Addressing delays to treatment in patients with Chronic Limb-Threatening Ischaemia

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Abstract

Patients with CLTI often face long delays from referral to the vascular surgery service and hospital admission to revascularisation, and there is limited evidence on the effect of these delays on patient outcomes. This thesis aims to identify factors associated with delays to treatment in patients with CLTI and explore interventions to address them.

The first cohort study estimated that only 51% of patients admitted as emergencies with CLTI have revascularisation within the recommended 5-days. Factors associated with delayed revascularisation were older age, more comorbidities, presence of infection and tissue loss, open procedures, and admission later in the week. The latter reflects how services are organised and supports arguments for 7-day vascular service. A further cohort study found that the delays from emergency admission to revascularisation were independently associated with higher 1-year mortality in patients undergoing revascularisation for CLTI with tissue loss but not in those with less severe forms of PAD, and there was no evidence of an association between delay and major amputation.

Subsequently, a Quality Improvement Collaborative (QIC) between eleven vascular centres was implemented to identify interventions that can reduce delays to revascularisation. These interventions significantly increased the proportion of patients revascularised within 5-days, and reduced the length of hospital stay and 30-day readmission rate compared to baseline performance. The reduction in LOS and readmission rate were significantly higher than in non-participating centres. A mixed methods study of semi-structured interviews and an online survey with participating clinicians identified factors that influenced the local uptake of changes and the success of this vascular QIC.

Finally, the COVID-19 pandemic was an important contextual factor during the QIC.A cohort study examining its effect found a 28% reduction in vascular lower limb activity during the COVID-19 pandemic more marked for elective revascularisation procedures, and increased mortality related to concomitant SARS-CoV-2 infection.

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Declaration

I confirm that this work is original and that if any passage(s) or diagram(s) have been copied from academic papers, books, the internet or any other sources these are clearly identified by the use of quotation marks and the reference(s) is fully cited. I certify that, other than where indicated, this is my own work and does not breach the regulations of HYMS, the University of Hull or the University of York regarding plagiarism or academic conduct in examinations. I have read the HYMS Code of Practice on Academic Misconduct, and state that this piece of work is my own and does not contain any unacknowledged work from any other sources. I confirm that any patient information obtained to produce this piece of work has been appropriately anonymised.

Contributors to the studies in this thesis

Chapter 2: Factors associated with delays to revascularisation in patients with chronic limb-threatening ischaemia: a population-based cohort study

Professor Ian Chetter (ICC), Mr Jonathan Boyle (JRB) and Professor David Cromwell (DAC) conceived the idea for this study and secured the funding for this work. I contributed to the study concept and design, performed the data analysis and interpretation, and completed the writing up. DAC oversaw the data analysis process. Dr Qiuju Li (QL) and Dr Amundeep Johal (AJ) provided statistical advice. Mr Sam Waton (SW), National Vascular Registry (NVR) project manager, provided the data from the NVR. All listed provided critical review of the final write-up. This chapter has been published in the British Journal of Surgery following peer review.

Chapter 3: The association of timing of revascularisation with postoperative outcomes of patients with chronic limb-threatening ischaemia

The idea for this study was conceived jointly with my supervisory team (ICC, JRB, DAC). I developed the study protocol, analysed and interpreted the data and wrote up the findings. DAC supervised and offered advice throughout the data analysis process. SW provided the data from the Hospital Episode Statistics and Office for National Statistics databases. All listed provided critical review of the final write-up.

Chapter 4: Implementation and short-term outcomes of the Peripheral Arterial Disease Quality Improvement Programme (PAD QIP)

The idea for the PAD QIP was conceived by JRB, ICC, and DAC, who secured the funding that supported this work and recruited the 11 participating centres. I designed the protocol for the PAD QIP and led the team of experts that oversaw its implementation, including JRB, ICC, DAC, SW, Mr Arun Pherwani (ADP), and Ms Eleanor Atkins (EA). I performed the data analysis, interpretation, and writing of the findings. DAC supervised and offered advice on the data analysis process for the short-term outcomes. SW provided the NVR data.

Chapter 5: The effect of the COVID-19 pandemic on the outcomes of lower limb vascular procedures for patients with peripheral arterial disease in the UK

The study was conceived by DAC, ICC, JRB, ADP and me. I performed the analysis and interpretation of the data and write-up of the results. DAC, QL, and AJ provided statistical advice. SW provided the NVR data that were used in the analysis. All listed provided critical review of the write-up. This chapter has been peer-reviewed and accepted for publication in the European Journal of Vascular and Endovascular Surgery.

Chapter 6: Factors that affected the implementation of the Peripheral Arterial Disease Quality Improvement Programme: a mixed methods study

This mixed methods study was conceived by ICC and me. I wrote the study protocol, which was reviewed by Dr Elizabeth Glidewell (EG), ICC, DAC, and JRB prior to submission to the ethics committee of Hull York Medical School. I designed the interview guide and the online survey, recruited and consented the participants, conducted the semi-structured interviews, analysed the data and wrote the results. EG and Dr Laura Sheard (LS) provided advice on the qualitative analysis and supervised the study. ICC, DAC, and LS provided critical review of the write-up.

Publications

Peer-reviewed publications relating to this research

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Birmpili P, Li Q, Johal AS, Waton S, Atkins E, Boyle JR, Chetter I, Williams R, Pherwani AD, Cromwell DA. Outcomes of Surgery for Patients with Peripheral Arterial Disease During the COVID-19 Pandemic in the United Kingdom: A Population Based Study. Eur J Vasc Endovasc Surg. 2023:S1078-5884(23)00124-7. doi:10.1016/j.ejvs.2023.02.002.

Other peer-reviewed publications during this research but not thesis related

Birmpili P, Li Q, Johal AS, Atkins E, Waton S, Chetter ICC, Boyle JR, Pherwani AD, Cromwell DA. Outcomes after minor lower limb amputation for peripheral arterial disease and diabetes: a population-based cohort study. Br J Surg. 2023 (Accepted for publication April 20, 2023)

Birmpili P, Atkins E, Li Q, Johal AS, Waton S, Williams R, Pherwani AD, Cromwell DA. Evaluation of the ICD-10 system in coding revascularisation procedures in patients with peripheral arterial disease in England: a retrospective cohort study using national administrative and clinical databases. eClinicalMedicine. 2022;55. doi:10.1016/j.eclinm.2022.101738

Birmpili P, Atkins E, Boyle JR, Sayers RD, Blacker K, Williams R, Pherwani AD. The Vascular PAD-QIF CQUIN: What is it, Why is it important, What does it mean for Vascular Units? Journal of the Vascular Societies of Great Britain and Ireland. 2022;1(3):63-64. doi:10.54522/jvsgbi.2022.018.

Li Q, **Birmpili P**, Johal AS, Waton S, Pherwani AD, Boyle JR, Cromwell DA. Delays to revascularisation for patients with chronic limb-threatening ischaemia in England. Br J Surg. 2022;109(8):717-726. doi:10.1093/bjs/znac109.

Atkins E, **Birmpili P**, Pherwani AD, Mani K, Boyle JR. Quality Improvement in Vascular Surgery. Eur J Vasc Endovasc Surg. 2022;63(6):787-788. doi:10.1016/j.ejvs.2022.03.013

Nickinson ATO, **Birmpili P**, Weale A, Chetter I, Boyle JR, Loftus I, Davies RSM, Sayers RD. What is the current practice for managing patients with chronic limb-threatening ischaemia in vascular surgery services? A survey of UK vascular surgeons. Ann R Coll Surg Engl. 2021;103(9):694-700. doi:10.1308/rcsann.2021.0075.

Johal AS, Naylor AR, Pherwani AD, Li Q, **Birmpili P**, Waton S, O'Neill R, Boyle JR, Cromwell DA. Carotid Endarterectomy Following Intravenous Thrombolysis in the UK. Eur J Vasc Endovasc Surg. 2021;62(1):9-15. doi:10.1016/j.ejvs.2021.03.033.

Presentations

Birmpili P. Reducing time to treatment in patients with CLTI. Invited oral presentation at the Vascular Societies' Annual Scientific meeting in Brighton, November 2022

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Chapter 1. Introduction

1.1 Chronic Limb-Threatening Ischaemia – the problem and context

1.1.1 Epidemiology

Peripheral Arterial Disease (PAD) is a circulatory condition where blood flow is reduced due to narrowing (stenosis) or blockage (occlusion) of the blood vessels. In some contexts, the term is used for all arterial diseases other that those involving the aorta and the coronary arteries, such as mesenteric, renal, upper limb, extracranial carotid and vertebral artery disease[1]. However, in this thesis, the term PAD is used to describe the condition affecting the arteries of the lower limbs, from common iliac to pedal. PAD can be acute or chronic. Presence of severe symptoms for less than 2 weeks is considered Acute Limb Ischaemia (ALI), which may present with pain, pallor, poikilothermia, paraesthesia, paralysis or pulselessness, and is associated with limb loss if not treated immediately[2]. PAD is considered chronic when symptom duration is longer than 2 weeks. Patients can be asymptomatic, present with claudication, defined as pain in the lower limbs on exertion that is relieved by rest, or have chronic limb-threatening ischaemia (CLTI). CLTI is the most severe form of PAD and includes any patient with:

- rest pain with objective haemodynamic changes indicative of ischaemia (Ankle-Brachial Pressure Index <0.40, ankle pressure <50 mmHg, toe pressure <30 mmHg, transcutaneous partial pressure of oxygen ($TcPO_2$) <30 mmHg, flat monophasic Doppler waveforms), or
- tissue loss, in the form of ulceration or gangrene[3].

It is caused by atherosclerosis of the lower limb arteries, while trauma, emboli, ALI, venous disease or non-atherosclerotic conditions, such as vasculitides and Buerger's disease are excluded from the definition[3]. The term CLTI replaced the previous term "Critical Limb Ischaemia" often used in the cited literature, which was introduced in 1982 only for patients without diabetes[4], and was further defined in the Trans-Atlantic Inter-Society Consensus (TASC) in 2000 as a condition characterised by chronic ischaemia with rest pain or ulcer necrosis and objective haemodynamic changes (ankle pressure ≤ 50-70 mmHg or toe pressure ≤ 30-50 mmHg) that usually results in major

amputation within 6 months if not treated[5]. The haemodynamic thresholds included in that definition only focused on ischaemia and did not take into consideration other aspects of the spectrum of the disease that can also lead to amputation, such as neuropathy, infection and wound characteristics. These aspects are included in the new broader CLTI definition and perfusion is considered in this context[3].

Globally PAD affects 237 million people or 5.6% of the population aged over 25 years, 73% of which live in low and middle-income countries[6]. This number increased by 17% between 2010 and 2015. In the United Kingdom (UK) in 2015, it was estimated that 3.2 million people or 6.9% of the population had PAD[6]. There is limited information about the epidemiology of CLTI, but due to the increase in the prevalence of diabetes and life expectancy that results in an aging comorbid population, the prevalence of CLTI has also gradually increased over the years. A US study reported a mean prevalence of 1.3% between 2003 and 2008, with 11% of patients with PAD progressing to CLTI[7]. In the UK it has been estimated that CLTI affects 500 to 1000 patients per million annually and costs £200 million to the National Health Service (NHS)[8].

1.1.2 Risk factors

Risk factors for PAD and CLTI include individual habits, such as smoking, diet, sedentary lifestyle, conditions such as diabetes, hypertension, dyslipidaemia, and chronic kidney disease, and patient demographic characteristics such as older age[6] (Table 1).

Table 1 – Risk factors for development of PAD

Risk factor	Odds ratio (OR), 95% CI
Current smoking	2.82 (2.00–3.98)
Obesity	1.55 (1.23–1.96)
Diabetes	1.89 (1.68–2.13)
Hypertension	1.67 (1.50–1.86)
Dyslipidaemia	1.51 (1.02–2.24)
Chronic Kidney Disease	1.79 (1.03–3.12)
Older age (10-year increments)	1.55 (1.38–1.75)
Male gender	0.74 (0.61–0.91)

Based on data in a meta-analysis by Song et al.[6]

Tobacco smoking is considered the most important modifiable risk factor for PAD. It promotes atherosclerosis by inducing endothelial cell dysfunction, macrophage differentiation into foam cells, smooth muscle cell proliferation and migration, and extracellular matrix remodelling through an increase in oxidative stress and inflammation[9]. Pack-years of tobacco smoking have a dose-response relationship with the development of PAD, which is stronger compared to coronary artery disease and stroke, and the effect on PAD persists for 30 years after smoking cessation as opposed to 20 years in coronary disease[10]. Compared to non-smokers, the risk of developing PAD is 3 times higher for current smokers (odds ratio (OR) 3.08, 95% Confidence Interval (CI) 2.56-3.69) and 1.8 times higher for ex-smokers (OR 1.76, 95% CI 1.58-1.97), based on a meta-analysis of 55 studies[11]. There is even evidence of the negative effect of exposure to environmental tobacco smoke on the development of PAD in non-smokers[12]. Smoking has also been associated with higher risk of disease progression, major adverse cardiovascular events (MACE)[13], delayed wound healing and re-occlusion of native arteries after endovascular intervention for CLTI[14], respiratory and wound complications and failure of bypass grafts after open revascularisation[15,16]. The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2017 highlighted smoking as the 2nd highest risk factor for mortality and disability-adjusted life-years after hypertension, with an increase in smoking-attributable deaths by 25% since 1990 and association with 17,000 deaths from PAD in 2017[17].

