Institution: University of East Anglia

Unit of Assessment: 1 - Clinical Medicine

Title of case study:

Influencing guidelines on management of hypertension following acute stroke

1. Summary of the impact

Two multicentre clinical trials conducted by Professor Potter have contributed to revised international guidelines for the management of hypertension following acute stroke, the single largest cause of adult disability worldwide. Before these trials, there was little evidence on the effects of using antihypertensive drugs immediately after stroke and there was concern that use of these drugs could extend the stroke. The trials found no serious adverse effects of using antihypertensive drugs immediately after stroke whilst mortality after 3 months was halved. The American Heart Association, the European Societies of Hypertension and of Cardiology, and the Royal College of Physicians all reference these trials in support of their recent Guidelines, thereby promoting better patient care and improved outcomes.

2. Underpinning research

Blood pressure abnormalities are common after acute stroke, and both hypertension and marked hypotension (high and low blood pressure) are associated with poor outcome. Stroke patients often have pre-existing hypertension (which is the most important risk factor for stroke, contributing to more than 50% of all strokes) which may or may not have been treated before the stroke. In these cases, there has been uncertainty as to whether usual antihypertensive treatments should be continued in the period immediately following the stroke. When stroke occurs, initial management is critical for the outcome of the disease as hypertension is associated with poor short-term and long-term outcomes. However, best practice for management of blood pressure in acute stroke has been uncertain because of a scarcity of data from which to draw evidence. Before our studies there was concern that continuing antihypertensive therapy would lower blood pressure and extend the stroke. Our studies have shown that antihypertensive therapy is not deleterious. Indeed the contrary is true as lowering blood pressure halves the 3-month mortality.

Our research has involved two large, UK, multi-centre trials to investigate management of blood pressure following acute stroke:

The CHHIPS (Controlling Hypertension and Hypotension Immediately Post-Stroke) trial assessed the feasibility, safety and effects of two antihypertensive drugs (labetalol and lisinopril) to lower blood pressure. CHHIPS was a randomised, placebo-controlled, double-blind trial. Patients were recruited at six centres in the UK from January 2005 to December 2007. Stroke patients (symptom onset within 36hr and systolic blood pressure above 160mmHg) were randomly assigned to receive either treatment or a matched placebo. In 179 patients, the primary outcome - death or dependency at 2 weeks - showed no difference between the active treatment and placebo groups. In addition, no neurological deterioration or serious adverse effects were found with active treatment, despite a significantly greater fall in systolic blood pressure within the first 24hr, compared to the placebo group. A striking result was that the 3-month mortality was halved in patients taking antihypertensives compared to the placebo group.

The conclusion was that labetalol and lisinopril are effective antihypertensive drugs for acute stroke that do not increase serious adverse effects (research references 1 & 2). A cost utility study performed at UEA by Dr Wilson and colleagues from the Health Economics unit at the Norwich Medical School and Professor Potter demonstrated that antihypertensive therapy in hypertensive patients immediately post stoke is both effective and cost-effective compared to placebo at 3 months after the stroke (research reference 3).

The COSSACS (Continue Or Stop post-Stroke Antihypertensives Collaborative Study) trial assessed efficacy and safety of continuing or stopping pre-existing treatment with antihypertensive drugs in patients who had recently had a stroke. COSSACS was a single-blind randomised

controlled trial. Patients were recruited at 49 UK NIHR Stroke Research Network centres from January 2003 to March 2009. 763 stroke patients (symptom onset within 48hr), who were currently taking antihypertensive drugs were randomly assigned to continue or stop the pre-existing treatment for a 2-week period. Clinicians, blinded to the group to which each patient belonged, assessed outcomes after two weeks and six weeks. No substantial differences were observed between the two groups in adverse events, 6-month mortality or major cardiovascular events. In addition, lower blood pressure levels in those who continued antihypertensive treatment were not associated with an increase in adverse effects. As hypertension is the major treatable risk factor for future stroke, continuation of antihypertensive in the immediate stroke period is safe and likely to improve long-term outcomes.

The conclusion was that there is no obvious harm associated with continuing pre-existing antihypertensive drugs for a 2-week period following acute stroke (research reference 4).

UEA researchers:
John Potter: Professor Potter was the principal investigator, developed the trials, sought and obtained funding and was responsible for the overall running, analysis and writing of all manuscripts. The studies were initiated at the University of Leicester and continued at UEA since 2006. Since joining UEA, Professor Potter maintained a lead involvement in the studies. Significant patient recruitment and data collection continued, and analyses and dissemination was undertaken while at UEA.

Edward Wilson: Lecturer in Health Economics at UEA 2003-2013.

