Institution: University of Edinburgh		
Unit of Assessment: 4		
Title of case study: F: Reversal in recommended standard of care of treating immobile stroke patients prevents deep vein thrombosis and improves survival after stroke		
Period when the underpinning research was undertaken: 2001 – 2015		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Martin Dennis	Chair of Stroke Medicine	1990 – present
Peter Sandercock	Chair of Medical Neurology	1987 – 2020
John Forbes	Reader in Health Economics	1987 – 2013
Gordon Murray	Chair of Statistics	1995 – 2016
William Whiteley	Scottish Senior Clinical Fellow	2010 – present
Period when the claimed impact occurred: August 2013 – December 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Underpinning Research: The large-scale randomised control trial CLOTS-3, led by Edinburgh Neuroscience researchers, showed that Intermittent Pneumatic Compression (IPC) prevents Deep Vein Thrombosis (DVT) and improves survival in immobile stroke patients. Previous trials led by the same group have shown that the normal practice of Graduated Compression Stockings (GCS) and heparin did not improve clinical outcomes.

Significance and Reach of Impact: At least 6 national and international guidelines now recommend IPC and advise against GCS and heparin for DVT prevention in immobile stroke patients based on Edinburgh Neuroscience trial results. This has led to a reversal in the recommended standard of care: Use of heparin and GCS has been dropped in immobile stroke patients, whereas the use of IPC increased from 0% to 53% in eligible patients in Scotland and from 0% to 55.2% in the UK between 2013 and 2017. Using the 2017 IPC application levels, 1,480 DVTs are avoided and 786 lives are saved each year in the UK as a direct result of the CLOTS-3 trial.

2. Underpinning research

The Challenge: Lack of clinical data for stroke prophylaxis

Approximately 110,000 people are admitted to hospital in the UK with a stroke each year, and about half of them (55,000) will be unable to walk. Of these patients, approximately 25% (13,750) die within 6 months. Deep vein thrombosis (DVT), a type of venous thromboembolism (VTE; a blood clot forming in a vein, preventing blood flow), will develop in approximately 20% (11,000) of the 55,000 immobile stroke patients, with clinical signs of potentially-fatal pulmonary emboli in 5% of them. Data from clinical trials on the relative risks and benefits of different prophylactic approaches using antithrombotic drugs or mechanical methods in stroke patients was previously lacking.

Prior to Edinburgh Neuroscience's research, routine practice to prevent DVT in stroke patients was to administer anticoagulants, specifically heparin, and provide graduated compression stockings (GCS). Another option was Intermittent Pneumatic Compression (IPC), a mechanical prophylactic method consisting of inflatable sleeves that are wrapped around the legs and compress them one at a time at intervals with an electric pump, thus increasing blood flow in the legs; this had previously been shown to be effective in surgical patients.

To determine the best method to improve survival after stroke, Edinburgh Neuroscience researchers carried out randomised controlled trials (RCTs) and meta-analyses to establish the balance of risk and benefits and determine the relative effectiveness of GCS, heparin and IPC in preventing DVTs in immobile stroke patients.

Graduated Compression Stockings do not prevent DVT
As reported in REF2014/4/B, the CLOTS-1 & -2 trials (2001–2009) led by Edinburgh Neuroscience researchers showed that, among stroke patients, routine application of full-length GCS did not significantly reduce clinical outcomes, i.e. DVT or pulmonary emboli [3.1], and those allocated knee-length GCS had a significantly higher risk of DVT than those allocated full-length GCS [3.2]. This led to changes in clinical guidelines and practice, but did not address the value of IPC or heparin in patients after stroke.

Anticoagulants do not improve post-stroke survival
The Edinburgh Neuroscience acute stroke team then conducted an individual patient data meta-analysis of 5 large multicentre RCTs of heparin in strokes, the largest of which was the Edinburgh-led trial IST. This confirmed earlier findings that whilst heparin might reduce risk of post-stroke DVT, it does not result in any net benefit in terms of survival or recovery [3.3].

Intermittent Pneumatic Compression reduces risk of DVT and death
In 2010, the Edinburgh Neuroscience stroke team led a Cochrane systematic review of trials of IPC administration after stroke. This identified 2 trials (177 patients), that showed a non-significant reduction in risk of DVT associated with IPC [3.4]. The subsequent CLOTS-3 trial, led by Dennis, (2008 to 2012) therefore aimed to provide definitive data on whether IPC reduced the risk of DVT. 1,438 immobile stroke patients were randomised to no IPC and 1,438 patients to receive IPC in 94 UK centres. The trial showed that IPC use reduced the absolute risk of post-stroke DVT by 3.6% (95% CI -5.8 to -1.4) by day 30, resulted in fewer all-cause deaths at 30 days (absolute reduction 2.3% (95% CI -0.1 to 4.7) and reduced the hazard of death at six months (hazard ratio: 0.86, 95% CI 0.73 to 0.99), but showed no improvement in disability [3.5, 3.6]. These data were not previously reported in REF2014.

