, Professor Martin M Brown of the **University College London Institute of Neurology** has been leading international, multicentre clinical trials to establish suitable treatments for reducing stroke risk in individuals with carotid artery stenosis

**STROKE IS THE** largest cause of adult disability and third largest cause of death in the UK and yet, when compared to other major illnesses such as cancer and heart disease, research into stroke is significantly underfunded. Many myths have historically surrounded strokes; that little can be done to prevent them, for example, or that their effects are limited to the elderly. It was because of this state of affairs that, over three decades ago, a young Martin M Brown decided to devote his career to improving stroke outcomes for patients. Now Professor of Stroke Medicine at the University College London (UCL) Institute of Neurology, Brown has seen considerable improvements since his early days in healthcare. However, much work remains to be done if stroke mortality and morbidity rates are to be reduced still further.

## CAROTID CARE

20 per cent of strokes are caused by narrowing (stenosis) of the internal carotid artery, which supplies the eyes and brain with oxygenated blood; this therefore constitutes a major subset of stroke cases. In 1988 Brown joined the North American Symptomatic Carotid Endarterectomy Trial (NASCET) in Canada as a neurological coordinator. "This stimulated my interest in both carotid disease and clinical trials," he reveals. Upon returning to the UK, Brown obtained a grant to further investigate this area – and thus the Carotid and Vertebral Transluminal Angioplasty Study (CAVATAS) was born.

The first international, multicentre trial to investigate endovascular treatment of carotid stenosis, from 1992-97 CAVATAS recruited over 500 carotid artery stenosis patients. Following its subjects for up to 11 years, the ultimate aim was to compare the long-term outcomes for patients given endovascular treatment by carotid angioplasty or stenting against conventional endarterectomy (carotid surgery). A number of interesting results emerged, including the finding that, although there was no significant difference in the rates of major stroke, restenosis (re-narrowing of the arteries) was more likely to occur following endovascular rather than surgical treatment. The results of the trial had a significant impact on medical guidelines and practices. However, the findings were not ultimately definitive because the stroke rates in the trial were considered too high and because the study became outdated after angioplasty was completely replaced as a technique by carotid stenting.

## SEARCHING FOR ANSWERS

Faced with wide confidence intervals and a clear need for additional long-term data, Brown decided to remedy the situation with a second international, multicentre project: the International Carotid Stenting Study (ICSS). This randomised clinical trial sought to establish the effectiveness of stenting compared to endarterectomy by following 1,700 participants across 50 centres spanning Europe, Canada, Australia and New Zealand over the course of a decade, from 2001 onwards.

This time round, the project produced some definitive results, including the finding that the risks associated with carotid stenting and surgery were not as high as CAVATAS had indicated. Although stenting posed an increased risk of minor stroke during the insertion procedure as opposed to surgery, it also avoided the potential dangers associated with carotid endarterectomy, such as cranial nerve injury. Overall, long-term disability, quality of life, and mortality did not differ significantly between the two treatments. There was also no difference in cost-effectiveness.

This led the ICSS researchers to call for greater awareness of the potential risks and benefits of each treatment for an individual patient. "The data from ICSS show that stenting can be offered to patients as an alternative to endarterectomy, so long as there are features suggesting that the risk of procedural stroke with stenting is likely to be similar or lower than that of endarterectomy," explains Brown.

## LOOK A LITTLE CLOSER

One way in which the risk of stenting versus endarterectomy for an individual patient can be established is through the use of brain scans to assess existing damage. An ICSS sub-study found that patients with above-average cerebral white matter damage were more at risk during stenting, while for those with lesser damage, there was no difference in risk. This suggests that brain scans hold significant promise when it comes to helping physicians and patients make informed decisions about the most suitable treatment options.

Indeed, this is something that Brown is investigating further: "We have been particularly interested in using magnetic resonance imaging (MRI) of the brain as a follow-up tool," he outlines. This is because recent evidence has indicated that MRI is effective at detecting cerebral infarction,



## INTELLIGENCE

# ECST-2

### THE 2<sup>ND</sup> EUROPEAN CAROTID SURGERY TRIAL

#### OBJECTIVE

To investigate the optimal treatment of patients with symptomatic or asymptomatic moderate or severe carotid stenosis at low or intermediate risk of future stroke. The trial compares the risks and benefits of treatment by modern optimised medical management alone versus the addition of immediate carotid surgery (or stenting) to optimised medical management.

#### PARTNERS

ESCT-2 is currently recruiting new centres and participants for this international, multicentre clinical trial.

