**Institution:** University of Glasgow

**Unit of Assessment:** Unit 1; Clinical Medicine

**Title of case study:** Redefining hypertension treatment practice to reduce primary and secondary stroke risk

## 1. Summary of the impact

Stroke is the leading cause of disability and a major cause of death in the developed world. Hypertension (high blood pressure) is the single most important modifiable risk factor for stroke, contributing to around 50% of all events. University of Glasgow researchers have played lead roles in the design, conduct and analysis of pivotal clinical trials on treatment regimens for hypertension. These research findings have informed European and UK hypertension and stroke guidelines, advancing treatment strategies, and contributed to the observed ~25% reduction in the incidence of primary (first) and secondary (recurrent) stroke.

## 2. Underpinning research

Working at the forefront of hypertension and stroke research for more than 40 years, investigators at the University of Glasgow are recognised leaders in both laboratory-based and clinical research into the causes of hypertension and its treatment. A theme of particular interest is the link between hypertension and stroke. University of Glasgow researchers have a global reputation in the design and execution of landmark clinical trials in this area.

### *Perindopril Protection Against Recurrent Stroke Study (PROGRESS; 1995–2000)*[1,2]

A University of Glasgow team – comprising Professors Kennedy Lees, John Reid and Matthew Walters – led ground-breaking clinical studies of the angiotensin-converting enzyme (ACE) inhibitor, perindopril, the first long-acting, once-daily preparation available for use in hypertensive patients. Previously, treatments that lowered blood pressure (BP) had been shown to reduce the risk of primary stroke, but it was unclear whether they also prevented secondary strokes. The University of Glasgow researchers designed and led the pioneering PROGRESS randomised controlled clinical trial, which established the safety and tolerability of perindopril among healthy volunteers and patients with hypertension or stroke (172 participating centres; 6,105 patients recruited). Members of the University of Glasgow research team also played significant roles in comparative studies of perindopril versus other BP-lowering drugs. Eligibility criteria for patient enrolment was broad (including previous stroke of any kind during the previous 5 years with no stroke-related disability), thus providing a heterogeneous population in which to test the efficacy of perindopril. The findings of PROGRESS (published in 2001) were profound, showing that a perindopril-based regimen reduced the overall relative risk of recurrent stroke by 28%. Results were far-reaching for the management of stroke risk, suggesting that all patients with stroke should receive BP-lowering therapy irrespective of their actual BP reading; this strategy represented a major departure from previous practice.

University of Glasgow researchers also led a very large epidemiological study of recurrent stroke (5.1 million people in Scotland), evaluating hospitalisations and outcomes over a 15-year period (1986–2001).[3] By comparing data from 1986 with those from 2001, this study demonstrated improved survival following stroke, with a 28% decreased risk of death and a 27% decreased chance of hospitalisation for recurrent stroke. These findings confirmed the value of secondary prevention strategies to improve stroke outcomes.

### *Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT; 1998–2002)*[4,5]

ASCOT was the largest study of hypertension ever conducted in Europe. University of Glasgow researcher Professor Gordon McInnes played an integral role in the design, direction and management of the ASCOT trial, and contributed greatly to patient recruitment. The ASCOT BP-lowering arm (ASCOT-BPLA), which was led by McInnes and recruited 19,257 patients with hypertension, was the first study to perform a head-to-head comparison of two different BP-lowering treatment regimens on cardiovascular (CVD) outcomes, including stroke. One treatment regimen combined perindopril with amlodipine (a calcium-channel blocker), while the other

combined atenolol (a β-blocker) and thiazide (a diuretic). The perindopril-amlodipine combination provided superior risk reduction over the atenolol-thiazide combination for multiple CVD parameters, including a 23% reduction in the composite end point of fatal and non-fatal stroke. The ambulatory BP-monitoring (ABPM) sub-study of ASCOT-BPLA tested whether this difference in CVD outcomes between the two treatment regimens could be attributed to the method used to monitor, and if so, whether ABPM a more useful predictor of CVD risk than a single-visit clinic measurement. Ambulatory BP-monitoring involves regular BP measurements during normal living and working conditions over a 24-hour period. ASCOT-ABPM revealed that people with high night-time ABPM readings were at increased risk of a CVD event, demonstrating incremental utility over clinic BP measures in this group of patients.

The two ASCOT studies clearly demonstrated the benefit of reducing CVD risk and mortality through: i) choice of BP-lowering regimen and ii) qualifying ABPM over single-visit BP readings in influencing CVD risk, especially stroke. These findings challenged long-held prescribing recommendations that first-line therapy for hypertension should comprise a diuretic plus β-blocker.

***Losartan Intervention For Endpoint reduction in hypertension study (LIFE; 1995–2001)***[6]

LIFE was another breakthrough hypertension trial that investigated the use of angiotensin II-receptor blockers (ARBs) among individuals with high CVD risk. ARBs first became available in the mid-1990s; they display similar benefits to ACE inhibitors but can potentially be offered as an alternative treatment for patients unable to tolerate ACE inhibitors. McInnes and Reid both played important roles in LIFE, with McInnes as the Principal Investigator of the fastest recruiting site (Glasgow) in this global multi-centre study. LIFE recruited 9,193 hypertensive patients and compared the first ARB (losartan) with the established β-blocker, atenolol. Treatment with losartan reduced both mortality and secondary CVD events, including fatal and non-fatal stroke (25% reduction). LIFE was the first study to directly compare the effects of ARBs and β-blockers on the rates of stroke-related outcome, independent of BP reading.

