Institution: The University of Edinburgh

Unit of Assessment: 4

Title of case study: B: Graduated compression stockings do not reduce the risk of post-stroke deep vein thrombosis (DVT)

1. Summary of the impact (indicative maximum 100 words)

Impact: Health and welfare: reducing morbidity; providing evidence to disinvest in an ineffective and damaging treatment; policy change.

Significance: Since 2009, applied clinical trial findings have resulted in approximately 6000 fewer complications (e.g., skin breaks) in the UK. Stocking use has decreased by 95%, which has saved the NHS in excess of £20M per annum.

Beneficiaries: Stroke patients worldwide, the NHS and healthcare delivery organisations, the economy.

Attribution: Trials were designed and led by Professor M Dennis, UoE.

Reach: Changed national guidelines in at least seven countries worldwide (Europe, N America, South Africa, Singapore).

2. Underpinning research (indicative maximum 500 words)

With £2.5M funding from the MRC, Chief Scientist Office and Chest, Heart and Stroke Scotland, Dennis (UoE 1990–present; now Professor of Stroke Medicine), Sandercock (UoE 1987–present; now Professor of Medical Neurology), Murray (UoE 1996–present; Professor of Medical Statistics), and Reid (Consultant Radiologist, NHS; honorary UoE position) designed, conducted and reported the Clots in Legs Or sTockings after Stroke (CLOTS)-1 & -2 trials to determine the role of graduated compression stockings (GCS) for DVT prophylaxis after stroke. These trials, which ran concurrently 2001–2009, demonstrated GCS to be ineffective.

Over 130,000 people in the UK have a stroke each year and 25% of these die within 6 months. DVT, and resulting pulmonary emboli, is a major course of death.

Sandercock showed a) in 1999 [3.1] that, in stroke patients, anticoagulants for DVT prophylaxis had no net benefit and b) in 2002 [3.2] that there was no reliable randomised trial evidence on the effects of GCS in stroke. A systematic review commissioned by the Health Technology Appraisal Group in 2005 showed that GCS and other physical methods of prophylaxis were effective in reducing DVT and pulmonary embolism in surgical patients. In 1999, a survey of 1716 physicians in the UK who managed stroke patients revealed that 46% thought GCS were useful for prevention of post-stroke DVT, 26% thought they were of no use and 28% were uncertain of their value (Ebrahim & Redfearn 1999). In Dennis's survey of 207 UK stroke units (unpublished), 132 (89%) of 148 responders claimed to routinely use GCS, suggesting widespread use of an unproven treatment.

Given the cost in terms both of the stockings themselves and of the nursing time involved in applying them, there was a clear need for a randomised controlled trial to establish the balance of risk and benefit and to determine the cost-effectiveness of GCS.

The CLOTS-1 trial patients were randomised either to a policy of 'routine application of full-length GCS' or to 'avoid GCS' in the acute phase of stroke. The CLOTS-2 trial patients were randomised to 'knee-length GCS' or to 'full-length GCS'.

The results of CLOTS-1 were reported in 2009 [3.3]. In 2518 patients with acute ischaemic stroke, routine application of full-length GCS excluded a clinically significant reduction in DVT or pulmonary embolism, but was associated with a small but significant (35/1000 patients treated) excess of adverse effects (e.g., skin breaks). The publication of these results led the CLOTS-2 trial

steering committee to close recruitment after 3114 patients had been entered and followed up. The results of the CLOTS-2 trial were published in 2010 [3.4]. This trial showed that, among stroke patients, those allocated knee-length GCS had a significantly higher risk of DVT than those allocated full-length GCS.

3. References to the research (indicative maximum of six references)

3.1 Gubitz G, Counsell C, Sandercock P, Signorini D. Anticoagulants for acute ischaemic stroke. Cochrane Database Sys Rev. 2000;2:CD000024. DOI: 10.1002/14651858.CD000024.

3.2 Mazzone C, Chiodo G, Sandercock P, Miccio M, Salvi R. Physical methods for preventing deep vein thrombosis in stroke. Cochrane Database Sys Rev. 2002;1:CD001922. DOI: 10.1002/14651858.CD001922.

3.3 Dennis M, Sandercock P, Reid J, et al. Effectiveness of thigh-length graduated compression stockings to reduce the risk of deep vein thrombosis after stroke (CLOTS trial 1): a multicentre, randomised controlled trial. Lancet. 2009;373:1958–65. DOI: 10.1016/S0140-6736(09)60941-7.

3.4 Dennis M, Sandercock P, Reid J, et al. Thigh-length versus below-knee stockings for DVT prophylaxis after stroke: a randomized trial. Ann Int Med. 2010;153:553–62. DOI: 10.7326/0003-4819-153-9-201011020-00280.

4. Details of the impact (indicative maximum 750 words)

CLOTS-1 showed that full-length GCS for stroke patients were ineffective, and in fact had adverse effects. CLOTS-2 indicated that knee-length GCS, which are more commonly used, might actually increase the risk of DVT.

Pathways to impact

The UoE trial team carried out a substantial programme of dissemination activities beyond the primary results publication: 20 local, national and international conference presentations, two webinars, materials posted on the CLOTS website (http://www.dcn.ed.ac.uk/clots/), engagement with five guideline committees (including the National Institute for Health and Care Excellence (NICE) and the Royal College of Physicians), and extensive media coverage. These efforts have directly impacted on both the revision of guidelines and on clinical practice. The outcome has been the diversion of valuable nursing time to other more effective areas of stroke care than applying and maintaining GCS compliance, ensuring greater comfort for patients by them not having to wear the stockings (which are hot, uncomfortable and often get soiled), and substantial cost savings.

