Institution: University of Birmingham

Unit of Assessment: UoA1

Title of case study: Improving clinical decision making and patient outcomes in severe limb ischaemia

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

Severe Limb Ischaemia (SLI), in which there is reduced blood flow to the leg(s), is the commonest cause worldwide of gangrene and limb loss. The BASIL trial, led by Professor Andrew Bradbury at the University of Birmingham, was the first (and remains the only) randomised controlled trial to investigate whether surgical bypass or endovascular ('keyhole') treatment is best at relieving symptoms and preventing amputation and/or death in patients with SLI. The outcomes of the study have been of worldwide interest, and the recommendations put forward by the team have been endorsed by a number of high profile clinical organisations. These findings are also nowincorporated within a series of national and international guidelines on SLI.

2. Underpinning research (indicative maximum 500 words)

SLI, a condition where atherosclerosis (*aka* 'hardening of the arteries') leads to a severe lack of blood supply to the leg(s), is a common cause of pain, gangrene, amputation and death; and represents a major health and social care issue in *all* developed and developing economies. The numbers of patients requiring lower limb revascularisation for SLI are likely to increase significantly worldwide as a result of ageing populations, the failure to significantly reduce tobacco consumption and the increasing global prevalence of diabetes, all of which are closely associated with the condition.

Failure to improve the blood supply to the leg(s) (termed' revascularisation')in SLI can be associated with amputation and death rates as high as 50% at 12 months. These risks can be dramatically reduced by timely intervention. The two principal treatment alternatives for SLI are bypass surgery and endovascular ('keyhole') treatment. The latter comprises the use of angioplasty (the stretching of the narrowed artery from the inside using a balloon)and stenting (the placing of metal tubes within the narrowed arteries to hold them open). Both revascularisation strategies have advantages and disadvantages, and for many years there has been fierce debate within vascular surgery as to which patient is best treated by which method.

The NIHR Health Technology Assessment (HTA)-funded (£1,012,736) Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial led by Chief Investigator Professor Andrew Bradbury (Sampson Gamgee Professor of Vascular Surgery, at the University of Birmingham since 2000) was the first (and remains the only) multicentre randomised controlled trial (RCT) to investigate whether a 'surgical bypass first' or an 'endovascular ('keyhole') treatment first' revascularisation strategy is best at relieving symptoms and preventing amputation and/or death in patients with SLI.

The initial results of the trial were published in the Lancet in 2005 [**1**] and suggested that, up to two years after randomisation, amputation-free and overall survival were similar following surgical bypass and endovascular treatment. However, further analysis of the survival curves suggested that surgical bypass might be better in the longer term with respect to health-related quality of life and overall survival of patients. A further application to the HTA to fund longer term follow-up was successful and the final results of the BASIL trial were published as an HTA Monograph [**2**], and in a dedicated supplement of the Journal of Vascular Surgery [**3-5**] in 2010.

These final BASIL trial data have been interpreted internationally as supporting an 'endovascular first' revascularisation strategy for patients with SLI who are expected to live for less than 2 years. However, for those patients expected live for more than 2 years, surgical bypass is preferred in most patients as it is associated with a significant improvement in overall survival and a better quality of revascularisation in the longer term. By implementing revascularisation strategies in accordance with BASIL data, and paying heed to the BASIL risk prediction model, it is anticipated that health and social care resources will be utilised in the most clinically and cost-effective manner in both developed and developing countries.

The success of the BASIL trial and the resulting widespread support from individual clinicians and organisations such as the US Society for Vascular Surgery, American Heart Association; European

Society for Vascular Surgery, Vascular Society of Great Britain and Ireland (VSGBI), British Society of Interventional Radiology (BSIR), UK Circulation Foundation, Diabetes UK, and National Institute for Health and Care Excellence (NICE) has led to a further RCT (BASIL-2) being recently funded (NIHR HTA, £2,004,572, Chief Investigator, Professor Andrew Bradbury). BASIL-2 will focus on diabetic (below the knee) vascular disease and evaluate modern endovascular interventions such as drug eluting stents and balloons (which were not available at the time of the original BASIL trial) for the management of SLI. The trial will take place in 11 UK regions from the south coast of England (Southampton) to the north of Scotland (Aberdeen) and is hosted by the University of Birmingham Clinical Trials Unit (BCTU).