3. References to the research

(UEA authors in bold)

1. **Potter JF**, Mistri A, Brodie F, Chernova J, **Wilson E**, Jagger C, James M, Ford G, Robinson T
   Controlling Hypertension and Hypotension Immediately Post Stroke (CHHIPS) – a randomised controlled trial
   Health Technology Assessment **2009** 13:article no.9
   doi: 10.3310/hta13090
2. **Potter JF**, Robinson TG, Ford GA, Mistri A, James M, Chernova J, Jagger C
   Controlling hypertension and hypotension immediately post-stroke (CHHIPS): a randomised, placebo-controlled, double-blind pilot trial
   Lancet Neurology **2009** 8:48-56
   doi: 10.1016/S1474-4422(08)70263-1
3. **Wilson EC**, Ford GA, Robinson T, Mistri A, Jagger C, **Potter JF**
   Controlling hypertension immediately post stroke: a cost utility analysis of a pilot randomised controlled trial.
   Cost effectiveness and resource allocation **2010** 8:article no.3
   doi: 10.1186/1478-7547-8-3
4. Robinson TG, **Potter JF**, Ford G, Bulpitt C, Chernova J, Jagger C, James M, Knight J, Markus H, Mistri AK, Poulter NR
   Effects of antihypertensive treatment after acute stroke in the Continue Or Stop post-Stroke Antihypertensives Collaborative Study (COSSACS): a prospective, randomised, open, blinded-endpoint trial.
   Lancet Neurology **2010** 9:767-75
   doi: 10.1016/S1474-4422(10)70163-0

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COSSACS: This study was funded with grants from The Health Foundation 2003-2009 (£310,000) and The Stroke Association. Professor Potter developed the trial, sought and obtained funding, reviewed the analysis and revised the manuscript.

CHHIPS: The trial was funded with a grant from the UK National Health Service Research and Development Health Technology Assessment Programme 2004-2008 (£1.1M). Professor Potter

was the principal investigator, developed the trial, sought and obtained funding and was responsible for the overall running, analysis and writing-up.

4. Details of the impact

Each year, in England alone, approximately 152,000 people suffer a stroke. In the UK, 1 in 5 strokes are fatal. The annual costs of stroke in the UK are estimated to be between £3.7 billion and £8 billion and the majority of this cost is rehabilitation and supporting activities of daily living (e.g. bathing, dressing and feeding) after stroke.

When stroke occurs, initial management is critical for the outcome of the disease. Hypertension is associated with poor short-term and long-term outcomes (see for example Annals Neurol **1998** 24:258–263 or J Internal Med **2001** 249:467–473). Hypertension is common after acute stroke, and is also a major risk factor for stroke. However, best practice for management of blood pressure in acute stroke has been uncertain because of a scarcity of data from which to draw evidence. This is a serious concern. The research described in this case study has been used to inform international guidelines on the management of hypertension following stroke, promoting better patient care with the goal of improving outcomes from stroke.

The American Heart Association used the research outcomes from the CHHIPS and COSSACS studies to inform the 2013 '**Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals**'. (corroborating source A)

Both the CHHIPS study (their reference 411) and the COSSACS study (their ref 433) are cited in the text as supporting evidence for the following recommendations in the guidelines which acknowledge the important contribution these trials have made to this controversial field.

Recommendation 2 (p892) states:

> "*Patients who have elevated blood pressure and are otherwise eligible for treatment with intravenous rtPA should have their blood pressure carefully lowered (Table 9) so that their systolic blood pressure is <185 mm Hg and their diastolic blood pressure is <110 mm Hg (Class I; Level of Evidence B) before fibrinolytic therapy is initiated. If medications are given to lower blood pressure, the clinician should be sure that the blood pressure is stabilized at the lower level before beginning treatment with intravenous rtPA and maintained below 180/105 mm Hg for at least the first 24 hours after intravenous rtPA treatment.*"

Specific reference to the COSSACS study is made in recommendation 10 (p893) which states:

> "*Evidence from one clinical trial indicates that initiation of antihypertensive therapy within 24 hours of stroke 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 (Class IIa; Level of Evidence B)*."

The 2013 '**Guidelines for the management of arterial hypertension**' from the European Society of Hypertension and of the European Society of Cardiology (corroborating source B) state that blood pressure management during the acute phase of stroke is a matter of continuing concern, and that this is a difficult area. The CHHIPS study is used as evidence of a beneficial impact of administering lisinopril in patients with acute stroke and a systolic blood pressure>160 mmHg.

The 2012 Royal College of Physicians '**National Clinical Guidelines for Stroke**' (corroborating source C) advise that parenteral drugs for control of blood pressure should at present only be used as part of a clinical trial (apart from certain conditions relating to patients with very high blood pressure or in preparation for thrombolysis) and highlight the need for further research in blood pressure management in acute stroke, with reference to the CHHIPS study.

As an additional approach to ensuring impact from the research, Potter has contributed to the preparation of clinical guidelines. For example, the 2008 guidelines from the Royal College of Physicians National Collaborating Centre for Chronic Conditions '**Stroke: national clinical guideline for diagnosis and initial management of acute stroke and transient ischaemic attack (TIA)**'.

5. Sources to corroborate the impact

A. **Guidelines for the Early Management of Patients With Acute Ischemic Stroke : A Guideline for Healthcare Professionals**
The American Heart Association/American Stroke Association
Stroke **2013** 44:870-947
doi: 10.1161/STR.0b013e318284056a
References to UEA research: pp.890 & p.891 (their reference 411) and p.890 (their reference 433)

B. **Guidelines for the management of arterial hypertension**
The European Society of Hypertension and The European Society of Cardiology
Eur Heart J **2013** 34:2159-2219
doi: 10.1093/eurheartj/eht151
Reference to the CHHIPS study is made on p42

C. **National clinical guideline for stroke**
Royal College of Physicians: Intercollegiate Stroke Working Party London, **2012**
www.rcplondon.ac.uk/sites/default/files/national-clinical-guidelines-for-stroke-fourth-edition.pdf
Reference to UEA research: p54 - the CHHIPs study is cited as a source reference for recommendations I and J