The prevalence of smoking has been falling in recent years, but the use of electronic vaping cigarettes is becoming more common. There is a growing body of evidence that vaping causes a temporary increase in blood pressure, heart rate and arterial stiffness, has an adverse impact on oxidative stress and platelet function, and is associated with increased risk of atrial fibrillation and myocardial infarction[18,19]. These effects are less severe than those of traditional tobacco combustion cigarettes, and electronic cigarettes are more effective in helping smokers of traditional cigarettes quit compared to nicotine replacement therapy[20]. However, their long-term safety especially for adolescents and young adults, and their association with the development of PAD still remain unclear and further research is urgently needed on this topic[21].

Nutritional intake also influences the development and progression of PAD. There is evidence that the Mediterranean diet, which is rich in polyunsaturated fats from olive oil, nuts and seeds, high amount of fibres and vegetables, and low intake of red and processed meats, is associated with lower incidence of PAD[22–24]. It is also protective from other cardiovascular events and mortality, thanks to its anti-inflammatory and antioxidant properties[25]. Specific food groups with protective properties against PAD include legumes, dietary fibre, vegetable protein and nuts[22,24]. Conversely, malnutrition and sarcopenia have a negative effect on wound healing, major amputation risk and incidence of major cardiovascular events and mortality in the CLTI population[26–28].

Additionally, increasing body mass index (BMI) was independently associated with development of CLTI in a longitudinal study of 13,988 patients without PAD at baseline, with obese patients having approximately 1.5 times higher risk of developing CLTI[29]. Obese patients are also more likely to develop surgical site infection and respiratory complications after revascularisation[30]. However, the "obesity survival paradox", according to which obese patients have significantly lower mortality compared to those with normal weight, has also been observed in multiple studies and a large meta-analysis of 5,735,578 individuals with PAD and CLTI regardless of age, gender and comorbidities[31–34]. Regarding exercise, there is evidence that the risk of hospitalisation due to CLTI decreases as the amount and intensity of physical activity increases[35]. Supervised exercise programmes are beneficial and part of the treatment armamentarium for patients with intermittent claudication[36], but individuals with CLTI cannot participate due to their reduced functional status, ischaemic pain and foot wounds that limit their mobility.

Diabetes is the second most important risk factor for PAD and CLTI, with a reported OR of 1.89 (95% CI 1.68-2.13)[6] and population attributable fraction of 14% (95% CI 10-19)[37]. The prevalence of PAD in patients with diabetes over 40 years of age has been reported as 20%[38], while 4.6% of patients with diabetes have a foot ulcer[39]. The global prevalence of diabetes increased by 130% between 1990 and 2017 and maintains an upward trend[40], therefore the association between CLTI and diabetes is of particular importance for service planning. Patients with diabetes exhibit different symptoms and disease morphology than non-diabetic PAD patients. For example, diabetes is associated more

strongly with femoro-popliteal and infrapopliteal atherosclerosis, while smoking and hypertension mainly affect aorto-iliac and femoral vessels[38]. It is worth noting that diabetes affects both main trunk arteries such as the crural arteries (macroangiopathy) as well as capillaries (microangiopathy), through increased inflammation, endothelial cell dysfunction that accelerates atherosclerosis, changes in platelet function and induction of a hypercoagulable state[38]. The associated motor neuropathy leads to foot deformity and the sensory neuropathy reduces sensation, including pain, which in turn delays the detection of ischaemia and ulcers. Finally, patients with diabetes are susceptible to infections that can deteriorate rapidly, due to impaired immune function, such as white blood cell function. Due to these characteristics, patients with PAD and diabetes have more diffuse distal disease, are likely to develop ulcers and necrosis early in the disease progression, experience delayed healing of their ulcers that often become infected and have a higher risk of major amputation (Hazard Ratio (HR) 1.86, 95% CI 1.37-2.53)[41,42]. They also tend to have other conditions related with diabetes, such as hypertension, hyperlipidaemia, ischaemic heart disease and renal disease. There is conflicting evidence on the effect of diabetes on major amputation risk after revascularisation for CLTI, as a US cohort study found no association[43], while a study using Swedish registry data reported a positive association (HR 1.45, 95% CI 1.32-1.60)[44]. However, poor glycaemic control has been associated with higher risk of restenosis (HR 1.49, 95% CI 1.31-1.78) and more major adverse limb events (MALE) after infrapopliteal revascularisation for CLTI[45].

Elevated blood pressure has also been associated with atherosclerosis and is a risk factor for the development of PAD and CLTI (Table 1). The population-attributable fraction of hypertension for PAD has been reported as 41% with a hazard ratio of 2.42[37]. In a study examining the relationship between blood pressure thresholds and risk of CLTI, individuals with systolic blood pressure (SBP) ≥ 140 mmHg were 3 times more likely to develop CLTI (adjusted HR 3.31, 95% CI 1.89–5.80) and those with SBP 130-139 mmHg were 2 times more likely (aHR 2.33, 95% CI 1.27–4.30), compared to normal SBP values below 120 mmHg[46]. Additionally, patients with diastolic blood pressure (DBP) ≥ 90 mmHg had 2.7 (95% CI 1.38–5.27) times higher risk of CLTI[46]. Despite the detrimental effect of hypertension on PAD, CLTI and other cardiovascular conditions, patients

remain undertreated, with 50% presenting with uncontrolled blood pressure that may accelerate disease progression[47,48].

Accumulation of apolipoprotein B-containing lipoproteins (low density and very low density lipoproteins) in the subendothelial space of the arterial wall contributes to atherosclerotic plaque formation, therefore dyslipidaemia is a risk factor for PAD and CLTI. High triglyceride levels and total cholesterol-to-high density lipoprotein cholesterol (HDL-C) ratio have been associated with the development of PAD, while increased HDL-C has a protective effect[49–51]. Interestingly, low-density lipoprotein cholesterol (LDL-C) and total cholesterol are risk factors for coronary disease but less so for PAD[49]. It is expected that novel lipid markers, such as the nuclear magnetic resonance-derived measures of LDL particle concentration currently being developed may allow better risk stratification for PAD[49].

Chronic Kidney Disease (CKD) is another independent risk factor for PAD and CLTI. This causal relationship is triggered by several pathophysiological mechanisms, such as changes in bone mineral metabolism, inflammation, and presence of uraemic toxins[52]. CKD-induced inflammation exacerbates vascular calcification and endothelial dysfunction, while the uraemic toxins have prothrombotic properties and further contribute to oxidative stress and inflammation. Simultaneously, the reduced production of proangiogenic mediators in CKD inhibits angiogenesis, thus impairing the development of a collateral vascular network that could reduce the severity of ischaemic symptoms[53]. The prevalence of PAD in patients with CKD is estimated to be 25-33%, compared to 9% in people with normal renal function[53]. A meta-analysis of 817,084 individuals found that deteriorating kidney function (CKD stage 3-5) was independently associated with 1.2 to 2 times higher incidence of PAD compared to those without kidney disease[54]. On the other hand, in a cohort study of 460,591 patients from Canada the prevalence of moderate to severe kidney disease (CKD stage 3-5) was 30% in the PAD population compared to 10% in those without PAD[55]. Combined presence of PAD and CKD is associated with higher risk of cardiovascular events, lower limb complications, amputations and mortality compared to PAD patients without CKD[54,55]. Similarly, a US study reported that 22.6% of over 2 million patients hospitalised with CLTI had CKD. These patients were less likely to undergo revascularisation and had higher

rates of in-hospital mortality (4.8% vs 2.5%, OR 2.01, 95% CI 1.93-2.11) and major amputation (OR 1.04, 95% CI 1.02–1.07) compared to patients without CKD[56]. The difference in adverse outcomes between people with and without renal disease is even more prominent after revascularisation, in terms of major cardiac events (5.2% vs. 2.5%; adjusted OR 1.74, 95% CI 1.40-2.16) and amputations (26.1% vs. 12.2%; aOR 1.33, 95% CI 1.19-1.50)[57]. Haemodialysis is also an independent risk factor for lower limb complications, as patients with CLTI on dialysis have 40% 1-year and 80% 5-year mortality after revascularisation[55,58].

Increasing age is strongly associated with development of PAD (Table 1). Globally, the prevalence of PAD is estimated as 3.6% in the 35-39 age group, compared to 6.6% in the 55-59, 12.9% in the 75-79 and 19.3% in the 85-89 age group[6] (Figure 1). The same study found an interesting relationship between PAD prevalence with gender. The condition was more frequent in women compared to men for age groups up to 70 years and in men over 70 years (Figure 1)[6]. This finding is in contrast with previous literature suggesting that women present with PAD on average 10 years later than men, due to the vascular protective effect of oestrogen[59]. The greater number of women in the population also means that there may be a higher total population burden of PAD in women (123.6 million vs. 113 million in 2015)[6], but women only account for 32-37% of participants in most studies of revascularisation outcomes[60]. Multiple studies have also found that women are older at the time of intervention, are more likely to present with CLTI and less likely to receive guideline-recommended medications[60,61]. Indicatively, a large study from Germany reported that more men were hospitalised with CLTI than women (57% vs 43%), men were younger, suffered more frequently from dyslipidaemia, diabetes and ischaemic heart disease and were more likely to undergo revascularisation procedures[62]. Additionally, they had worse overall survival and amputation-free survival during follow-up[62]. Men with CLTI were also reported to have a higher mortality risk (HR 1.08, 95% CI 1.05-1.10) in a recent systematic review[63]. However, the gender effect on survival after revascularisation is uncertain with studies generating inconsistent results, and further research is required in this area[60].

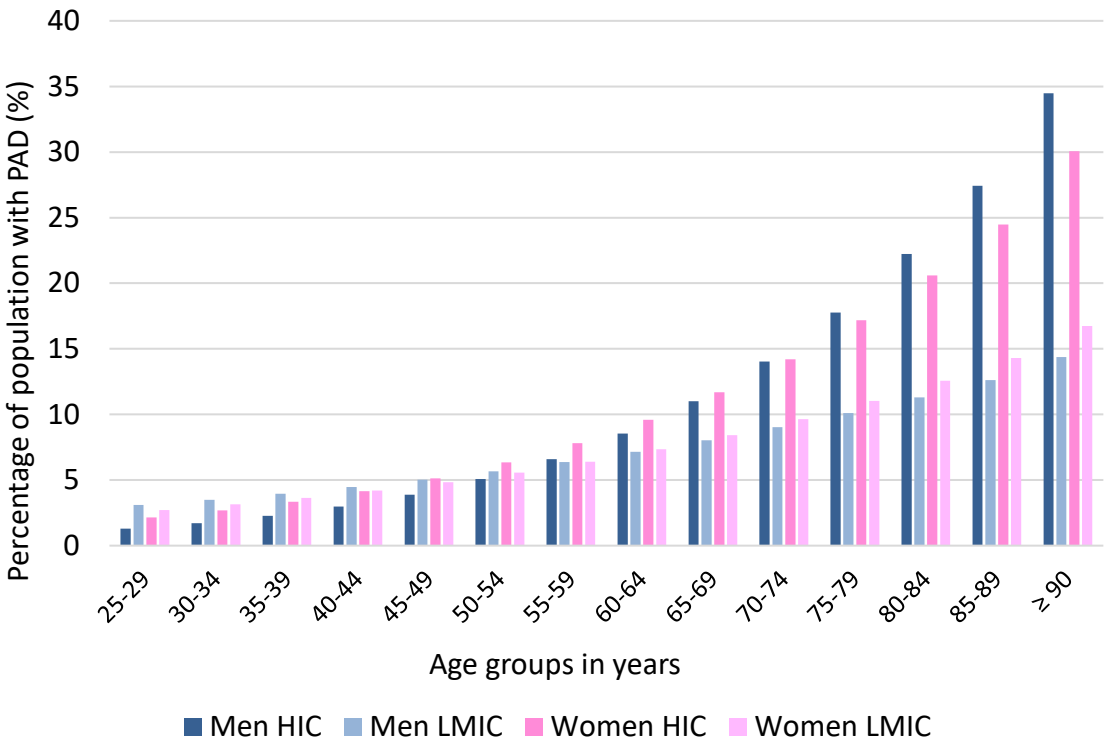

Figure 1 – Prevalence of PAD (%) by age and gender in high-income countries (HIC) and low and middle-income countries (LMIC)

1.1.3 Diagnostic assessment

Clinical presentation of CLTI

The diagnostic process for CLTI starts with clinical evaluation through a careful history and clinical examination, when a patient presents with relevant symptoms and signs. Typical symptoms include calf pain when walking very short distances and at rest. Patients usually describe pain in their forefoot that is worse at night or when raising the leg and is relieved by dependency, which often results in them sleeping in a reclining chair with their foot hanging down. In more advanced stages, patients can present with gangrenous lesions or with ischaemic ulcers in the feet, especially when foot deformity, diabetic neuropathy or altered biomechanics are present. Other symptoms that indicate peripheral neuropathy are tingling sensation, burning pain, and numbness in the feet, which increase the risk of ulcer formation in areas of abnormal pressure. It is also important to ascertain the patient's comorbidities, cardiovascular risk factors, medications, previous revascularisation attempts and functional ambulatory status.

These factors may affect the decision-making process and treatment options suitable for individual patients[64,65]. For example, previous revascularisation procedures with vein grafts may limit the choice of available conduits, while patients with poor functional status have high risk of adverse events after revascularisation for CLTI and uncertain benefit[66].

Signs of ischaemia that can be found during clinical examination include absence of pulses, thin and hairless skin that is cool to touch, and increased capillary refill time (over five seconds)[3]. Rubor on dependence and pallor on elevation, also known as sunset foot, form a positive Buerger sign and indicate severe ischaemia[67]. Conversely, erythema and warmth that persists with elevation may be indicative of infection, ranging from cellulitis to abscess. Palpation of the pulses (femoral, popliteal, dorsalis pedis and posterior tibial) is an important diagnostic tool, because their absence may indicate the level of atherosclerotic disease[68,69]. The feet and toes should also be checked for wounds, and their size, depth and location should be noted, so they can be monitored after treatment has commenced. Finally, the ulcer depth and bone involvement should be checked with a probe-to-bone test, which has high sensitivity (87%, 95% CI 75-93%) and specificity (83%, 95% CI 65-93%) for osteomyelitis[70].

