Institution: University of Leicester

Unit of Assessment: UoA1

Title of case study: Blood pressure management following acute stroke: informing changes to UK and US stroke guidelines

1. Summary of the impact

Stroke is the third most common cause of death and single most important cause of adult disability in the UK, affecting over 150,000 individuals per annum and costing the economy approximately £8 billion annually in health, social and indirect care costs.

High blood pressure (BP) is the most common modifiable risk factor to prevent stroke, but the use of BP-lowering therapy in the acute phase of stroke is controversial. Clinical trials co-ordinated at the University of Leicester have confirmed the safety of continuation of pre-existing BP-lowering therapy in acute stroke and the de novo treatment of high blood pressure in acute intracerebral haemorrhage. This has resulted in changes to the most recent US (2013) and UK (2012) guidelines, which will significantly impact on clinical management of this common clinical problem in acute stroke.

2. Underpinning research

Hypertension is the most important modifiable risk factor to prevent stroke and its recurrence, the single most important cause of adult neurological disability and the third highest cause of mortality in the UK. Furthermore, acutely following stroke, hypertension is associated with a worse prognosis. However, while acute antihypertensive therapy may improve prognosis particularly by reducing cerebral oedema (in all strokes), preventing haematoma expansion and/ or recurrent bleeding (in haemorrhagic stroke), and preventing haemorrhagic transformation (in ischaemic stroke), acute antihypertensive therapy may also be associated with harm.

This is because the process of cerebral autoregulation usually ensures a constant cerebral blood flow across a range of blood pressures. This process is impaired acutely after stroke so that cerebral blood flow becomes directly related to blood pressure; therefore, sudden reductions in blood pressure reduce cerebral blood flow with associated neurological deterioration.

In addition, an increasing proportion (up to 50%) of patients admitted with acute stroke are already on BP-lowering therapy, and there is a question about whether this therapy should be continued or stopped, as well as the introduction of de novo antihypertensive therapy.

Co-ordination of acute stroke blood pressures trials

The Ageing and Stroke Medicine Group at Leicester University (membership listed below) has an international and national reputation for acute stroke BP research, and over many years has investigated the pathophysiology of blood pressure changes following stroke, changes in cerebrovascular autoregulation and the prognosis of these variables. This has culminated in the co-ordination of acute stroke blood pressures trials which have informed both US and UK guidelines for the management of this common clinical problem following acute stroke.

Increased casual and 24-hour BP within 24 hours of symptom onset is associated with poor 30-day mortality, dependency and functional outcomes, and long-term mortality (Robinson, Potter in 1997, 2001, 2004). A number of possible underlying mechanisms for impaired BP control have been explored, including impaired heart rate change due to stretching of the carotid artery caused by increased BP (cardiac baroreceptor sensitivity), impaired peripheral vasomotor responses, increasing vascular stiffness, and increased beat-to-beat BP variability; impaired cardiac baroreceptor sensitivity being predictive of poor long-term outcome in its own right (Robinson, Panerai, Potter, Dawson, Eveson, James in 1997, 2000, 2003 [1], 2005).

Development of non-invasive assessments of cerebral autoregulation
Importantly, the Ageing and Stroke Medicine research team in Leicester has been at the forefront of the development of non-invasive assessments of cerebral autoregulation, demonstrating impaired autoregulation in the acute stroke period, as well as refining methods of cerebral autoregulation assessment (Robinson, Panerai, Potter, Eames, Dawson, Brodie in 2000, 2002, 2010, 2011, 2012). Finally, a number of preliminary studies have been undertaken to assess the contribution of commonly used individual antihypertensive agents, including thiazide diuretics and angiotensin converting enzyme inhibitors to impairments in cerebral autoregulation and safety in acute stroke BP management (Robinson, Potter, Eveson, Eames in 2004, 2007).

This preliminary research over many years has demonstrated the importance of hypertension following acute stroke as a common complication associated with poor prognosis. Furthermore, despite associated impairments of cerebrovascular autoregulation, which maintains adequate and stable blood flow to the brain, preliminary data indicated that it was safe to reduce blood pressure acutely following stroke with commonly used antihypertensive therapy without further adverse effects on these mechanisms.