3. References to the research

[3.1] CLOTS Trials Collaboration. Dennis M, Sandercock PA, Reid J, Graham C, Murray G, Venables G, Rudd A, Bowler G. 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.

[3.2] The CLOTS Trials Collaboration. 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

[3.3] Whiteley WN, Adams HP, Bath PM, Berge E, Sandset PM, Dennis M, Murray GD, Wong KS, Sandercock PA. Targeted use of heparin, heparinoids, or low-molecular-weight heparin to improve outcome after acute ischaemic stroke: an individual patient data meta-analysis of randomised controlled trials. Lancet Neurology. 2013;12:539-45. doi: 10.1016/S1474-4422(13)70079-6

[3.4] Naccarato M, Chiodo F, Grandi F, Dennis M, Sandercock P. Physical methods for preventing deep vein thrombosis in stroke Cochrane Database Syst Rev 2010;8:CD001922 doi: 10.1002/14651858.CD001922.pub3.

[3.5] CLOTS (Clots in Legs Or sTockings after Stroke) Trials Collaboration. Effectiveness of intermittent pneumatic compression in reduction of risk of deep vein thrombosis in patients who have had a stroke (CLOTS 3): a multicentre randomised controlled trial. The Lancet 2013;382:516–24. doi: 10.1016/S0140-6736(13)61050-8.

[3.6] CLOTS (Clots in Legs Or sTockings after Stroke) Trials Collaboration. Effect of intermittent pneumatic compression on disability, living circumstances, quality of life, and hospital costs after stroke: secondary analyses from CLOTS 3, a randomised trial. Lancet Neurology 2014;13:1186-92. doi: 10.1016/S1474-4422(14)70258-3.

Key grants:
[3.7] A randomised trial to establish the effectiveness of graduated compression stockings (GCS) to prevent post stroke deep venous thrombosis and pulmonary embolism (PE). Medical Research Council 2003-2009 GBP1,069,000 (MRC Ref No: G0200531)

[3.8] The CLOTS trial 3 (Clots in Legs Or sTockings after Stroke): a multicentre randomised trial to evaluate the effectiveness of Intermittent Pneumatic Compression (IPC) to prevent venous thromboembolism after stroke. HTA 2010 - 2014 GBP2,500,000

4. Details of the impact

Impact on policy and guidelines

All citing Edinburgh Neuroscience's CLOTS-3 trial, the UK's National Institute for Health and Care Excellence (NICE; 2018) [5.1], Scottish Intercollegiate Guidelines Network (SIGN; 2014) [5.2], Royal College of Physicians (RCP; 2016) [5.3], European Stroke Organisation (ESO; 2016) [5.4], Danish Stroke Society, Heart and Stroke Foundation of Canada and American Heart Association (AHA; 2018) [5.5] have changed their recommendation to apply IPC for DVT prophylaxis within 3 days of acute stroke. An important issue considered by NICE was that some people who survive a stroke do so with residual disability, so it is vital to communicate to patients and carers that IPC does improve survival, but sometimes this is accompanied by disability. Overall, however, the NICE expert committee *"regarded the risk/benefit trade-off such that there is likely to be sufficient overall health gain to justify considering use of IPCD* [IPC devices] *in this population."* [p.242; 5.1].

Based on Edinburgh Neuroscience's trial results, the RCP, ESO, Canadian Stroke and AHA updates (all since REF2014) also recommend to not routinely give heparin for prevention of DVT in immobile stroke patients. RCP guidance states: *"[…] do not attempt to select those patients in whom the risk of VTE is sufficiently high to warrant the use of heparin. Do use intermittent pneumatic compression instead"* [p. xviii; 5.3]. The updated AHA guidelines for Management of Acute Ischemic Stroke (2018) now recommend IPC for DVT, and specifically do not recommend heparin, citing Edinburgh Neuroscience research: *"The benefit of prophylactic-dose subcutaneous heparin […] in immobile patients with AIS [acute ischaemic stroke] is not well established"* [p.e81-e82; 5.5]. AHA guidelines also specifically state that elastic compression stockings should not be used in ischaemic stroke.