Due to the multitude of other conditions that can resemble CLTI, such as Buerger's disease, vasculitides and collagen diseases, the clinical findings should be supported by haemodynamic evaluation and if appropriate arterial imaging of the lower limbs. These can support diagnosis and guide treatment planning.

Haemodynamic tests

Bedside haemodynamic tests to evaluate the presence and severity of CLTI are recommended as first line diagnostic investigations. These include the ankle-brachial pressure index (ABPI), toe-brachial pressure index (TBPI), ankle pressure (AP) and toe pressure (TP) measurements, and continuous wave Doppler (CWD)[71] (Table 2). The ABPI is calculated as the ratio of the highest systolic blood pressure in the ankle (dorsalis pedis and posterior tibial arteries) and the highest systolic blood pressure in the brachial arteries using a sphygmomanometer cuff and a Doppler probe with the patient supine[72]. ABPI values below 0.9 are considered diagnostic for PAD, below 0.4 diagnostic for CLTI,

and over 1.4 are considered inaccurate and alternative assessment methods should be used[72]. It is also possible to perform post-exercise ABPI measurements, which have greater sensitivity than resting ABPI (88% vs 64%, respectively)[73]. Even though ABPI and AP tests are easy to perform, their findings may be less reliable in people with diabetes and CKD, due to the heavy medial arterial calcification that renders the arteries incompressible and give falsely elevated ankle pressures[74,75].

In these cases, TP, TBPI and toe waveforms are preferred, because digital arteries are often spared from atherosclerosis. TP is measured by placing a mini-cuff around the first toe and return of flow is detected using photoplethysmography or continuous wave Doppler. TBPI is calculated as the ratio of toe systolic blood pressure to brachial systolic blood pressure. In a large meta-analysis, measurement of ABPI detected stenosis of 50% or more with a 61% (95% CI 55-69%) sensitivity and 92% (95% CI 89-95%) specificity, while for TBPI sensitivity was 81% (95% CI 70-94%) and specificity 77% (95% CI 66-90)[76]. Seven direct comparative studies of the two modalities showed that TBPI had higher sensitivity (82% vs 52%) and overall diagnostic accuracy (diagnostic OR 16.4 vs 11.0) compared to ABPI, but lower specificity (77% vs 94%)[76].

Monophasic and low amplitude waveforms obtained using CWD also indicate severe ischaemia compared to normal triphasic waveforms, but are harder to interpret. In a recent systematic review of bedside tests for PAD, loss of the triphasic signal during CWD performed best at ruling-out PAD compared to ABPI, TBPI and TP measurements, while the other methods were better at diagnosing the disease[74].

Finally, transcutaneous oximetry is a newer method that assesses tissue perfusion by measuring the transcutaneous partial pressure of oxygen ($TcPO_2$) in the distal limb using electrodes and comparing it to a reference value. It is not affected by calcification, but it is time consuming and may have limited accuracy when oedema and infection are present[3]. This method can predict wound healing in patients with CLTI with moderate sensitivity (72%, 95% CI 61-81%) and good specificity (86%, 95% CI 68-95%)[77]. $TcPO_2$ < 10 mmHg has also been found to predict major amputation in patients with CLTI (OR 2.3, 95% CI 1.5-3.5)[78].

Haemodynamic values used to diagnose CLTI are presented in Table 2. Based on a systematic review published in 2020, TP ≥ 30 mmHg, TcPO2 ≥ 25 mmHg and skin perfusion pressure ≥ 40 mmHg were the most useful tests at predicting the probability of healing of diabetic foot ulcers, while AP < 50 mmHg, ABPI < 0.5, TP < 30 mmHg, and TcPO2 < 25 mmHg were associated with increased probability of major amputation[79].

Table 2 – Haemodynamic values that represent normal perfusion and manifestations of CLTI

Haemodynamic test	Normal values	Rest pain	Tissue loss
ABPI	> 0.9	< 0.4	
AP		< 50 mmHg	< 70 mmHg
TBPI	> 0.7	< 0.3	
TP		< 30 mmHg	< 50 mmHg
$TcPO_2$	> 60 mmHg	< 20 mmHg	<40 mmHg

Duplex ultrasound (DUS)

The main limitation of the previously discussed bedside haemodynamic tests is that they do not provide information about the anatomic characteristics and location of the atherosclerotic lesions, therefore imaging is required to determine the extent and severity of disease. Duplex ultrasound is recommended as the first-line imaging modality by national and international guidelines[3,80]. It has important benefits over other imaging methods, as it allows both evaluation of plaque morphology in calcified vessels and haemodynamic measurements, such as flow volume and velocity, without the use of contrast or ionising radiation. It can be used to ascertain the patency of the infrapopliteal and pedal vessels, but examination may be hindered by the presence of leg ulcers, and it may be hard to visualise the aorta and iliac arteries, due to body habitus and bowel gas[81]. It is also a dynamic test that depends on the skill of the operator and very few images can be saved, so the operating clinician is mainly guided by the imaging report. Duplex ultrasound can also be used to assess graft or stent patency following revascularisation and during follow-up to detect “at risk” grafts or native artery re-stenoses[82,83].

Computed Tomography Angiography (CTA)

For aorto-iliac lesions, cross-sectional imaging in the form of CTA has advantages over DUS. CTA is fast, less operator dependent, and usually available in- and out-of-hours. CTA provides a wealth of information about the anatomic distribution of the arterial disease and severity of stenoses[84]. Images can be reconstructed and viewed in multiple planes, which is helpful when planning an intervention. A systematic review and meta-analysis reported 95% (95% CI 92-97%) sensitivity and 96% (95% CI 93-97%) specificity of CTA to detect more than 50% stenosis or occlusion compared to classic angiography[85]. However, it involves exposure to radiation and administration of iodinated contrast, which may be contraindicated in patients with renal disease, acutely unwell or dehydrated patients due to the risk of contrast-induced Acute Kidney Injury (AKI)[86]. Additionally, imaging of crural vessels may be suboptimal, due to the artefact from heavy calcification in small vessels[84].

Magnetic Resonance Angiography (MRA)

MRA is also a non-invasive imaging modality often used as an alternative to CTA. Its advantages over CTA include the lack of radiation and use of gadolinium instead of iodinated contrast, which is safer for patients with impaired renal function. This modality allows visualisation of the entire lower limb arterial tree without degrading from arterial calcification and is recommended by the National Institute for Health and Care Excellence (NICE) guidelines as the second line investigation after Duplex ultrasound[80]. A meta-analysis of studies comparing MRA with digital subtraction angiography in PAD reported sensitivity of 95% (95% CI 92-96%) and specificity of 96% (95% CI 94-97%) for MRA[87]. Its main limitation is the long image capture time and the limited availability of MRA slots especially out of hours, which are of particular importance in CLTI, where timely diagnosis and treatment is crucial. Moreover, it may not be well tolerated by patients with claustrophobia, while patients with older non-MRI compatible implanted devices such as pacemakers and defibrillators cannot be scanned. Finally, gadolinium-based contrast agents have been associated with risk of nephrogenic systemic fibrosis in patients with renal disease[88]. To mitigate this risk, non-contrast MRA techniques have been developed, which are highly accurate (sensitivity 88%, 95% CI 85-

91%; specificity 94%, 95% CI 92-96%) and can be used in patients with renal failure or contrast allergy, but are not currently widely adopted in the NHS[89].

Digital Subtraction Angiography (DSA)

DSA is still considered the gold standard for evaluating the lower limb arterial circulation, especially for infrapopliteal vessels, and is usually performed when revascularisation is considered. It allows the visualisation of the extent of the arterial disease from the aorta to the foot and provides information about collateral circulation. However, it is an invasive procedure with possible access site complications, and exposure to ionising radiation. Due to the iodinated contrast, it also carries the risk of contrast-induced nephropathy in patients with impaired renal function[90]. CO_2 angiography has been used as an alternative in patients at risk of renal injury or with contrast allergy, but image quality is inferior and it is not widely available in all centres[91].

PAD and CLTI Classifications

Several classification systems have been developed to grade arterial disease severity based on signs and symptoms at presentation, haemodynamic criteria, and anatomic location of the disease. Their purpose is to aid communication between healthcare professionals and guide clinical decision-making as prognostic tools, estimating the risk of amputation and mortality and potential benefit from revascularisation. The classification used throughout this thesis is the Fontaine classification, developed by Fontaine et al in 1954, which is based on patient symptoms[92] (Table 3). The Rutherford classification, developed in 1986 and updated in 1997, is similarly guided by patient symptoms but has additional objective criteria of ischaemia in terms of ankle or toe pressures[93]. These two classification systems do not provide accurate risk stratification, because they focus on perfusion characteristics without considering the extent of tissue loss and the presence of infection, which influence prognosis in CLTI especially in patients with diabetes[94]. Infection can worsen the underlying ischaemia, as the resulting inflammation, swelling and abscess formation increase the tissue pressure and require higher capillary/arterial pressure to maintain the pressure gradient and achieve tissue oxygenation. Bacteria may cause tissue necrosis and destroy the arteriole network, which further exacerbates ischaemia.

To address these limitations, the Society for Vascular Surgery (SVS) developed the Wound, Ischaemia and foot Infection (WIfI) classification in 2014, which characterises lower limb lesions in terms of the wound characteristics (size, location, type [ulcer or necrosis]), the degree of ischaemia (using objective haemodynamic measurements), and the presence and severity of infection (localised or systemic), which are the main factors leading to amputation[95]. Each component is graded on a spectrum from zero (none) to three (severe), and the resulting combination has been assigned one of four clinical stages of amputation risk (1-Very low, 2-Low, 3-Moderate, 4-High) through a Delphi consensus process[95]. The global vascular guidelines recommend the use of the WIfI classification system in all patients presenting with CLTI, as it can be used to predict amputation risk and wound healing[3]. According to a recent systematic review and meta-analysis, the estimated risk of 1-year major amputation in CLTI patients was 0% for WIfI stage I, 8% (95% CI 3-21%) for stage II, 11% (95% CI 6-19%) for stage III, and 38% (95% CI 21-58%) for stage IV, but the overall level of evidence of the included studies was low[96]. Other studies have demonstrated that WIfI is independently associated with wound healing in diabetic foot ulcers (WIfI 4 vs 1 HR 0.44, 95% CI 0.33-0.59, WIfI 4 vs 3 HR 0.77, 95% CI 0.67-0.88)[97,98], and 2-year mortality risk in CLTI patients undergoing endovascular revascularisation (HR 1.18, 95% CI 1.01-1.38)[99]. The WIfI classification can also be used to identify patients that would benefit from revascularisation, as patients in the questionable benefit cohort often required amputation despite revascularisation, possibly due to the wound size or infection burden)[100,101]. Finally, WIfI restaging at 1- and 6- months after revascularisation is also recommended, as it has been associated with amputation-free survival and may identify patients at increased risk of limb loss[102].

Separate classification systems have been developed for diabetic foot ulcers (DFU)[103]. The Meggitt-Wagner classification was described in 1976 and graded wound depth and gangrene on a scale from zero to five, but did not include a haemodynamic component to differentiate ischaemic from infective gangrene, and did not separate bone from soft tissue infection[104]. Similarly, the University of Texas classification provided a matrix to grade ulcer depth and the presence or absence of infection and ischaemia (ankle-brachial index < 0.8), but did not consider gangrene and did not grade the severity of ischaemia and infection[105]. More recently, the Infectious Diseases Society of America

(IDSA) and the International Working Group on the Diabetic Foot (IWGDF) developed a system with four grades solely to describe the severity of infection in DFUs, which has been validated as risk prediction tool for hospitalisation, major and minor amputation[106,107]. The most widely used tool currently in the UK is the Site, Ischaemia, Neuropathy, Bacterial infection and Depth (SINBAD) classification, which is easy to use, as it does not require measurements with specialist equipment, includes all the important factors that may delay would healing and has high inter-observer reliability[108]. To clear the confusion around the multitude of DFU classification systems currently in use, the IWGDF recommended in its 2019 guidelines three classifications depending on context and purpose: SINBAD for communication among health professionals and audit, WIfI for assessment of perfusion and benefit of revascularisation, and IDSA/IWGDF for assessment of infection[107].

Finally, the Global Limb Anatomic Staging System (GLASS) has been proposed in the 2019 global vascular guidelines as a classification system for the anatomic pattern of infrainguinal arterial disease in CLTI[3]. The anatomic stage in GLASS (I – III) correlates with the technical complexity of revascularisation of the "target arterial path" that achieves pulsatile in-line flow to the foot (Table 4). It is determined by combining the femoro-popliteal disease grade (0-4) and the infrapopliteal disease grade (0-4), which are based on length of disease, location, and level of occlusion, and increase by one if there is severe calcification (>50% of circumference). There are additional categories for aorto-iliac (stage I, II) and infra-malleolar arteries (P0, P1, P2). GLASS stage I represents low complexity disease with less than 10% technical failure and over 70% 1-year estimated limb patency, while stage III is high complexity disease with more than 20% technical failure and less than 50% 1-year limb patency[3]. GLASS is superior to previous anatomic classification schemes such as TASC II, because it accounts for the presence of multilevel lesions encountered from the aorta to the foot, whereas previous ones focused on location and severity of individual arterial lesions[109]. However, the grades have complex definitions and require detailed angiographic imaging, which may not be available for all patients. Additionally, it is less suitable for open surgical interventions, as it does not take into account the bypass conduit or the quality of distal run-off. In the first validation study published in 2020, GLASS stage was strongly associated with amputation-free

survival (HR 1.37, 95% CI 1.01-1.85), limb salvage (HR 1.96, 1.12-3.43), and freedom from MALE (HR 1.49, 1.04-1.87) following endovascular interventions but not after bypass[110]. Two further studies had mixed results, therefore further research is required to evaluate this classification as prognostic and decision tool[111,112].