Major UK multi-centre studies
This led to two major UK multi-centre studies designed and co-ordinated by the group, the HTA-funded Controlling Hypertension and Hypotension Immediately Post Stroke (CHHIPS; Potter (CI), Robinson, Mistri [2]) of de novo antihypertensive therapy in acute stroke, and the Stroke Association and Health Foundation-funded Continue or Stop post Stroke Antihypertensives Collaborative Study (COSSACS ; Robinson (CI), Potter, Mistri, Eames, Brodie [3]) of continuing or stopping pre-existing antihypertensive therapy in acute stroke.

Leicester's expertise has been recognised internationally, with Robinson being invited to join the Executive Committee with responsibility for the design, funding and management of two international multi-centre trials co-ordinated by The George Institute and by Leicester University within the UK. The recently completed, Australian National Health and Medical Research Council-funded Intensive blood pressure reduction in acute intracerebral haemorrhage trial (INTERACT2; Robinson (UK CI) [4]), and ongoing Australian National Health and Medical Research Council and Stroke Association-funded Enhanced control of hypertension and thrombolysis trial (ENCHANTED; Robinson (UK CI)).

Leicester Ageing and Stroke Medicine Group
Robinson, Stroke Association-funded Clinical Research Fellow (1993 to 1995), Stroke Association-funded District Stroke Co-ordinator (1997 to 2000), Senior Lecturer (2000 to 2007), Professor (2007 to date).
Brodie, Clinical Research Fellow (2006 to 2009)
Dawson, Clinical Research Fellow (1996 to 1998), Consultant Physician/ Honorary Senior Lecturer (2001 to date)
Eames, Clinical Research Fellow (1998 to 2006), Consultant Neurologist (2010 to date)
Eveson, Clinical Research Fellow (2001 to 2004), Stroke Association Clinical Fellow (2005 to 2006), Consultant Stroke Physician (2006 to date)
James, Clinical Research Fellow (1993 to 1995)
Mistri, Clinical Research Fellow (2004 to 2006), Senior Lecturer (2008 to 2012), Honorary Senior Lecturer (2012 to date)
Panerai, Senior Lecturer (1992 to 2000), Professor of Physiological Measurement (2000 to date)
Potter, Senior Lecturer (1988 to 1992), Foundation Professor of Ageing and Stroke Medicine (1992 to 2006)

Selected Grant Income
Stroke Association. Prognostic Significance of Cardiac Baroreceptor Sensitivity Following Acute Stroke. £151,620. 2002-2006
PPP Foundation. Continue of Stop Post Stroke Anti-Hypertensive Collaborative Study (COSSACS) £310,000. 2003-2006
NHS HTA. Control of Hypertension and Hypotension Immediately Post Stroke (CHHIIPS) £1.1

million. 2004-2007
EPSRC. New methods for the assessment of blood flow regulation in the brain. £109,688. 2009-2012
Stroke Association. MRI Assessment of Post-Stroke Focal versus Global Cerebrovascular Autoregulation. £102,332. 2009-2012
Stroke Association. ENCHANTED. £202,055 2013-2016
BHF. Blood pressure variability – Definition, Natural History, Prognosis and Treatment Following Acute Stroke. £878,180. 2013-2017
EPSRC. Diversity in blood flow control of the brain: moving from individual modelling towards personalised treatment of the injured brain. £320,853. 2013-2016.

3. References to the research

1. **Robinson TG**, Cardiac baroreceptor sensitivity predicts long-term outcome after acute ischaemic stroke. Stroke 2003; 34: 705-712.

2. **Potter JF, Robinson TG, Potter JF, Robinson TG, Mistri A, James M,.**. Controlling Hypertension and Hypotension Immediately Post Stroke (CHHIPS): A Randomised, Placebo-controlled, Double-blind Pilot Trial. Lancet Neurology 2009; 8: 48-56.

3. **TG Robinson Potter JF, , James MA, Mistri AK, COSSACS Investigators..** Effects of antihypertensive treatment after stroke in the Continue Or Stop post-Stroke Antihypertensives Collaborative Study (COSSACS): a prospective, randomised, open, blinded-endpoint trial. Lancet Neurol 2010; 9: 767-775.