#### FUNDING

National Institute for Health Research (NIHR) Research for Patient Benefit Programme

The Stroke Association

#### CONTACT

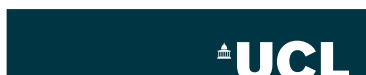
**Professor Martin M Brown**  
Professor of Stroke Medicine

UCL Institute of Neurology  
The National Hospital for Neurology & Neurosurgery  
Queen Square  
London  
WC1N 3BG  
UK

T +44 203 448 4753  
E office@ecst2.com

[www.ecst2.com](http://www.ecst2.com)

**MARTIN M BROWN** qualified in Medicine from Cambridge University and the Middlesex Hospital Medical School in 1975. In 1999, he was appointed as the foundation Professor of Stroke Medicine at the UCL Institute of Neurology. He is also Consultant Neurologist at University College Hospital and the National Hospital for Neurology and Neurosurgery, Queen Square. He has been involved in setting up three stroke units, runs a specialised clinic for rare causes of stroke, and has played a major role in establishing training in stroke medicine for junior doctors. He is Past President of the British Association of Stroke Physicians.



sensitive to microscopic haemorrhages (microbleeds), and may even be able to predict future risk of vascular events.

#### BETTER TOGETHER

In order to maximise the findings of trials such as ICSS, Brown set up the Carotid Stenting Trialists Collaboration in 2009, together with colleagues from Germany and France, with the aim of progressing stroke research and pooling data. It was through this joint initiative that the Collaboration was able to combine ICSS findings with data from two other major European trials – the Endarterectomy Versus Angioplasty in patients with Symptomatic Severe carotid Stenosis trial (EVA-3S) and the Stent-Protected Angioplasty versus Carotid Endarterectomy in symptomatic patients trial (SPACE).

The Carotid Stenting Trialists Collaboration analysis brought to light an additional factor that may be used to predict an individual's stenting risk: age. It was found that, for patients over the age of 70, stenting posed a significantly higher risk than endarterectomy, whereas for patients under 70 the difference in risk was insignificant. Indeed the younger the patient, the greater the potential benefits of stenting over surgery.

This finding has been supported by findings from the North American Carotid Revascularization Endarterectomy versus Stenting Trial (CREST), which joined the Carotid Stenting Trialists Collaboration (now known as the Carotid Stenosis Trialists Collaboration) at a later stage. "On the whole, it is remarkable how consistent the results of the four trials included in the Carotid Stenosis Trialists Collaboration have been," Brown comments.

#### PAVING THE WAY FOR PERSONALISED TREATMENT

Being able to accurately calculate the stroke risk of an individual with carotid artery stenosis holds clear benefits; at present, five-year risk can range from 5-40 per cent. For over a quarter of a century, stroke risk for carotid artery stenosis patients has been predicted using a model developed by the Oxford Stroke Prevention Unit. Given that this method does not take into account the significant developments that have taken place in stroke medicine in the past 25 years, the prediction strategy is clearly in need of revision to improve its accuracy.

This is where Brown's current project, the Second European Carotid Surgery Trial (ECST-2), comes in. "We will be testing a revised version of the risk model," Brown reveals. This new trial will make use of novel imaging techniques to reveal the composition of the carotid plaque, which Brown expects to accurately predict five-year stroke risk. The plan is to develop an even more accurate risk model so that such scores can ultimately be used when deciding how best to treat a carotid artery stenosis patient.

In terms of determining a patient's treatment options, ESCT-2 also aims to establish the benefits of optimised medical therapy compared with carotid endarterectomy. Brown predicts that such research is essential for the development of innovative, effective stroke therapies. In the future, the hope is that clinicians will have the knowledge and capacity to offer patients with carotid artery stenosis the best courses of treatment for the individual.



### Carotid comparisons

Over the course of the clinical trials he has overseen, Professor Martin Brown has endeavoured to establish the best of four major treatments for carotid artery stenosis:



#### CAROTID ANGIOPLASTY

A small balloon is temporarily inserted into the affected artery and then expanded, thus opening up the artery and restoring a healthy flow of blood



#### STENTING

A small metal mesh tube, or 'stent', is placed within the artery to hold the artery wide open



#### ENDARTERECTOMY

A surgical procedure to remove plaque from the artery walls via a small incision in the neck to reach the narrowed section of the artery



#### OPTIMISED MEDICAL TREATMENT

Medical therapy adjusted to achieve individualised optimum levels of blood pressure and serum cholesterol levels, combined with targeted lifestyle modifications and antiplatelet therapy