Table 3 – Fontaine and Rutherford classifications for chronic limb ischaemia

		Fontaine classification		**Rutherford classification**
	Stage I	Asymptomatic	0	Asymptomatic
	Stage II	Mild claudication	1	Mild claudication
	Stage IIA	Claudication distance > 200m	2	Moderate claudication
	Stage IIB	Claudication distance < 200m	3	Severe claudication
CLTI	Stage III	Rest pain	4	Rest pain
	Stage IV	Necrosis and/or gangrene	5	Minor tissue loss (non-healing ulcer, focal gangrene)
			6	Major tissue loss (extending above transmetatarsal level, functional foot not salvageable)

Table 4 – GLASS stage (I-III), determined by combining the femoro-popliteal and infrapopliteal grade

Femoro-popliteal grade	**Infrapopliteal grade**				
	0	**1**	**2**	**3**	**4**
4	III	III	III	III	III
3	II	II	II	III	III
2	I	II	II	II	III
1	I	I	II	II	III
0		I	I	II	III

1.1.4 Management

The aim of treatment in CLTI is to relieve ischaemic pain, preserve a functional limb, help with wound healing, reduce the risk of major cardiovascular adverse events, improve quality of life, and prolong survival. To decide on the most appropriate treatment, the patient's periprocedural risk, benefit from the intervention and life expectancy should be considered along with the anatomic pattern of disease and the risk of limb loss based on presence of ischaemia, infection, and tissue loss. Therapeutic approaches for patients with CLTI include medical treatment with cardiovascular risk factor modification, and revascularisation in the form of open surgery, endovascular, or hybrid interventions. When revascularisation is not possible or advisable, options are mostly limited to primary amputation or palliative management with symptom control. Failure of the revascularisation procedures over time by re-occlusion of the vessels or delay in treatment may also lead to amputation. National[113] and European[114] guidelines outline the optimal management of patients with CLTI based on current research evidence, but they sometimes do not translate into everyday medical practice[115].

Cardiovascular risk factor modification

Cardiovascular mortality is 3 to 5 times higher in patients with CLTI compared to the general population, reaching 11% at 1-year and 29% at 5-years in a Dutch study[116]. Risk factor modification aims to reduce cardiovascular morbidity and mortality in patients with PAD and can be performed through lifestyle changes (smoking cessation, exercise, diet) and pharmacological treatment. Specifically, antithrombotic and lipid-lowering medications are considered best medical therapy and form part of the primary and secondary prevention of PAD, while control of blood pressure and glycaemic control in people with diabetes are also strongly recommended[80]. Adherence to these guideline-recommended therapies can decrease MACE (HR 0.64, 95% CI 0.45-0.89), MALE (HR 0.55, 95% CI 0.37-0.83), and mortality (HR 0.56, 95% CI 0.38-0.82) in patients with PAD, compared to patients who do not receive all of them[117].

Smoking cessation is the most important lifestyle change for patients with CLTI, associated with significantly lower risk of all-cause mortality in patients with PAD and other cardiovascular risk factors[13,118]. Various national and international CLTI guidelines

recommend that active smokers receive counselling, behavioural modification therapy or pharmacotherapy, such as nicotine replacement therapy (NRT), bupropion, varenicline and cytisine, at the time of diagnosis with PAD or CLTI and at every subsequent medical review[1,3,80]. Nevertheless, a study evaluating adherence to guideline-recommended therapy in three countries reported that only 72% of patients with PAD received smoking cessation counselling[115]. A Cochrane network meta-analysis of 267 trials concluded that pharmacologic interventions for smoking cessation were effective in the general population of smokers[119]. However, a recent meta-analysis of six randomised controlled trials (RCTs) found that smoking cessation programmes comprising of physician advice, behavioural counselling and NRT were not effective in helping people with PAD to quit smoking (risk ratio (RR) 1.48, 95% CI 0.84-2.61)[120].

In addition to advice about lifestyle changes, all patients with CLTI should receive an antiplatelet agent to prevent cardiovascular events according to guidelines, and various studies have explored the optimal treatment regime for this population[1,3,121]. Even though studies in the 90s showed the efficacy of Aspirin in reducing cardiovascular events[122–124], a meta-analysis of 18 studies comparing Aspirin with placebo in patients with PAD found that Aspirin had no effect on cardiovascular mortality or myocardial infarction and only conferred decreased risk of non-fatal stroke[125]. Regarding the effectiveness of Clopidogrel, the CAPRIE RCT found that treatment with Clopidogrel was associated with 23.8% (95% CI 8.9-36.2%) relative reduction in risk of ischaemic stroke, myocardial infarction and vascular death compared to Aspirin in the PAD group[126], while the EUCLID RCT concluded that Ticagrelor was not superior to Clopidogrel in reduction of cardiovascular events or major bleeding[127]. More recently, a meta-analysis of 49 RCTs reported that Aspirin, Vorapaxar, Cilostazol, and Picotamide were ineffective in reducing MACE, while a significant reduction was observed with Ticagrelor plus Aspirin, Clopidogrel (RR 0.72, 95% CI 0.58-0.91), Ticlopidine, and Clopidogrel plus Aspirin. Ticlopidine and Clopidogrel plus Aspirin significantly increased the risk of bleeding, therefore Clopidogrel was considered the option with the most favourable benefit-harm profile[128]. Summarising all the available evidence on the efficacy of antiplatelets in patients with PAD, an umbrella review of 28 meta-analyses published in 2020 concluded that antiplatelet monotherapy showed benefit only in reducing non-fatal strokes in

asymptomatic patients with PAD, while it reduced cardiovascular death (RR 0.78, 95% CI 0.63-0.96) and increased the risk of major bleeding in symptomatic patients (RR 1.7, 95% CI 1.22-2.45)[129]. Moreover, two large RCTs explored the combination of Aspirin with the direct oral anticoagulant Rivaroxaban in PAD[130,131]. Patients with symptomatic lower limb PAD randomised to low-dose Rivaroxaban plus Aspirin in the COMPASS study had 26% lower relative risk of MACE (HR 0.74, 95% CI 0.58-0.92) and 45% lower relative risk of MALE, including major amputation (HR 0.55, 95% CI 0.35-0.85), compared with patients in the Aspirin group, with a 61% increase in the relative risk of major bleeding (HR 1.61, 95% CI 1.12–2.31)[130,132]. Based on this evidence, the CLTI Global vascular guidelines and PAD NICE guidelines recommend the use of Clopidogrel as antiplatelet monotherapy in these patients, and encourage the consideration of low-dose Aspirin plus Rivaroxaban (2.5 mg twice daily)[3]. No studies have compared Clopidogrel with the Aspirin-Rivaroxaban combination yet.

In addition to cardiovascular risk reduction, antithrombotic medications are beneficial after revascularisation procedures. Evidence from a network meta-analysis suggests that dual antiplatelet therapy (DAPT) after revascularization significantly reduces major amputations compared to Aspirin alone (RR 0.68, 95% CI 0.46-0.99), but has a slightly higher risk of major bleeding[128]. DAPT is also independently associated with higher amputation-free survival after endovascular revascularisation in patients with CLTI[45]. Additionally, an umbrella meta-analysis reported improved prosthetic bypass graft patency (RR 1.47, 95% CI 1.08-2.02) but higher risk of major bleeding with DAPT after intervention, highlighting that more evidence is needed for the use of DAPT after endovascular intervention[129]. Comparably, low dose Aspirin plus Rivaroxaban reduced cardiovascular and limb adverse events (acute limb ischaemia, major amputation, myocardial infarction, ischaemic stroke or cardiovascular death) after revascularisation compared to Aspirin monotherapy (HR 0.85, 95% CI 0.76–0.96) in the VOYAGER PAD study, albeit with increased risk of major bleeding (HR 1.42, 95% CI 1.10-1.84)[131]. Therefore, the global vascular guidelines weakly recommend DAPT with Clopidogrel and Aspirin in patients who have a prosthetic bypass graft for 6-24 months and in those who have undergone endovascular intervention for at least 1 month, while all other patients should continue long-term on a single antiplatelet[3].

Lipid-lowering medications have also been shown to reduce the risk of all-cause and cardiovascular mortality in CLTI. The global vascular guidelines recommend moderate to high intensity statin therapy in patients with CLTI, to reduce all-cause and cardiovascular mortality[3], and the European Society of Cardiology guidelines recommend specific targets of below 1.8 mmol/L for LDL-C or reduction by 50% or more if baseline LDL-C is 1.8-3.5 mmol/L[1]. The recommendations were partly based on the UK Heart Protection Study, which reported that compared to placebo, patients with PAD receiving 40mg of Simvastatin daily had 22% (95% CI 15-29) relative risk reduction in major vascular events[133]. A meta-analysis of 2 RCTs and 22 observational studies also found that statin therapy was associated with lower all-cause mortality (HR 0.74, 95% CI 0.70-0.78), MACE (HR 0.78, 95% CI 0.65-0.93) and amputations (HR 0.74, 95% CI 0.62-0.89) compared to no statin in PAD patients[134]. A further systematic review of 19 studies including only CLTI patients reported a lower risk of major amputation (HR 0.75, 95% CI 0.59-0.95), MACE (HR 0.50, 95% CI 0.39-0.66) and all-cause mortality (HR 0.62, 95% CI 0.52-0.75) for statin compared to no statin therapy[135]. Comparison of the two systematic reviews indicates a greater effect of statins in the CLTI group, which has also been observed when statin therapy is initiated after the revascularisation procedure[136].

Additionally, statin therapy seems to have a dose-response effect on cardiovascular risk reduction[137]. Adherence to the recommended high-intensity statin dose in patients ≤75 years old and moderate-intensity statin in older patients undergoing revascularisation for CLTI has been associated with lower mortality (HR 0.77, 95% CI 0.60-0.99) and lower adverse limb events (HR 0.71, 95% CI 0.51-0.97) compared to those not on the recommended dose[138]. These results are supported by a meta-analysis of PAD patients, according to which high dose statin resulted in lower risk of all-cause mortality (HR 0.74, 95% CI 0.62-0.89) and major amputation (HR 0.78, 0.69-0.90) compared to low or moderate dose statin[134]. The main side effect of statin therapy is muscle aching, which can be mitigated by reducing the dose to the maximum tolerated and adding a non-statin lipid-lowering drug. Newer medications that reduce the LDL-C have also recently been assessed in RCTs, most notably the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors[139,140]. A therapeutic agent of this category, Evolocumab, was associated with a 27% (9.5% vs 13%) relative risk reduction in MACE (HR 0.73, 95% CI

0.59-0.91, for cardiovascular death, myocardial infarction, stroke) in PAD patients already on a statin compared to statin monotherapy in the FOURIER RCT[141]. As PCSK9 inhibitors are very expensive compared to statins, an Australian study evaluated their cost-effectiveness and reported an absolute risk reduction of 6.1% (95% CI 2.0-9.3) in MACE and 13.7% (95% CI 4.3-21.5) in MALE in the CLTI population, compared to 3.2% and 5.3% in claudicants respectively, concluding that they are likely cost-effective in CLTI[142].

Control of blood pressure is also highlighted by international guidelines as important for cardiovascular risk factor modification. Two RCTs, the SPRINT and ACCORD studies, have compared more intensive (SBP < 120 mmHg) with standard (SBP < 140 mmHg) blood pressure control in patients at high risk for cardiovascular events with and without diabetes, respectively[143,144]. The SPRINT study group reported significantly lower MACE (myocardial infarction, stroke, acute coronary syndromes, heart failure and cardiovascular death, HR 0.73, 95% CI 0.63-0.86) and all-cause mortality (HR 0.75, 95% CI 0.61-0.92) in the intensive control group, while ACCORD found no difference in MACE between groups (HR 0.88, 95% CI 0.73-1.06). Notably, both studies had significantly higher rate of serious adverse events attributed to antihypertensive therapy such as hypotension, syncope, and AKI, in the intensive control group[143,144]. Additionally, a recent Cochrane systematic review of 7 RCTs in people with previous myocardial infarction, angina, stroke and PAD did not find a significant difference in all-cause mortality, cardiovascular mortality or MACE between people with hypertension treated to a lower (SBP/DBP 135/85 mmHg) compared to standard (140-160/90-100 mmHg) blood pressure target[145]. These studies were not PAD-specific, but a recent cohort study of patients with PAD also suggested that patients with SBP lower than 120 mmHg had higher risk of MACE (myocardial infarction, stroke, cardiovascular death) compared to patients with SBP 121-140 mmHg (aHR 1.36, 95% CI 1.08-1.72)[146]. These findings are supported by a sub-analysis of the INternational VErapamil-SR/Trandolapril STudy (INVEST) RCT, which reported a J-shaped relationship between SBP and the composite outcome death/myocardial infarction/stroke in patients with PAD, with greater risk in patients with SBP above 145 mmHg and below 130 mmHg that was not observed in the non-PAD group[147]. Even though these studies did not specifically refer to the CLTI

population, there is equivocal evidence about intensive blood pressure control in PAD and the recommended target levels currently are less than 140 mmHg for systolic and less than 90 mmHg for diastolic blood pressure[1,3].