Impact on public policy

Prior to the publication of the results of CLOTS-1, the draft NICE guidelines on the prevention of venous thromboembolism in hospital patients recommended GCS in stroke patients. However, the final publication of the guidelines was delayed for 3 months so that the results of the CLOTS-1 trial could be taken into account. The final recommendation (March 2011) was: “Do not offer anti-embolism stockings for venous thromboembolism prophylaxis to patients who are admitted for stroke” [5.1].

The US guidelines now also recommend against routine use of GCS in stroke patients [5.2]. The American College of Physicians quoted the CLOTS trials and recommended “against the use of mechanical prophylaxis with graduated compression stockings for prevention of venous thromboembolism (grade: strong recommendation, moderate-quality evidence)” in stroke patients [5.3].

Also in response to the trial results, national guidelines in at least Scotland [5.4], Singapore [5.5], Canada [5.6], Italy and South Africa no longer recommend use of GCS in stroke patients.

Impact on practitioners and services

The trial results and resultant altered guidelines have had a clear effect on healthcare provision in the UK and beyond. The results of a 2011 web-based survey of practice amongst UK stroke

physicians showed "the virtual eradication of use of stockings for thromboprophylaxis in acute stroke in the UK" and concluded that "the CLOTS studies have had a dramatic impact on clinical practice" [5.7]. These findings are supported by another study; "Data on GCS use were available for 1,971 patients with acute stroke enrolled into the Efficacy of Nitric Oxide in Stroke trial from February 2003 to April 2011. The use of GCS in the UK declined from 60.7% (398/656) to 3.5% (20/567) ($p < 0.001$) after publication of the CLOTS-1 trial results. Similar reductions were seen in other GCS-using countries. Practice change was apparent within 3 months of the study publication" [5.8].

Impact on the economy

The study findings are applicable to the approximately 65,000 immobile stroke patients admitted to hospital in the UK each year. Based on published figures [5.9], the "virtual eradication" of GCS use in the UK is estimated to have saved, per annum, £1.3M (assuming three pairs/patient costing £7 each) for the GCS themselves, £20M in nursing time to size, fit and monitor the stockings, plus additional annual cost associated with the treatment of the 1500 patients with skin breaks caused by stocking use.

Impact on health and welfare

As a result of the CLOTS trials, stroke patients are no longer subjected to wearing ineffective uncomfortable stockings for prolonged periods in hospital. Furthermore, they are at less risk of developing skin damage/ulceration that may themselves prolong hospital admission, estimated as 6000 fewer cases since 2009.

5. Sources to corroborate the impact (indicative maximum of 10 references)

5.1 National Institute for Health and Care Excellence (2010 as amended). Venous thromboembolism: reducing the risk -full guideline. http://guidance.nice.org.uk/CG92. *[UK guidelines.]*

5.2 Lansberg M, O'Donnell M, Khatri P, et al.; American College of Chest Physicians. Antithrombotic and thrombolytic therapy for ischemic stroke: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012; 141:e601S–36. DOI: 10.1378/chest.11-2302. *[North American guidelines.]*

5.3 Qaseem A, Chou C, Humphrey L, Starkey M, Shekelle P for the Clinical Guidelines Committee of the American College of Physicians. Venous thromboembolism prophylaxis in hospitalized patients: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2011;155:625–32. DOI: 10.7326/0003-4819-155-9-201111010-00011. *[Recommendations of the American College of Physicians.]*

5.4 SIGN Guideline 118 (2010). Management of patients with stroke: rehabilitation, prevention and management of complications, and discharge planning. http://www.sign.ac.uk/pdf/sign118.pdf *[Scottish guidelines.]*

5.5 Venketasubramanian N, Pwee K, Chen C on behalf of the Singapore Ministry of Health Clinical Practice Guidelines Workgroup on Stroke and Transient Ischaemic Attacks. Singapore ministry of health clinical practice guidelines on stroke and transient ischemic attacks. Int J Stroke. 2011;6:251–8. DOI: 10.1111/j.1747-4949.2011.00602.x. *[Singaporean guidelines.]*

5.6 Canadian Best Practice guidelines, fourth edition (2013). http://www.strokebestpractices.ca/index.php/acute-stroke-management/inpatient-management-and-prevention-of-complications-following-acute-stroke-or-tia/. *[Canadian guidelines.]*

5.7 Sett A, Mistri A. A dramatic impact of the CLOTS studies on clinical practice in the UK. Int J Stroke. 2011;6(suppl 2):15. DOI: 10.1111/j.1747-4949.2011.00684.x. *[Corroborates the impact of CLOTS on UK clinical practice.]*

5.8 Ankolekar S, Renton C, Bereczki D, et al. Effect of the neutral CLOTS 1 trial on the use of graduated compression stockings in the Efficacy of Nitric Oxide Stroke (ENOS) trial. J Neurol Neurosurg Psychiatry. 2013;84:342–7. DOI: 10.1136/jnnp-2012-303396. *[Corroborates the impact*

of CLOTS on clinical practice.]

5.9 Bath P, England T. Thigh-length compression stockings and DVT after stroke. Lancet. 2009;373:1923–4. DOI: 10.1016/S0140-6736(09)60990-9. *[Corroborates cost savings in the UK.]*