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

1. Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial. Adam DJ, Beard JD, Cleveland T, Bell J, **Bradbury AW**, Forbes JF, Fowkes FG, Gillepsie I, Ruckley CV, Raab G, Storkey H; BASIL trial participants. Lancet. 2005 Dec 3;366(9501):1925-34. *PMID: 16325694*

2. Multicentre randomised controlled trial of the clinical and cost-effectiveness of a bypass-surgery-first versus a balloon-angioplasty-first revascularisation strategy for severe limb ischaemia due to infrainguinal disease. The Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial. **Bradbury AW**, Adam DJ, Bell J, Forbes JF, Fowkes FG, Gillespie I, Raab G, Ruckley CV. Health Technol Assess. 2010 Mar;14(14):1-210, iii-iv. *doi: 10.3310/hta14140. PMID: 20307380*

3. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: Analysis of amputation free and overall survival by treatment received. **Bradbury AW**, Adam DJ, Bell J, Forbes JF, Fowkes FG, Gillespie I, Ruckley CV, Raab GM; BASIL trial Participants. J Vasc Surg. 2010 May;51(5 Suppl):18S-31S. *doi: 10.1016/j.jvs.2010.01.074*. Erratum in: J Vasc Surg. 2010 Dec;52(6):1751. Bhattachary, V [corrected to Bhattacharya, V]. PMID: 20435259

4. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: Health-related quality of life outcomes, resource utilization, and cost-effectiveness analysis. Forbes JF, Adam DJ, Bell J, Fowkes FG, Gillespie I, Raab GM, Ruckley CV, **Bradbury AW**; BASIL trial Participants. J Vasc Surg. 2010 May;51(5 Suppl):43S-51S. *doi: 10.1016/j.jvs.2010.01.076. PMID: 20435261*

5. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: A survival prediction model to facilitate clinical decision making. **Bradbury AW**, Adam DJ, Bell J, Forbes JF, Fowkes FG, Gillespie I, Ruckley CV, Raab GM; BASIL Trial Participants. J Vasc Surg. 2010 May;51(5 Suppl):52S-68S. doi: 10.1016/j.jvs.2010.01.077. Erratum in: J Vasc Surg. 2010 Dec;52(6):1751. Bhattachary, V [corrected to Battacharya, V]. *PMID: 20435262*

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

Impact on UK clinical practice and patient care

The BASIL trial led to a number of recommendations, many of which have been actively embraced by NICE as part of their recently published (August 2012) Peripheral Arterial Disease (PAD) Clinical Guidelines [**1**]. Professor Bradbury was a member of the NICE PAD Guidelines Development Group. Specifically linked to BASIL findings, the guidelines emphasise:

- Significant health gains for patients with SLI lie in earlier diagnosis and imaging; the implementation of evidence-based best medical therapy; appropriate imaging; and prompt referral to a specialist vascular service
- The best outcomes for SLI are achieved when vascular surgeons and interventional radiologists work closely together with other professionals as part of a multidisciplinary team in specialist, high-volume centres
- The decision whether to perform bypass surgery or balloon angioplasty first appears to depend upon co-morbidities (life expectancy); pattern of disease; availability of a vein as a bypass conduit; and patient preference

In the context of these guidelines, in terms of clinical practice and patient care the BASIL findings translate to the following changes:

- SLI patients expected to live less than 2 years should usually be offered endovascular intervention first, as it is associated with less morbidity and cost, and such patients are unlikely to enjoy the longer-term benefits of surgery
- Those patients expected to live beyond 2 years should usually be offered bypass surgery

first, especially where a vein is available as a conduit
- Many patients who could not undergo a vein bypass would probably have been better served by a first attempt at balloon angioplasty than prosthetic bypass. Surgeons should make every effort to use vein and should view prosthetic material as a last resort