Selected guidelines specifically recommend the use of angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) as first-line antihypertensive medications, but calcium channel blockers and beta blockers have also been used to lower blood pressure in people with PAD[1,121]. The HOPE study is the only RCT reporting outcomes of an antihypertensive on a PAD population and found that administration of Ramipril reduced the risk of MACE (HR 0.75, 95% CI 0.61-0.92) compared to placebo[148]. Additionally, two observational cohort studies found lower mortality (HR 0.70, 95% CI 0.57-0.86) with ACEI/ARB in patients with CLTI undergoing revascularisation, while there are conflicting results about the effect of ACEIs on major amputation and re-intervention rates after revascularisation[149–152]. Finally, two systematic reviews reported that there was no negative effect from beta-blockers and other anti-hypertensive agents on ABPI and intermittent claudication symptoms[153,154]. Further research is required on the effect of anti-hypertensive medications on patients with CLTI.

Poor perioperative glycaemic control (haemoglobin A1c > 7%) has also been associated with higher risk of major cardiovascular and limb events including major amputation[155–158], increased mortality[159], and higher incidence of restenosis after revascularisation in people with PAD[45], even though some studies have not found this association in patients with CLTI[157,159,160]. Currently, the recommended target haemoglobin A1c is less than 7%, with the global vascular guidelines suggesting Metformin as first line treatment[3]. Other options include sodium-glucose co-transporter 2 (SGLT-2) inhibitors, dipeptidyl peptidase-4 inhibitors, and insulin. Empagliflozin in particular, an SGLT-2 inhibitor, has been associated with reduced cardiovascular (HR 0.57, 95% CI 0.37-0.88) and all-cause mortality (HR 0.62, 95% CI 0.44-0.88) in patients with PAD[161], but there is evidence of increased risk of amputation (OR 1.89, 95% CI 1.37-2.60) with Canagliflozin, another medication of this class, which should be avoided in this patient group[162,163].

Revascularisation

Revascularisation strategies include open surgery, endovascular interventions, and hybrid procedures, the latter being a combination of the two approaches. Their aim is to restore pulsatile in-line flow to the foot. More than 7,600 open surgical or hybrid and 16,000 endovascular revascularisation procedures are performed in the UK every year[164]. Open surgery usually consists of a bypass with or without endarterectomy or endarterectomy alone. Endarterectomy involves removal of the intima and media layers of the diseased arterial wall along with the atherosclerotic plaque and closure of the artery with a patch, usually made of bovine pericardium or vein[165]. A bypass can be performed to treat long segments of diseased arteries by joining the proximal (inflow) and distal (outflow) healthy arteries with a graft. The common femoral and superficial femoral arteries are the most common inflow vessels. Residual disease in the inflow vessels reduces flow in the graft and may lead to graft occlusion. Therefore, in case of iliac or femoral inflow disease, these should be treated prior to or during the bypass procedure with endovascular techniques or endarterectomy[165]. The outflow artery should provide continuous runoff to the foot and should also be free of disease to ensure the long-term patency of the graft.

The choice of conduit is of critical importance for the success and durability of the bypass. Autogenous vein is the first choice graft, especially for infrapopliteal outflow target vessels, and availability of a suitable vein should be explored through Duplex vein mapping prior to the procedure[3]. The great saphenous vein (GSV) of the ipsilateral limb is the most frequently used conduit. When it is not available because it has already been used for a coronary bypass or previous lower limb bypass, has been obliterated during varicose vein surgery or is inadequate, other options include the GSV of the contralateral limb, small saphenous veins, and the cephalic or basilic vein of the upper limbs, that can be spliced to provide a longer graft[165]. Vein grafts can be used in situ, non-reversed translocated or reversed, with non-reversed or in-situ grafts requiring careful lysis of the vein valves with a valvulotome[165]. Synthetic grafts are made of Dacron or polytetrafluoroethylene (PTFE) and there is some evidence suggesting that Dacron grafts are superior to PTFE for femoral to above-knee bypass in terms of secondary patency[166,167]. Vein and prosthetic grafts have been compared in a Cochrane meta-

analysis of 19 RCTs that showed better primary patency rates for vein grafts (OR 0.47, 95% CI 0.28-0.80)[167], as well as a large meta-analysis[168] and retrospective studies that demonstrated lower 1-year major amputation rate (11%, 95% CI 9-13; vs 24%, 95% CI 14-42) and higher patency[169–171] and limb salvage rates[172,173] for GSV compared to non-autogenous grafts. However, there are arguments that the choice of postoperative antithrombotic therapy may also play a role in prosthetic graft patency[174].

Endovascular interventions for chronic disease consist of plain balloon angioplasty (PBA), drug-coated balloon angioplasty (DCB), and stenting with bare metal stents (BMS), drug-eluting stents (DES) or covered stents. Their main advantage is that they are minimally invasive and can be performed under local anaesthetic, making them a good option for patients at high surgical risk, but their technical success depends on the complexity of atherosclerotic lesions and the severity of calcification. A Cochrane meta-analysis of seven trials comparing angioplasty versus stenting for infrapopliteal disease in CLTI patients did not find a difference in short-term patency, periprocedural complications, major amputation and mortality[175]. A similar Cochrane meta-analysis for iliac lesions was inconclusive due to lack of high quality studies comparing the two techniques[176]. A larger meta-analysis of prospective studies reported that 1-year primary patency of PBA in the superficial femoral artery (SFA) was 86% (95% CI 70-100%), while for infrapopliteal lesions it was 66% (95% CI 51-85%), with DES having better (73%, 95% CI 65-81%) and BMS worse (50%, 95% CI 42-60%) primary patency in the CLTI population[168]. Additionally, an American registry study reported 1-year MACE of 29.5%, and MALE of 34.0% in patients with CLTI undergoing endovascular revascularisation, with previous intervention and haemodialysis being predictors of MALE and cardiac, renal and respiratory disease predictors of MACE[177]. The variety of available endovascular devices and techniques has greatly increased in recent years thanks to technological advancements, with new lithotripsy, atherectomy, and deep venous arterialisation devices promising better outcomes than conventional PBA for patients unsuitable for open surgery[178,179]. However, more evidence of their effectiveness and durability is required before their widespread use in clinical practice.

Hybrid approaches are increasingly used to treat complex multilevel atherosclerotic disease, with the endovascular component being proximal or distal to the surgical

intervention[180,181]. These procedures are longer in duration, may be performed jointly by vascular surgeons and interventional radiologists and require hybrid operating theatres with both surgical and radiographic equipment. Typical examples include common femoral endarterectomy or femoro-distal bypass combined with iliac angioplasty and stenting to treat inflow disease, or common femoral endarterectomy with tibial angioplasty to improve flow to the foot. In 2021, 1,608 hybrid revascularisation procedures were recorded in the UK National Vascular Registry (NVR), of which 863 had endovascular interventions proximal to the surgical element and 312 distal to it, with the rest being more complex[164]. The complication rate was higher for hybrid cases with proximal endovascular elements compared to distal (16.4% proximal vs 9.2% distal in elective cases, 26.8% proximal vs 24.2% distal in non-elective cases)[164]. Limb salvage rates after hybrid revascularisation for CLTI have been reported as 91% at 1-year and 86% at 5-years, with survival rate of 80% and 51% at 1-year and 5-years, respectively[181].

The optimal strategy to achieve adequate in-line flow to the foot depends on patient factors, the anatomic pattern of the disease, and the availability of suitable autogenous vein, but local expertise and facilities may also weigh in the decision-making process. The choice of revascularisation technique has been the focus of much debate, even though few RCTs have been performed so far and more are underway[182,183]. The Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) RCT compared endovascular-first versus bypass-first approach for infrainguinal CLTI and demonstrated that there was a trend for higher mortality up to 6 months in those randomised to surgery (HR 1.27, 95% CI 0.75-2.15), but mortality was lower after 2-years of follow-up in those who survived for 2-years (HR 0.61, 95% CI 0.50-0.75), with equivalent amputation-free survival (AFS)[184,185]. Re-intervention rate was higher in those who underwent surgical procedure (11% difference, 95% CI 4-19%). Notably, there were no statistically significant differences in mortality or amputation-free survival between the two interventions for the subgroup of patients with infrapopliteal disease[186]. Additionally, most patients randomised to the endovascular-first group ultimately required bypass, and patients who had bypass after a failed endovascular revascularisation attempt experienced worse outcomes compared to those with primary bypass (AFS for primary

bypass vs. secondary: HR 1.58, 95% CI 1.03-2.44)[187,188]. The recently published BEST-CLI RCT also compared the two treatment modalities in patients with infrainguinal CLTI and reported that patients undergoing surgical revascularisation with great saphenous vein had lower risk of re-intervention (HR 0.35, 95% CI 0.27-0.47) and major amputation (HR 0.73, 95% CI 0.54-0.98) compared to those undergoing endovascular revascularisation, and similar risk of all-cause mortality[189]. Contrarily, there were no differences in major amputation rate or all-cause mortality between patients undergoing surgical treatment with conduits other than GSV and those having endovascular treatment (HR 1.10, 95% CI 0.65-1.87, and HR 1.15, 95% CI 0.77-1.72, respectively)[189]. Similarly, a Cochrane meta-analysis of 6 RCTs comparing bypass to balloon angioplasty found no difference in major amputation, re-intervention or mortality rates, but revealed higher periprocedural complications and higher 1-year primary patency with bypass surgery (OR 1.57, 95% CI 1.09-2.24, and OR 1.94, 95% CI 1.20-3.14, respectively)[190].

The results from non-randomised studies that do not directly compare the two revascularisation techniques are similar and reflect a larger cohort of patients with CLTI, albeit with higher risk of bias and residual confounding. In-hospital mortality in patients admitted non-electively with CLTI was higher for open surgical compared to endovascular procedures (4.8%, 95% CI 4.1-5.7 vs 4.1%, 95% CI 3.3-5.0) while 30-day readmission rate was lower (13.2%, 95% CI 11.9-14.6 vs 19.8%, 95% CI 18.1-21.5) in the 2022 Annual NVR report[164]. Another large cohort study of CLTI patients found no difference in 30-day mortality, but lower rate of MACE (OR 0.6, 95% CI 0.4-0.9), surgical site infection (OR 0.1, 95% CI 0.1-0.2), and unplanned reoperation (OR 0.7, 95% CI 0.5-0.8) and higher rate of secondary revascularizations (OR 1.6, 95% CI 1.04-2.3) within 30 days for endovascular-first as opposed to bypass-first approach[191]. The authors also noted that age over 80 years, tissue loss, functional dependence, diabetes, end-stage CKD, and tibial lesions were associated with decision for endovascular-first approach[191]. Additionally, a cohort study of 11,106 propensity matched patients with CLTI found lower in-hospital complications (OR 0.83, 95% CI 0.78-0.88) and shorter length of stay (OR 0.75, 95% CI 0.73-0.78) after endovascular procedures compared to open, no difference in 6-month mortality, but 18% higher risk of major amputation at 6-months in the endovascular revascularisation group (HR 1.18, 95% CI 1.08-1.29), which however

was not observed in high-volume centres[192]. Evaluating longer-term outcomes, a meta-analysis of revascularisation studies in patients with CLTI with at least one year of follow-up reported no significant difference in major amputation and overall mortality between the two treatment modalities, but bypass surgery was associated with higher primary patency rate (OR 2.50, 95% CI 1.25-4.99)[193]. In summary, surgical procedures seem to have higher patency rate and longer durability but are often associated with higher postoperative morbidity and greater length of stay. On the other hand, endovascular procedures have good short-term outcomes but long-term patency is lower and re-intervention rates higher[194]. Based on this evidence, the Global vascular guidelines for CLTI suggest a three-step approach consisting of 1) estimating patients' periprocedural risk; 2) determining the limb stage using the WIfI classification; and 3) determining the anatomic pattern of disease using the GLASS classification, taking into account the presence of a vein conduit, and provide specific recommendations for each patient[3].

After a revascularisation procedure, patients should continue best medical therapy and are usually followed up for a period of two years to monitor the patency of the graft, stent or treated native artery[3]. Graft stenosis can develop at the anastomotic sites or in the graft, occasionally due to a remaining venous valve. Endovascular procedures may also fail in time due to residual stenosis, recoil or stent occlusion. Surveillance protocols vary in terms of timing and modality by country and centre, with a systematic review identifying 96 different protocols after endovascular revascularisation in the literature[195]. Modalities used for surveillance include measurement of ABPI, DUS, and DSA[82,83], with DUS being the investigation of choice. Grafts at risk can be identified through flow abnormalities in DUS (peak systolic velocity (PSV) >300 cm/s, PSV ratio >3.5, mid-graft PSV <45 cm/s), and intervention may prevent the graft from occluding[196]. Surveillance visits usually start 6 weeks post-procedure and continue for a mean 21 months, with more intensive follow-up in the first year after treatment for infrapopliteal compared to femoro-popliteal interventions[195,197].

Management without revascularisation

In some cases, it is not possible to restore blood flow to the ischaemic tissues due to extensive arterial calcification or when the anatomy is unsuitable for revascularisation, such as lack of arteries crossing the ankle, so the options are limited to primary amputation, pharmacological treatments or interventions aiming at symptom control. These options should also be considered in patients who have limited life expectancy, an unsalvageable limb with extensive tissue loss, or poor functional status with significant comorbidities, such as hemiplegia, fixed flexion deformities, and spinal paralysis[3].

Minor amputations are defined as amputations at or below the ankle joint and include toe, ray, transmetatarsal, Lisfranc's and Chopart's midfoot and Symes' through-ankle amputations[198]. The commonest indications for a minor amputation are spreading infection from a diabetic foot ulcer, osteomyelitis, and gangrenous toes. Depending on the severity of ischaemia, the minor amputation wound may heal spontaneously or require a revascularisation procedure to achieve adequate distal perfusion for healing. When removal of more than two toes is required, transmetatarsal amputation may be preferable, as removal of multiple toes alters foot biomechanics which may lead to further ulcers[199]. Minor amputations for PAD or diabetes are associated with postoperative mortality of 20% and 44%[200], and ipsilateral major amputation rate of 10% and 14% at 1 and 5 years, respectively[201,202]. Open surgical revascularisation, end-stage CKD, hyperlipidaemia, congestive heart failure and high BMI have been associated with limb loss after minor amputation[203].