**Key Researchers:** Kennedy Lees (Professor of Cerebrovascular Medicine, 1985–present); John Reid (Regius Professor of Medicine and Therapeutics, 1978–2010); Matthew Walters (Senior Lecturer in Medicine, 2003–2008; Reader, 2008–2010; Professor of Clinical Pharmacology, 2010–present); Gordon McInnes (Professor of Clinical Pharmacology, 1980–2007). **Key positions held in clinical trials:** PROGRESS: Lees and Reid, members of Management Committee; regional Principal Investigators. ASCOT: McInnes, Steering Committee; Lead for ASCOT-ABPM sub-study; Regional Trial Coordinator for UK and Ireland. LIFE: McInnes and Reid, Principal Investigators, Glasgow study centre. **Key research collaborators:** PROGRESS: Stephen MacMahon and John Chalmers (University of Sydney, Australia). ASCOT: Neil Poulter and Peter Sever (Imperial College, London); Björn Dahlöf (Sahlgrenska University Hospital, Sweden). LIFE: Dahlöf (as above).

## 3. References to the research


1. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet* 2001; 358: 1033–1041 doi:10.1016/S0140-6736(01)06178-5.
2. Walters MR *et al.* Effect of perindopril on cerebral and renal perfusion in stroke patients with carotid disease. *Stroke* 2001; 32: 473–478 doi:10.1161/01.STR.32.2.473.
3. Lewsey J *et al.* Temporal trends in hospitalisation for stroke recurrence following incident hospitalisation for stroke in Scotland. *BMC Medicine* 2010; 8: 23 doi:10.1186/1741-7015-8-23.
4. Dahlöf B *et al.* Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* 2005; 366: 895–906 doi:10.1016/S0140-6736(05)67185-1.
5. Dolan E *et al*. Ambulatory blood pressure monitoring predicts cardiovascular events in treated hypertensive patients - an Anglo-Scandinavian cardiac outcomes trial substudy. *J Hypertens.* 2009; 27: 876–885 doi:10.1097/HJH.0b013e328322cd62.

6. Dahlöf B *et al*. Cardiovascular morbidity and mortality in the Losartan Intervention for Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002; 359: 995–1003 doi:10.1016/S0140-6736(02)08089-3.

## 4. Details of the impact

In the UK, approximately 152,000 strokes cause around 50,000 deaths annually; furthermore, 1.1 million stroke-related deaths are recorded in Europe each year. The resulting economic burden attributed to stroke in the UK alone is £3.75 billion. University of Glasgow research has driven improvements in management of patients with hypertension, exerting marked influence on stroke prevalence and fatality by underpinning clinical guideline recommendations and implementation.

### *Clinical guidelines for hypertension and stroke*

The University of Glasgow's international reputation in hypertension and stroke research has invited involvement in clinical guideline development at the highest level. Professor Anna Dominiczak – Regius Professor of Medicine in the University's Institute of Cardiovascular and Medical Sciences – held a key role on the Scientific Council for the 2013 European Society for Hypertension (ESH) guidelines. Lees currently serves as President Elect of the European Stroke Organisation (ESO) and was a co-author of the 2008 ESO guidelines. The University of Glasgow's contribution to landmark studies on hypertension provided a strong evidence-base that has informed both European and UK guideline recommendations published since 2008.

*2013 ESH/European Society of Cardiology (ESH/ESC) joint guidelines for the management of arterial hypertension*[a]

- The PROGRESS,[1] ASCOT-BPLA,[4] and LIFE[6] studies are included in the key underpinning evidence (Table 16) used to develop the '*Summary of recommendations on treatment strategies and choice of drug*' (Section 5.2.3), which list a series of hypertension treatment paradigms relating to ACE inhibitors, calcium-channel blockers and ARBs.
- The influence of PROGRESS[1] in defining the clinical utility of BP reduction in preventing recurrent stroke is highlighted by its citation as one of only two to three references underpinning the following recommendations: "*Antihypertensive treatment is recommended in hypertensive patients with a history of stroke or TIA even when initial SBP is in the 140–159 mmHg range"* and *"In hypertensive patients with a history of stroke or TIA, a SBP goal of <140 mmHg should be considered*" (Section 16.10.4).

*2008 ESO guidelines for management of ischaemic stroke and transient ischaemic attack*[b]

- The BP-lowering effects of losartan demonstrated in the LIFE[6] study are cited in the key underpinning evidence base for the following recommendation to reduce vascular risk factors and prevent first-time stroke (primary prevention): "*Blood pressure should be checked regularly. It is recommended that high blood pressure should be managed with lifestyle modification and individualized pharmacological therapy (Class I recommendation, Level A evidence) aiming at normal levels of 120/80 mmHg.*"
- The value of the PROGRESS[1] findings in demonstrating BP reduction to prevent recurrent stroke (secondary prevention) is cited in the evidence base to support the following: "*It is recommended that BP be checked regularly. BP lowering is recommended after the acute phase, including in patients with normal BP (Class I recommendation, Level A evidence*)."