Impact on clinical management

Following clinical guideline updates, the CLOTS trials have led to a dramatic shift worldwide in best practice and management of stroke patients to prevent DVT and reduce the risk of VTE. Citing CLOTS-3, the president of the American Academy of Emergency Medicine and colleagues recommend the use of IPC: *"We have the clinical evidence—let's use it. […] This landmark study should transform the clinical practice of DVT prevention in stroke patients"* [5.6]. In 2014, the NHS recognised the importance of reducing VTE-related mortality and made available GBP1,000,000 'pump priming' funding for 6 months' supply of IPC sleeves for all stroke units in England [5.7], acknowledging that the major barrier to practice change was the cost of procuring IPC sleeves. The number of IPC sleeves procured by stroke units in Scotland increased from zero in 2014 to 270 in 2015 and 2,900 in 2018 [5.8]; thus showing a 10-fold increase since 2015.

Impact on clinical practice

A 2017 National Institute for Health Research review cited a stroke consultant's summary of the impact of CLOTS-3 as: *"The CLOTS 3 trial has dramatically altered how patients are managed in stroke units to prevent deep vein thrombosis. IPC devices have now replaced compression stockings as the primary preventative measure in UK stroke units as a direct result of this trial."* [p.25; 5.9].

Routine clinical data are being collected by the Scottish Stroke Care Audit and the Sentinel Stroke National Audit Programme (SSNAP). Before the publication of the CLOTS-3 trial results (2013), IPCs were never applied to immobile stroke patients. In Scotland, the percentage of immobile patients being offered IPC more than doubled from 23% in 2014 (when recording began) to 53%

in 2017 [p.25; Chart 3.10; 5.10]. In England, Wales and Northern Ireland (SSNAP reach), the percentage of all stroke patients who had IPC applied increased from 0% in 2013 to 8.6% in 2014/15 to 27.6% in 2017/18 [p.38; 5.11]. Approximately 50% of stroke patients are immobile; thus, approximately 55.2% of those eligible for IPC were receiving it in 2017/18.

Impact on health & welfare
Using 2017/18 IPC application levels in the UK (53% Scotland, 55.2% rest) [5.10; 5.11]), 1,480 DVTs are avoided and 786 lives are saved every year as a direct result of the CLOTS-3 trial [5.11].

5. Sources to corroborate the impact

[5.1] NICE 2018. Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism

[5.2] SIGN 122 Oct 2014. Prevention and management of venous thromboembolism

[5.3] RCP 2016. National clinical guideline for stroke

[5.4] European Stroke Organisation (ESO) guidelines for prophylaxis for venous thromboembolism in immobile patients with acute ischaemic stroke. Dennis M, et al. 2016 for the European Stroke Journal, 1(1), 6–19. doi: 10.1177/2396987316628384

[5.5] AHA Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Powers WJ, et al 2018 Stroke, 49:e46–e99 doi: 10.1161/STR.0000000000000158

[5.6] Reiter & Fengler 2015. Two Steps Can Reduce the Incidence of Secondary Stroke.

[5.7] NHS 2014. Intermittent Pneumatic Compression (IPC) sleeves Programme FAQs

[5.8] Data from NHS National Services Scotland – the data are from the National Distribution Centre and analysed by Martin Dennis. (Data were originally in an Excel spreadsheet but has been converted to a PDF for PURE purposes)

[5.9] National Institute for Health Research 2017. Roads to Recovery - Organisation and quality of stroke services

[5.10] Scottish Stroke Care Audit 2018. Scottish Stroke Improvement Programme

[5.11] Sentinel Stroke National Audit Programme Clinical audit April 2013 – March 2018 Annual Public Report.

The DVTs averted and lives saved were calculated as follows:

- There are approximately 110,000 stroke admissions per year in the UK. Approximately 50% (i.e. 55,000) will be immobile and potentially benefit from IPC.
- From CLOTS 3, any DVT occurred in 21.1% when none received IPC (11,605/year) and 16.2% in those who did receive IPC (8,910/year) – a reduction of 2,695. However, in routine practice only 55% of patients received IPC in reality, leading to a reduction of 1,480 DVTs per year.
- Similarly for deaths, in the trial 25.5% of those without IPC died by 6 months (14,025/year) while 22.9% of those receiving IPC died (12,595/year) – a reduction of 1,430 if all eligible patients were treated with IPC. Since in routine practice 55% received IPC, this averted 786 deaths per year.