Approximately 12% of patients with CLTI will require major amputation within 3 months of presentation[8]. Major amputations are those above the ankle level and consist of trans-tibial (below the knee, BKA), through-knee (Gritti Stokes), and trans-femoral (above the knee, AKA) amputations and hip disarticulation. They are often performed to remove extensive tissue loss, uncontrolled infection or to relieve ischaemic pain when there are no revascularisation options[204]. The level of amputation is crucial, as more proximal amputations have higher primary healing rates, while more distal amputations are associated with better functional outcomes and possibility of ambulation with

prosthetics but may fail to heal and require re-interventions[205,206]. Currently, there is no reliable method to assess tissue perfusion and predict healing of the amputation wound[3]. Additionally, all major amputations are associated with an increase in basal energy expenditure and energy cost of walking with prosthesis, which is greater for more proximal amputations and partly explains why elderly frail patients with cardiovascular comorbidities experience difficulties ambulating postoperatively[207]. A post-amputation ambulatory rate of 46-49% at 1-year has been reported, which was strongly associated with BMI and frailty[205,208]. There are currently no high quality studies comparing through knee and above knee amputations[209]. The mortality after major amputation varies from 4% to 22% at 30-days and from 34 to 48% at 1-year[206,210–212]. At 5-years, mortality after BKA ranges from 40% to 82% and after AKA from 40% to 90%[212,213]. More proximal amputation (AKA vs BKA), older age, coronary artery disease, cerebrovascular disease, end-stage CKD or dialysis, non-ambulatory status, and increased comorbidity burden have been associated with higher risk of mortality after major amputation[210,211,213].

When symptom control is desirable in patients with rest pain and no revascularisation options, interventions such as spinal cord stimulation and intermittent pneumatic compression have been shown to decrease pain, while lumbar sympathectomy is not recommended[3]. Spinal cord stimulation has been associated with higher 1-year limb salvage (RR 0.71, 95% CI 0.56-0.90) and pain relief compared to conservative management, by increasing relaxation of smooth muscle cells and decreasing vascular resistance, but is not cost-effective and has 17% risk of complications[214]. Evidence suggests that intermittent pneumatic compression may also improve limb salvage, wound healing, and pain control through an increase in the arteriovenous pressure gradient and stimulation of collateral flow, but high quality evidence of its effectiveness is currently lacking[215,216].

Regarding pharmacological treatment, prostanoids such as iloprost, vasoactive agents such as Naftidrofuryl and Cilostazol, and hyperbaric oxygen therapy have been used in patients with no-option CLTI[3]. A Cochrane review concluded that prostanoids, with their vasodilatory and antithrombotic properties, have positive effect on reduction of rest pain (RR 1.30, 95% CI 1.06-1.59) and ulcer healing (RR 1.24, 95% CI 1.04-1.48), but not

on major amputations and mortality, with associated adverse effects such as headache, nausea, vomiting, and diarrhoea (RR 2.11, 95% CI 1.79-2.50)[217]. Hyperbaric oxygen may also increase the rate of ulcer healing for DFUs (RR 2.35, 95% CI 1.19-4.62), with no effect on major amputation rate (RR 0.36, 95% CI 0.11-1.18) based on low-quality evidence[218,219], while there is insufficient evidence to support the use of vasoactive agents in patients with CLTI[220]. It is also worth mentioning that multiple trials of gene and cellular therapies have been performed or are underway in patients with CLTI, but no phase three trials have demonstrated their effectiveness in improving amputation-free survival so far[221,222].

Conservative non-operative management of CLTI has been associated with 1-year all-cause mortality of 18% (95% CI 13-25%), 1-year major amputation rate of 27% (95% CI 20-36%), and 1-year AFS of 60% (95% CI 52-67) in a meta-analysis of 27 studies with 1642 individuals[223]. In a further study of 150 patients with non-revascularisable CLTI and longer follow-up, 5-year all-cause mortality was 35%, 5-year major amputation 33%, and 5-year AFS 43% with conservative management[224], which are not excessively worse than outcomes after revascularisation. Additionally, in a cohort of patients with no revascularisation options and diabetic foot ulcers 38% healed primarily, 12% underwent minor amputation, 17% major amputation, and 33% died without healing[225]. On the other hand, quality of life can be maintained or slightly improved with conservative management of CLTI or primary major amputation, whereas improvement with surgical or endovascular intervention is small to moderate[226].

Prognosis

Overall, all-cause mortality in patients with CLTI irrespective of treatment received has been reported as 4% at 30-days, 18% at 1-year, and 46% at 5-years[227]. The 1-year mortality rate after revascularisation procedures for CLTI in English studies using the Hospital Episode Statistics (HES) dataset ranges from 11.2-12.8%, but this includes both elective and emergency admissions[194,228], and these studies are limited by the inability to accurately define the CLTI cohort in HES[229]. A registry-based study of 38,470 patients with CLTI undergoing revascularisation from the US Vascular Quality Initiative reported a 30-day, 2-year and 5-year mortality rate of 2%, 19% and 31%, respectively[230], while

higher mortality rates reported in similar studies from Germany (28% at 1-year)[62], Japan (32.3% at 2-years for endovascular revascularisation)[99], and the US Medicare database (49-55% at 5-years)[231]. Older age, male gender, chronic obstructive pulmonary disease, severe CKD or haemodialysis, ischaemic heart disease, smoking status, lower BMI, non-independent ambulatory status and WIfI stage have been independently associated with higher mortality[99,230,232].

Major amputation rate after revascularisation for CLTI ranges from 8% to 15% at 1-year[44,233] and 8-11% at 4-years[231]. Factors associated with major amputation after revascularisation include male gender, high comorbidity burden, diabetes, haemodialysis, severe frailty and living in a high deprivation area, as well as presence of tissue loss and open surgical procedure[232–234]. A Cochrane meta-analysis of RCTs, a larger meta-analysis and the BEST-CLI trial did not find a significant difference in this outcome between procedure types[189,190,193]. Finally, predictors of 30-day AFS after revascularisation for CLTI include emergency procedure, congestive heart failure, haemodialysis, abnormal white blood count, and body temperature of 38 degrees Celsius or above[235].

1.1.5 Challenges in timely treatment

It is evident that CLTI represents a severe form of cardiovascular atherosclerotic disease and is associated with risk of adverse outcomes, which can be decreased with medical and surgical treatment. However, a National Confidential Enquiry into Patient Outcome and Death (NCEPOD) report published in 2014 and the NHS Improvement Getting it Right First Time (GIRFT) report on vascular surgery, published in 2018, highlighted deficiencies in the management of patients with CLTI[206,236]. The reports indicated that these deficiencies have a detrimental effect on patient outcomes and revealed a variation in practice across England. The authors also identified areas where the provision of care could be improved, such as the assessment, investigation and treatment of these patients, in order to potentially avoid amputations.

In response to those findings, the Vascular Society of Great Britain and Ireland (VSGBI) published a “Best Practice clinical Care Pathway for Peripheral Arterial Disease” in March 2019[237]. This document outlined a Quality Improvement Framework (QIF) for the

management of patients with PAD that included 16 standards and suggested specific timelines from referral to treatment for patients with CLTI (Figure 2). The overall timelines from receipt of referral to revascularisation were 5 days for admitted patients with deep tissue injury, infection or uncontrolled pain, and 14 days for non-admitted patients with minor necrosis, ulcers or controlled pain[237].

This guidance was based on expert opinion rather than evidence, due to the scarcity of studies exploring the association between treatment delays and patient outcomes. More specifically, the writing committee consisted of Consultant vascular surgeons, interventional radiologists, and vascular anaesthetists, but the standards and timelines were discussed and agreed in five VSGBI Audit and Quality Improvement Committee meetings in 2018 and 2019, which were attended by representatives from Podiatry, vascular nurses, vascular technologists, health services researchers and patients. Consecutive drafts of the document were also circulated to the committee for review and comments prior to publication. Even though research evidence was lacking, the committee members reached a clinical consensus on the timelines as it was considered that revascularising too early (within 1-2 days) may not allow enough time for medical optimisation, while delaying more than 5 days may cause adverse outcomes. Additionally, it was acknowledged that the timescales were "deliberately challenging", due to the limited resources and high service demand in most vascular units.

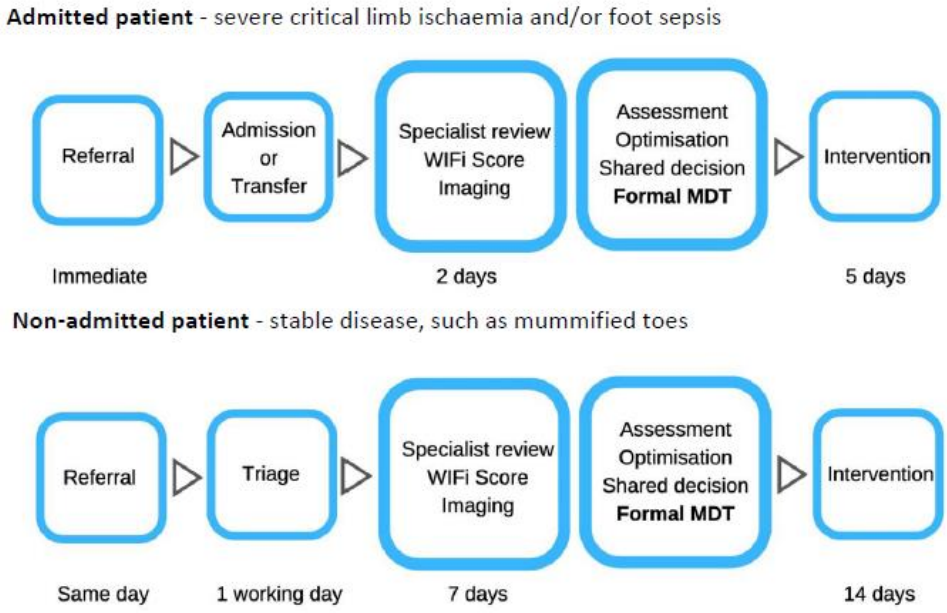

Figure 2 – Recommended timelines according to the VSGBI PAD QIF document

Nevertheless, specific recommendations on how to achieve them were not provided, other than suggestions for delivery of urgent outpatient appointments and vascular presence in networked hospitals, again due to lack of evidence-based effective interventions[237]. Similar timelines had been suggested for carotid and aneurysm procedures, and according to annual NVR reports, many units have not been meeting these targets[238]. Further increasing the demand on vascular services would most likely lead to failure without careful planning and change in the resource allocation and delivery of care to the CLTI patient group.

The main steps in the patient pathway from presentation to the healthcare services with symptoms of CLTI to treatment can be described as follows: a) referral of patient to the vascular specialist; b) clinical assessment by a member of the vascular team; c) diagnosis through point-of-care tests and imaging investigations; d) multidisciplinary team (MDT) discussion of treatment options taking into account patient wishes and shared decision-making; e) cardiovascular risk assessment and optimisation by care of elderly or anaesthetic teams; and f) treatment[239]. Delays can arise at each step of the pathway and have been described in a systematic review by Nickinson et al.[240] For example, due to the centralisation of vascular services, only vascular tertiary centres have constant presence of vascular surgeons and can perform major arterial procedures. Therefore, the hospital of presentation plays a significant role in timeliness of treatment, with presentation at network (spoke) hospitals associated with longer delays compared to arterial hubs[241]. Additionally, increasing the availability of outpatient clinic slots so that patients can be reviewed by a vascular specialist shortly after referral may also contribute in the reduction of delays[242].

Currently, it is unclear which factors contribute most to the delays to treatment for patients with CLTI, what the consequences of the delays are and which interventions are the most effective in reducing the delays. It is also worth noting that any changes in the vascular service that aim to address delays may have wider consequences for other patients, the workforce or the organisation itself and their effectiveness may depend on the context in which they are implemented. Therefore, any such efforts should adhere to the principles of quality improvement and implementation science, with clear measurement and evaluation processes.

1.2 Implementation Science and Quality Improvement

1.2.1 Introduction to Implementation Science

Implementation science (IS) is a discipline that studies strategies to promote the uptake of evidence-based interventions into routine practice, using a broad range of methodologies that guide the implementation, scale-up and dissemination of effective interventions, taking into account the local context[243]. Its aim is to guide healthcare improvement, namely "any systematic effort intended to raise the quality, safety and value of healthcare services" and improve patient outcomes[244]. It focuses on understanding the process of implementation (what, when, why, how), identifying the systems, behaviours, and practices that influence it, and evaluating strategies to address them[245]. Outcomes of interest for implementation efforts usually include the adoption, acceptability, appropriateness, feasibility, fidelity, cost, and sustainability of an intervention, rather than clinical effectiveness[246]. It is an interdisciplinary research field, which draws on theories from sociology, psychology, philosophy, and economics.

Implementation studies consist of an implementation strategy and the intervention being implemented[247]. Implementation strategy is the method used to adopt, implement and sustain an intervention, such as the development of data collection systems, templates, access to resources and training, facilitation and feedback[248]. The intervention is the specific activity, practice or process that is introduced into a service to improve its performance[244]. The choice of implementation strategy depends on the desired change and on the factors that are expected to enable or hinder implementation, so it can address them. These factors are related to the nature of the intervention itself, the individuals involved, the place where change happens, the wider social, economic, and political environment, and the processes of implementation[245].