4. S, Heeley E, Huang Y, Wang J, Stapf C, Delcourt C, Lindley R, **Robinson T,** Lavados P, Neal B, Hata J, Arima H, Parsons M, Li Y, Wang J, Heritier S, Li Q, Woodward M, Simes RJ, Davis SM, Chalmers J, for the INTERACT2 Investigators. Rapid blood pressure lowering in acute intracerebral haemorrhage:. New England Journal of Medicine 2013. DOI: 10.1056/NEJMoa214609..

4. Details of the impact

For a population of one million, the average population served by a large acute UK teaching hospital, there will be 2,000 incident strokes per annum and 10,000 prevalent strokes alive at any one time. Nearly 11,000 of these stroke victims will require antihypertensive therapy, and lowering systolic blood pressure by an average of 10mmHg will prevent over 180 recurrent strokes per annum. Given that the usual outcome from recurrent stroke is that a third of patients die and a third are left with moderate to severe disability (requiring assistance with personal care on a daily basis), better and more timely prevention of recurrent stroke has significant cost benefit for health and social services, as well as personal benefit for patients and their families. Importantly, the risk of recurrent stroke is front-loaded after the presenting transient ischaemic attack (TIA or mini-stroke) or stroke, and therefore prompt introduction of blood pressure-lowering therapy is essential.

Changes to UK and US stroke guidelines
The COSSACS trial (CI: **Robinson**) has provided evidence that continuing blood pressure-lowering therapy, a clinical dilemma in 50% of stroke patients, in patients with minor stroke is safe and associated with a 14% reduction in 2-week death and dependency. Indeed, COSSACS has directly impacted on the most recent iterations of both the UK and US stroke guidelines. The Guidelines for the Early Management of Patients with Acute Ischemic Stroke, jointly published by the American Heart Association and American Stroke Association in 2013 [1], incorporates a revision from the previous version: 'Evidence from one clinical trial indicates that initiation of antihypertensive therapy is relatively safe. Restarting antihypertensive medications is reasonable after the first 24 hours for patients who have pre-existing hypertension and are neurologically stable unless a specific contraindication to restarting treatment is known'.

From a UK perspective, the latest iteration of the National Clinical Guidelines for Stroke [2] has

also changed, reflecting the publication of the COSSACS trial, stating: 'Non-dysphagic patients admitted on antihypertensive medication should continue oral treatment unless there is a contraindication'.

The INTERACT2 trial (UK CI: **Robinson**) has provided evidence that intensive (compared to standard) blood pressure-lowering within six hours of acute intracerebral haemorrhage onset , the most devastating cause of stroke, is safe and associated with a significant 13% shift towards better outcome at three months. The current revision to the US stroke guidelines was delayed pending the publication of the INTERACT2 results, and the latest revision is presently awaited.

Change to guidelines impacts on medical practice worldwide

This change in both UK and US guidelines affects the way in which stroke patients are managed around the world, enabling practitioners to prescribe oral antihypertensive treatment in nearly all patients within the first few days of mildly or non-disabling stroke, with resulting improvements to patient outcomes (1, 2, 3). Furthermore, there is now evidence that intensive blood pressure lowering in intracerebral haemorrhage is safe, and associated with improved functional outcome for the most devastating form of stroke (4, 5).

5. Sources to corroborate the impact

1. EC Jauch et al. Guidelines for the Early Management of Patients with Acute Ischemic Stroke: A Guideline for Healthcare Professionals from the American Heart Association/ American Stroke Association. Stroke 2013; DOI: 10.1161/STR.0b013e318284056a. (COSSACS)

2. Intercollegiate Stroke Working Party. National Clinical Guidelines for Stroke (Fourth Edition). Royal College of Physicians, London, UK, 2012. (COSSACS)

3. C Anderson. A step forward in resolving uncertainties over blood-pressure management in acute stroke. Lancet Neurol 2010; 9: 752-752. (COSSACS)

4. JA Frontera. Blood pressure in intracerebral haemorrhage – how low should we go? New England Journal of Medicine 2013. DOI: 10.1056/NEJMe130547. (INTERACT2)

5. Rapid blood pressure lowering may improve outcomes in haemorrhagic stroke. British Medical Journal 2013; 346: f3584. (INTERACT2)