Effective management of hypertension has the greatest impact on reducing stroke incidence. Consequently, national guidance documents that align with international guideline recommendations play an important role in influencing patient care at a local level. Guidelines developed by the UK National Institute for Health and Care Excellence (NICE) and the Scottish Intercollegiate Guidance Network (SIGN) are instrumental in driving best practice within the NHS.

*2011 NICE guideline Hypertension – the clinical management of primary hypertension in adults*[c]
This guideline replaces NICE CG34 (2006), in which the findings ASCOT-BPLA[4] and LIFE[6] were extensively cited in the evidence synthesis for recommendations on hypertension treatment strategies and algorithms (i.e. preferential use of ACE inhibitors or ARBs over β-blockers). The

2011 update (CG127) cites PROSPER,[1] ASCOT-BPLA[4] and LIFE in the evidence base;[6] furthermore, many of the original recommendations supported by University of Glasgow research remain in CG127, testament to the enduring impact of this body of work.

*2008 Scottish Intercollegiate Guidelines Network (SIGN) guideline 108 – management of patients with stroke or TIA*[d]
SIGN has responsibility for development of evidence-based clinical guidelines for use within NHS Scotland. The SIGN 108 recommendations on the secondary prevention of stroke draw directly on the University of Glasgow research:

- "*All patients with a previous stroke or TIA should be considered for treatment with an ACE inhibitor (for example, perindopril) and thiazide (for example, indapamide) regardless of blood pressure, unless contraindicated."* PROGRESS[1] is cited in the underpinning evidence for this Class A advisory on the secondary prevention of ischaemic stroke.
- *"Lowering blood pressure (non-acutely) following ICH using a combination therapy of ACE inhibitor and thiazide diuretic should be considered to prevent further vascular events."* PROGRESS[1] is cited in the underpinning evidence for this Class A advisory on the secondary prevention of haemorrhagic stroke.

***Uptake of UK clinical guidance***

A 2010 NICE implementation uptake report evaluated national trends following publication of NICE CG34 (2006).[e] Findings confirmed a sharp drop in the prescribing of β-blockers from 14% (July–September 2005) to 3% (April–June 2009), while use of ACE inhibitors rose from 27% to 48% in the same period. By June 2009, 75% of all newly diagnosed hypertensive patients aged less than 55 years were prescribed either an ACE inhibitor or an ARB.

In Scotland, SIGN takes a proactive approach to dissemination and implementation of its guidelines. Named individuals within each of the 14 regional Scottish Health Boards are recruited to promote new and updated SIGN guidelines and to draw up plans for their subsequent implementation. In the 2 months following publication, SIGN 108 was downloaded 66,150 times.[f] In addition, the following national strategies and action plans draw on the recommendations of SIGN 108: i) *Better Heart Disease and Stroke Care Action Plan* (2009) and ii) *Clinical Standards for Stroke Services* (2009).[f]

The Quality and Outcomes Framework (QOF) is an incentive scheme for GP practices providing financial rewards for patient care across multiple disease domains. Where available, QOFs are based on NICE and SIGN guidelines. The SIGN 108 and NICE CG34 guidelines are cited in the 2011–2012 QOF guidance on stroke and hypertension, respectively. PROGRESS[1] is cited in the evidence base for QOF stroke indicator 6 (secondary prevention); around 85% of patients in England with a previous stroke received treatment to target BP-lowering during 2011–2012.[g]

**5. Sources to corroborate the impact**

a. ESH/ESC guidelines for the management of arterial hypertension, 2013 [doi:10.1097/01.hjh.0000431740.32696.cc]. Cites PROGRESS (ref 296; p1304, 1306, 1313, 1314, 1323, 1324); ASCOT-BPLA (ref 423; p1310, 1313, 1314); LIFE (ref 457; p1313, 1314). See Table 16 (p1314); Section 5.2.3 (p1315–1316); Section 6.10.4 (p1324).
b. ESO guidelines for management of ischaemic stroke and transient ischaemic attack, 2008. Cites PROGRESS (ref 290; p39, 83); LIFE (ref 213; p30). See recommendations (p29, 38)
c. NICE CG127 guideline on the clinical management of primary hypertension in adults, 2011. Cites PROGRESS (ref 500; Table 3, p201); ASCOT-BPLA (ref 157; p206, 248); LIFE (ref 154; p35).
d. SIGN 108 guidelines on management of patients with stroke or TIA, 2008. Cites PROGRESS (ref 228, p37 and 40).
e. NICE CG34 implementation uptake report, 2010. (Figure 4, Table 2).
f. SIGN 108 download data – available on request.
g. QOF guidance for GMS contract (p52, 53, 56) and QOF data (STROKE06), 2011–2012.