Evaluation of implementation studies aims to assess the impact of an implementation strategy on the processes of care and is usually conducted using qualitative and quantitative data[249]. Quantitative data are collected through surveys of clinician or patient attitudes, administrative data that measure baseline performance and change in practice, and fidelity measures[249]. Qualitative data collection is performed through semi-structured interviews with stakeholders, focus groups, documentary review, and

ethnographic methods[250]. Mixed methods designs are also used to evaluate implementation studies, with the qualitative and quantitative data integrated at various stages of the project[251]. In such studies, the two elements can have equal weighting or one may be prioritised over the other and they may be combined through: convergence (both used to answer the same question); complementarity (answering different but related questions); expansion (qualitative data used to explain quantitative results); development (one method provides information to guide use or development of the other); and sampling (using one method to identify participants for the other)[251].

Additionally, effectiveness-implementation hybrid designs can be used to assess both the clinical effectiveness and the implementation of an intervention[252]. Typically, clinical and implementation studies have different aims, units of analysis, and outcome measures, but the combination of the two can expedite the translation of research into practice, using one of three approaches. Hybrid Type I studies evaluate the effect of a clinical intervention on outcomes, while collecting data on the implementation process. In Hybrid II studies the clinical intervention and implementation strategy are being tested simultaneously, usually when the effectiveness of the intervention itself is not well established but is being implemented widely. Finally, the primary focus of Hybrid III studies is to determine the utility of an implementation strategy, while collecting information about the impact of the clinical intervention on outcomes, and is used to evaluate how an intervention with established effectiveness performs in different contexts[253].

1.2.2 Theory in Implementation Science

Theory underpins the design of the implementation strategies and interventions and explains how and why they are effective in specific contexts. In implementation science, theoretical approaches are divided into five categories: process models that describe the steps in the process of knowledge translation into practice; determinant frameworks, with domains of factors that influence implementation; classic theories that describe how change happens; implementation theories, which provide a better understanding of certain implementation aspects; and evaluation frameworks, which are used to evaluate implementation efforts[254]. Theories explain the causal mechanisms

of implementation and have predictive capacity, models provide a simplified representation of a process, and frameworks describe theoretical constructs that affect implementation without specifying the relationship between them[254]. These theoretical approaches are often applied retrospectively to interpret the findings after an implementation project is complete, but ideally they should be used to design implementation strategies and plan their evaluation, in order to create generalizable knowledge and advance this field of study[255].

A systematic review of full-spectrum theories, models and frameworks (TMF) identified 18 process models, 3 evaluation frameworks, 3 determinant frameworks and 8 classic theories used in implementation science, offering the most complete overview of existing theoretical approaches to date[256]. The most commonly used TMFs were: the Consolidated Framework for Implementation Research (CFIR)[257], the Theoretical Domains Framework (TDF)[258], the Promoting Action on Research Implementation in Health Services (PARIHS) framework[259], the Reach Effectiveness Adoption Implementation Maintenance (RE-AIM) evaluation framework[260], and the Diffusion of Innovations theory[261], but as many as 159 TMFs have been reportedly used in implementation studies[262,263]. Therefore, the selection of the best theoretical approach for a project can be complex. To aid with this decision, a Theory Comparison and Selection Tool (T-CaST) has been developed through a concept mapping exercise with experts and provides four criteria: usability; testability; applicability; and acceptability by key stakeholders, which should be used to compare frameworks and choose the most suitable one[264]. Another approach to identify an appropriate theoretical approach is to consider five elements: the level of analysis (individuals, teams, entire health service); the timing (prior to implementation for planning, during implementation, after implementation for evaluation); the purpose and intended outcomes (measure change, understand factors affecting change, understand implementation process); the method of data collection; and the available resources (experience, number and time of staff)[265].

In addition to the previously described middle-range theories and frameworks, there are also programme theories, which describe how and why an intervention is expected to lead to its intended outcomes, and is specific to that project or intervention[266]. The programme theory, which is also called Theory of Change, outlines the assumptions

about the mechanisms that link the inputs with the processes and the outcomes of a project[267]. It can be articulated in a series of if-then statements, whereby if something is done, then some effect will be generated, but should also explain using research evidence why the specific outcomes are expected. By making these assumptions explicit, the programme theory can guide the choice of outcomes, measurement methods, and data collection techniques and provide the basis for evaluation, refinement and adaptation of the intervention or strategy[268]. The programme theory can be depicted graphically in the form of a Logic model. The Logic model consists of the inputs required for an intervention, its components, its outputs, and its outcomes[269]. The inputs or resources are the raw materials required for an intervention, such as knowledge and skills of individuals, infrastructure or a toolkit; components are the activities and mechanisms through which the resources lead to a change; outputs are the immediate results of the intervention activities; and outcomes are the final results observed in patients or the service[268].

In summary, the steps of an implementation project include: (1) identification of the problem to be addressed, (2) selection of theoretical approach, (3) stakeholder engagement to support the project, (4) development of the logic model, (5) selection of research and evaluation methods, (6) identification of factors affecting implementation, (7) selection and tailoring of implementation strategies, (8) implementation period, (9) evaluation of the implementation, and (10) reporting of outcomes[270].

1.2.3 Factors affecting implementation

There are multiple barriers and enablers which influence implementation outcomes that have been described and categorised in determinant frameworks. These factors can refer to different levels, from the individual to the organisation, and may have derived from combining findings from empirical studies, from the researchers' own experiences of implementation, or from classic theories[271]. Despite the broad range of factors included in each framework, most of them include: (1) the characteristics of the intervention, (2) the attributes of individual healthcare professionals, (3) the organisational and health system context, and (4) the processes through which implementation occurs[271].

Intervention

The intervention or innovation is a specific activity or tool introduced into a healthcare system to improve its performance[244]. The template for intervention description and replication (TIDieR) guide recommends that when describing an intervention, the following aspects should be described: the procedures, processes or activities involved; the physical or information materials used; the rationale or theory supporting the essential elements; the mode of delivery (in-person, online, via telephone, in groups, individually); the location where they occurred; the frequency, timing, duration, and intensity of the intervention; the intervention providers and their background, expertise and training; and any adaptations or modifications to the intervention[272]. Most interventions tested in implementation studies are complex interventions, consisting of multiple components, targeting many levels, settings or behaviours, and requiring advanced skills or expertise for their delivery[273].

Several characteristics of the interventions have been described as important for implementation. Firstly, the validity of the source that developed the intervention and whether it was externally or internally developed can affect its acceptance by stakeholders, as is the quality and strength of evidence supporting it[274]. The adaptability to different contexts may also help with transferability and adoption in different settings. The ability to test the intervention on a small scale and its level of complexity and compatibility with existing practices, values, and perceived needs have a role in its uptake, while the quality of supporting materials and the presentation of its components may affect the ease of use[261]. Finally, its relative advantage compared to current practices or alternative solutions and its cost should also be taken into account[261]. It is worth noting that these factors do not represent objective characteristics but rather subjective perceptions of stakeholders, which affect their attitude towards the intervention and their willingness to implement it.

Individuals

In addition to the intervention itself, the attitude of healthcare professionals intended as users towards a proposed change is determined by intrinsic characteristics of these individuals. Social-cognitive and motivational theories have been used to inform

behaviour change in implementation studies, by exploring these characteristics[275]. The most widely used is the theory of planned behaviour, which postulates that a professional's adoption of a desired behaviour is determined by their positive or negative attitude towards that behaviour, their thoughts on the difficulty in performing the behaviour (perceived control), and the pressure from others (social norm)[276]. The plethora of human behaviour change theories was reviewed and distilled into the 14 domains and 84 constructs of the TDF, which postulates that the behaviour of individuals towards an intervention is determined by multiple factors[277,278]. These include their knowledge, opinions, and beliefs about the intervention, as well as their values, goals, skills, emotions, and social influences, which can be summarised into three core components: capability, opportunity, and motivation[258]. Other factors related to individuals that influence implementation efforts include their belief in their capabilities to carry out the change (self-efficacy), their relationship with and commitment to the employing organisation, and their stage of readiness to use the intervention[274].

Context

Context is considered a crucial element affecting the success of implementation studies and the generalisability of their findings. It can be defined as the physical and sociocultural characteristics of the environment, such as the external environmental factors, organisational climate, resources, and leadership, and the interpretation of these factors by healthcare professionals, patients and carers, but many different definitions have been described in implementation literature[244,279]. Its importance for implementation is reflected by the fact that most determinant frameworks include factors related to context, even though few provide a specific definition for it[280].

In an attempt to systematise the use of the term, Rogers described three levels of context with relevant determinant factors of implementation: system-level, organisational-level, and team-level[281]. System-level factors refer to the social, political, and economic environment and the healthcare system outside the implementing organisation. These include professional standards and guidelines, social norms and customs, funding and the economic climate, political support, national laws and policies, inter-organisational networks, local infrastructure, and the patients with their needs and

preferences[282]. Organisational-level factors include the available resources, organisational support, leadership engagement with the implementation effort, organisational culture and climate, readiness for change, inter-departmental communications, and the structural characteristics of the organisation, such as its size, procedure volume or catchment area. Organisational culture usually refers to the values, norms, and expectations in an organisation, while readiness for change includes the commitment of the organisation to change, incentives, the prioritisation of implementing change, and the ability to adopt innovations.

Finally, team-level determinants pertain to: characteristics of the team, such as its size, turnover, and workload; the quality of teamwork and relationships among its members; the compatibility of the intervention with the team aims and workflows; the team culture; and the belief of team members in their ability to use the intervention[281]. The factors most commonly included in determinant frameworks are organisational culture, leadership, resources, organisational support, social relations, and organisational readiness to change[280]. The first four are also the factors most commonly reported in implementation studies as affecting implementation, in addition to the presence of champions and inter-departmental communication[283].

Process

The implementation process can be divided into four phases, planning, stakeholder engagement, execution, and evaluation[274]. The way of progressing through the phases can influence the success of the implementation. For example, implementation goals and timelines should be set during the planning phase, as they will guide subsequent steps. Evaluation of the implementation efforts should also be performed regularly, through analysis of the collected data and feedback that is shared within the team. Most importantly, engagement of key stakeholders, opinion leaders, and implementation champions can be crucial in driving change, even when obstacles are encountered[261,284]. These individuals usually have the respect of their colleagues thanks to their expertise or professional status and are appointed or volunteer to promote the use of a new intervention in an organisation. Their influence on implementation can be explained by

the Diffusion of Innovations theory, which describes why and how an innovation gradually spreads from enthusiastic early adopters to the majority of users[285].

Finally, even though the factors that influence implementation efforts are neatly listed and categorised in determinant frameworks, there are dynamic relationships between them that should be taken into account and highlighted during evaluation[286]. Complexity represents such an example, as it is a characteristic of the intervention, and the context, while culture, resources and leadership support could be considered characteristics of teams and organisations alike.

1.2.4 Implementation strategies

Implementation strategies have been defined as "methods or techniques used to enhance the adoption, implementation, and sustainability of a clinical program or practice"[248]. They should be purposefully selected depending on the nature of the change and the context to support implementation of a specific intervention. They have been used inconsistently until their systematic review and definition through a modified Delphi process by the Expert Recommendations for Implementing Change (ERIC) project[287]. The resulting 73 implementation strategies can be used as "building-blocks" and combined to create a tailored multicomponent multilevel strategy for implementation of an intervention[287]. Implementation strategies can be categorised into dissemination, implementation process, integration, capacity building, and scale-up[288]. Examples of implementation strategies addressing different aspects of implementation include audit and feedback, creation of learning collaboratives, development of educational materials, identification of champions, involvement of executive boards, site visits, facilitation, and financial incentives[287].

The selection of implementation strategies to match the barriers and facilitators of an intervention in a specific setting is a complex endeavour. It starts with conducting an assessment of the factors that may influence the implementation processes and outcomes and then continues with selecting strategies that address the previously identified context-specific barriers[289]. Determinant frameworks like the CFIR can be used in the first step, as they provide a comprehensive list of such factors to consider, and the ERIC compilation of strategies is useful for the second step. However, when

implementation researchers were asked to match the 39 barriers from the CFIR with ERIC implementation strategies that would best address them, a considerable heterogeneity of opinion was observed, indicating the inconsistent relationship between the two[290]. Despite that, methods that can be used to link the strategies with specific requirements of an implementation programme include concept mapping, intervention mapping, group model building and conjoint analysis[289]. All these methods are based on the engagement of multiple stakeholders in brainstorming and idea-generating exercises to create visual maps of concepts, causal loop diagrams, preferred change or service profiles, and determinant matrices, but ultimately can only be used as a guide[289]. In summary, defining and reporting the implementation strategy is an important aspect of the evaluation of an intervention[247].

1.2.5 Quality Improvement

Quality improvement (QI) has a narrower scope than implementation science. The term is used for concerted activities undertaken by multiple stakeholders, such as organisational leaders, healthcare professionals, researchers, patients and carers, to improve patient outcomes, healthcare services, and system performance in a specific local setting[291]. The need for formal Quality Improvement studies in healthcare became obvious in two landmark reports of the US Institute of Medicine in 1999 and 2001, that reported failures in processes and systems rather than individuals, and called for urgent redesign of care systems to achieve improvements[292,293]. QI utilises systematic change methods and tools, such as the Plan-Do-Study-Act (PDSA) cycles, Fishbone diagrams, and driver diagrams, and measurement methods, such as statistical process control (SPC) charts, to improve patient experience and outcomes[294].