Impact on international clinical guidelines

The impact of these findings and their clinical uptake is not limited to the UK. Following publication of the trial outcomes Professor Bradbury has been invited to present the BASIL data in Europe, the Middle and Far East, North and South America and Australia. The novel insights and recommendations emanating from BASIL were consequently adopted into and highlighted in a number of key international guidelines which are now guiding clinical practice in this area:

- The 2011 European Society of Cardiology Guidelines on the diagnosis and treatment of PAD [**2**], endorsed by the European Stroke Association, reference BASIL-1 in their recommendations for surgical revascularisation in with respect to revascularisation state: *"When surgery is considered to revascularise infra-iliac lesions, autologous saphenous vein is the bypass graft of choice."*
- The 2011 American College of Cardiology Foundation/American Heart Association updated guidelines for 'Management of Patients with Peripheral Artery Disease' [**3**] discuss the BASIL trial and how this has led to two new recommendations:
    - *For patients with limb-threatening lower extremity ischemia and an estimated life expectancy of 2 years or less or in patients in whom an autogenous vein conduit is not available, balloon angioplasty is reasonable to perform when possible as the initial procedure to improve distal blood flow.*
    - *For patients with limb-threatening ischemia and an estimated life expectancy of more than 2 years, bypass surgery, when possible and when an autogenous vein conduit is available, is reasonable to perform as the initial treatment to improve distal blood flow*

As noted above, BASIL-1 has been endorsed by a number of key organisations; most recently, as part of the process of applying to the HTA for funds to conduct BASIL-2 (NIHR HTA, £2,004,572, Chief Investigator, Professor Andrew Bradbury):

- ***Circulation Foundation:****"The original BASIL trial has had profound impact worldwide, indeed I personally have heard BASIL data referred to and discussed at meetings on at least 5 continents! Trials of such importance have a major effect on clinical practice and patient care"*[**4**].
- ***European Society of Vascular Surgery****: "The BASIL-1 trial has had a profound effect on the management of lower limb ischaemia at a time when more and more clinicians had been moving towards an endovascular first approach*" [**5**]

As a result of this work, the World Federation of Vascular Societies, (WFVS) Society for Vascular Surgery (SVS) and European Society for Vascular Surgery (ESVS) have agreed on the need for clear standards for peripheral arterial care, and come together to develop standard guidelines. Professor Andrew Bradbury was elected as the WFVS Representative to lead this initiative by an Executive group at which there were representatives from all the supporting continental societies: ESVS; SVS; Australasian Vascular Society; Asian Vascular Society; Southern African Society; Indian Vascular Society, Japanese Vascular Society and Society of Vascular Surgery and Angiology for Latin America. These societies represent almost all vascular surgical societies in the countries in the world, and Prof Bradbury will now lead the discussions and collaborations across not only Europe but also Asia, Australasia and Southern Africa that take this important area of patient care forward.

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

1. 'Lower limb peripheral arterial disease: Diagnosis and management' NICE Clinical Guideline 147; Methods, evidence and recommendations August 2012 (http://guidance.nice.org.uk/CG147)

2. 'ESC Guidelines on the diagnosis and treatment of peripheral artery diseases', European Heart Journal (2011) 32, 2851–2906 *doi: 10.1093/eurheartj/ehr211*

3. 2011 ACCF/AHA focused update of the guideline for the management of patients with

peripheral artery disease (updating the 2005 guideline). American College of Cardiology Foundation; American Heart Association Task Force; Society for Cardiovascular Angiography and Interventions; Society of Interventional Radiology; Society for Vascular Medicine; Society for Vascular Surgery, Rooke TW, Hirsch AT, Misra S, Sidawy AN, Beckman JA, Findeiss LK, Golzarian J, Gornik HL, Halperin JL, Jaff MR, Moneta GL, Olin JW, Stanley JC, White CJ, White JV, Zierler RE. Vasc Med. 2011 Dec;16(6):452-76. doi: 10.1177/1358863X11424312. *PMID: 22128043*

4. Circulation Foundation letter of support for BASIL-2.

5. European Society of Vascular Surgery letter of support for BASIL-2

6. E-mail from World Federation of Vascular Societies informing Prof Bradbury of his appointment