QI and IS share the goal of improving the quality and effectiveness of healthcare services, but use different approaches and methods (Table 5). QI is usually performed to address a particular issue in a specific department or organisation, using small test interventions and measuring outcomes using Plan-Do-Study-Act cycles. Due to its relevance to a particular setting, QI studies do not consider the role of contextual factors in the outcomes and its tools do not have a theoretical basis[295]. QI has its origins in the management and manufacturing fields, and concepts such as strategy, leadership,

management, and organisational learning[296]. On the other hand, IS seeks to increase the uptake and spread of evidence-based interventions, measuring outcomes such as fidelity and adoption, and using formal theoretical approaches from the behavioural and social sciences[296]. Its central tenet is to produce generalizable knowledge that can be applied in other settings and the role of context is central to implementation[297].

Due to its more robust methodology and theoretical background, IS is used more commonly by researchers exploring the uptake of interventions in healthcare settings, while healthcare practitioners are more knowledgeable in QI. However, it is becoming increasingly acknowledged that the two approaches can be aligned and used in combination[297,298]. For example, some QI tools could also be used in implementation studies, including the feedback loops and some process measures that can be used by local implementation teams. On the other hand, understanding and taking into account the organisational and system context and adopting behaviour change methods could be valuable additions in QI studies[295]. Additionally, introducing interventions that do not have solid supporting evidence in implementation studies may expand the range of practices that can potentially address a problem[296].

Table 5 – Comparison of Implementation Science and Quality Improvement

	Implementation Science	**Quality Improvement**
Problem	Lack of use of evidence-based practice – "implementation gap"	Suboptimal care-"quality chasm"
Setting	Multi-organisational	Limited to a particular setting
Intervention	Evidence-based	Any potential solution
Theory-informed	Yes	No
Influences	Psychology, sociology, economics	Management, manufacturing
Context	Considered as factor, generalizable findings	Not considered - local, not generalizable findings
Measurement	Qualitative and quantitative	Quantitative (SPC charts)
Outcomes	Adoption, fidelity, acceptability, feasibility, cost, sustainability	Clinical effectiveness, process measures
Tools	Theories, models, frameworks	PDSA cycles, Six-Sigma, Root Cause Analysis, driver diagrams
Users	Researchers	Healthcare practitioners and researchers

1.2.6 Quality Improvement Collaboratives

A Quality Improvement Collaborative (QIC) is a structured approach that includes multidisciplinary teams from multiple healthcare organisations working together to improve the quality of care delivered to patients through learning and sharing of ideas and data on service performance, as well as identification of best practice and change strategies[294]. They have been implemented successfully in various healthcare settings in the community and hospital sector[299,300]. Most QICs follow the US Institute of Healthcare Improvement's Breakthrough Series Collaborative model[301] (Figure 3).

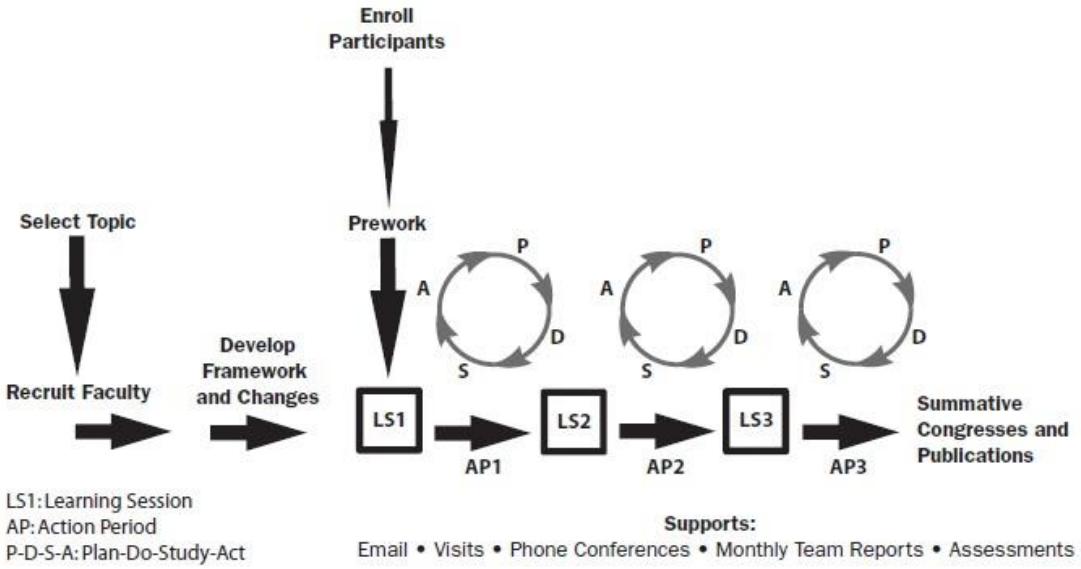

Figure 3 – Breakthrough series Collaborative model, reproduced from the Institute of Healthcare Improvement Breakthrough series white paper[301]

QICs consist of five elements:

- a healthcare area or issue that requires improvement;
- an expert team, that gathers scientific evidence about the intervention and selects implementation strategies, often in the form of a "change package";
- multidisciplinary teams from multiple healthcare organisations;
- a model for improvement, that includes specific measurable aims and data collection on performance; and
- structured collaborative activities such as meetings, that promote learning and sharing of ideas and experiences[300].

The theory of change supporting the QICs is that by benchmarking and working together, teams are motivated to make changes, which improve services and patient outcomes, spread innovations, and create long-term learning networks[299]. This is based on the Partnership Synergy Theory, according to which partners who collaborate and share knowledge and experience can achieve more together than individually, and the Diffusion of Innovations theory, which explains that an innovation spreads from early adopters to the majority of users by demonstrating its merits and increasing the confidence of more conservative parties[285,302]. QICs also offer participants the opportunity to seek advice and learn from experts, as well as develop inter-organisational relationships and support networks[303]. Additionally, they provide training in QI processes for healthcare professionals that can be applied in subsequent projects and infrastructure such as data collection and analysis.

Study designs of QICs include RCTs, controlled before-after studies, and interrupted time series, with most studies ranging from 7 to 24 months in duration[299]. A systematic review of healthcare QICs reported that 83% of the 64 included studies were successful in improving at least one of the primary effect measures, which were clinical processes and/or patient outcomes[299]. The interventions implemented by the QICs were also sustainable and cost-effective[299]. Factors associated with the success of QICs include participation in collaborative activities, support by expert faculty, and formation of a team whose members interact well, understand each other's strengths and have mutual respect[304]. The effect of organisational readiness, leadership support, and availability of resources on success was mixed[304]. Based on an evidence review, the Health Foundation recommends that to be effective, QICs should: gain support from senior leaders, keep participation voluntary, ensure multidisciplinary composition of teams, define the theory of change, set clear goals, allow tailoring of interventions to the local context, use simple measurement and data collection tools, and secure resources and time for change [294]. Finally, it is important that studies involving QICs are adequately reported, as a recent review identified many reporting deficiencies, especially regarding the rationale for choosing the QIC approach and the processes of the collaborative[299].

1.3 Aims of this Thesis

The above literature review highlighted the importance of timely intervention in patients presenting with CLTI, but noted that there has only been a limited number of small studies investigating the effect of treatment delays on outcomes of patients with CLTI. Additionally, there has been no coordinated effort to apply best practice guidance in a systematic manner in the management of this patient group.

This thesis aimed to identify factors associated with delays to treatment in patients presenting with CLTI and explore ways to address them. To achieve that, a Quality Improvement Collaborative programme was developed, implemented, and evaluated using implementation science principles. The following research aims were set:

- Identify factors that affect the timing of revascularisation in patients with CLTI
- Evaluate the association of the timing of revascularisation with patient outcomes
- Assess if implementation of a QI programme reduces the time to revascularisation, in line with the VSGBI best practice guidance, and improves outcomes for patients with CLTI
- Identify factors that influence the uptake of change and the success of a QIC in the vascular surgery setting
- Explore the effect of the global pandemic of coronavirus-19 on vascular surgical procedures, outcomes, and implementation efforts.

Chapter 2. Factors associated with delays to revascularisation in patients with chronic limb-threatening ischaemia: a population-based cohort study

2.1 Introduction

The 2018 Vascular Surgery GIRFT report highlighted considerable regional variation in the time to revascularisation for patients with CLTI across the UK and recommended the provision of scheduled operations on the weekends, in an attempt to increase the early availability of revascularisation surgery and reduce the excessive waits for urgent procedures[236]. The VSGBI PAD Quality Improvement Framework published in 2019 was the first document to specify a recommended target time for revascularisation in the UK, which was 5-days from referral for inpatients with CLTI and 14-days for non-admitted stable patients, thereby generating a definition for what constitutes a delay[237].

The relationship between the timing of lower limb revascularisation and patient outcomes has not been studied extensively, particularly when compared to the impact of delay prior to carotid endarterectomy or hip fracture surgery[305,306], but it has been suggested that earlier intervention leads to improved outcomes. Shorter time to revascularisation increases the probability of healing for ischaemic diabetic foot ulcers[307], and limb salvage rates in diabetic patients with CLTI[308]. However, the short timeframe is challenging to achieve and factors associated with delays have not been studied in detail.

The aim of this study was to identify patient and pathway factors that affect the timing of revascularisation for patients presenting as emergencies with CLTI, in order to inform the reconfiguration efforts of NHS vascular services and improve the quality of care for CLTI patients.

2.2 Methods

The study was based on a prospective, population-based cohort of vascular procedures collected by the NVR. The NVR is a national clinical audit, commissioned by the Healthcare Quality Improvement Partnership (HQIP), and collects demographic and clinical information on five major vascular procedures undertaken within NHS hospitals in the United Kingdom. Approximately 90% of open and 40% of endovascular lower limb revascularisation procedures performed in NHS hospitals are captured in the NVR[238]. The study involved secondary analysis of existing pseudo-anonymised data and therefore was exempt from UK National Ethics Committee approval.

2.2.1 Study population

The study cohort was defined to be adult patients who presented as emergencies with chronic limb-threatening ischaemia, and who underwent either open or endovascular lower limb revascularisation between January 2016 and December 2019. Open revascularisation procedures consisted of lower limb bypasses and endarterectomies with or without an endovascular component, and endovascular procedures included balloon angioplasties with or without stent. Patients were identified as having CLTI if their admission Fontaine score was documented as III (rest pain) or IV (ulceration or gangrene) and their presenting problem was chronic limb ischaemia, neuropathy, tissue loss or uncontrolled infection. Acute limb ischaemia, aneurysms and trauma were excluded. For non-emergency patients, the median time from admission-to-intervention was 0 days (Interquartile range [IQR] 0-1) which suggested these patients followed an outpatient pathway and therefore they were not included in the study.

If a patient underwent multiple revascularisation attempts during one inpatient episode, only the first revascularisation procedure during that admission was included. Patient records were excluded if data were missing on key variables (age, gender, comorbidities, smoking status, presenting problem and Fontaine score), if patients were treated as day-cases (no preoperative or postoperative hospital stay) or if their admission-to-intervention interval exceeded 100 days, as this indicated the patient was unfit for surgery on admission. Data from non-arterial centres and hospitals that did not perform

at least one procedure of each type every year of the study period were also excluded from the study.

2.2.2 Patient characteristics

The NVR dataset contained demographic (patient age, gender, comorbidities, smoking status) and clinical information (presenting problem, Fontaine score, date of admission, date and type of procedure, hospital of treatment). Information on comorbidities included the presence of diabetes, chronic lung disease, ischaemic heart disease, chronic heart failure, chronic renal disease, stroke and cancer. Diabetes was included in the model as a distinct comorbidity as there can be different care pathways for these patients. The other comorbidities were grouped into a variable that indicated if patients had none or one comorbidity, two comorbidities, or three or more comorbidities. A variable for centre volume of procedures was defined as the mean number of revascularisation procedures (open and endovascular) per year conducted at each hospital and the hospitals were stratified into 3 categories (high-, medium- and low-volume) so there was approximately an equal number of procedures in each[309] (Table 6). The volume for endovascular procedures at each hospital was estimated using activity recorded in the Hospital Episode Statistics database rather than the NVR due to low case-ascertainment[238].

Table 6 – Description of hospital volumes for open and endovascular procedures undertaken in NHS hospital between 2016 and 2019

Hospital volume	**Open procedures**				**Endovascular procedures**			
	Hospitals	Cases	Annual procedures		Hospitals	Cases	Annual procedures	
			Median	Range			Median	Range
Low	39	1,807	48	3-69	29	1,778	150	66-219
Medium	23	2,102	85	70-123	9	1,780	265	220-319
High	13	2,064	160	124-209	12	1,867	345	320-551

2.2.3 Outcomes

The primary outcome was the proportion of patients who underwent revascularisation within 5-days from admission, the timeframe set by the VSGBI recommendation in 2019. Time to intervention was defined as the number of calendar days from admission to the first revascularisation procedure performed during that admission. The secondary outcome was the waiting time from admission to procedure in days.

2.2.4 Statistical analysis

The study was based on a complete case analysis. Summary statistics were used to describe the demographic and clinical characteristics of patients. Age was categorised into four groups (<60, 60-69, 70-79, ≥80 years). Categorical variables were expressed as frequencies and proportions. The pattern of variation of patient factors across the days of admission was explored by calculating the Mahalanobis distance[310] for each patient and plotting the resulting distribution for each day. The distance is a measure of how different a specific patient is from the "typical" patient in the cohort.

Univariable and multivariable Poisson regression with robust standard errors was used to estimate the crude and adjusted effects of patient and admission characteristics on the primary outcome[311]. Logistic regression was not used, because odds ratios overestimate the risk ratio for common outcomes[311]. The multivariable Poisson model estimated the incidence rate ratios (IRR) of the primary outcome controlling for patient age, gender, presence of diabetes, comorbidity burden, smoking status, Fontaine score, presenting problem, weekday of admission, procedure type, and hospital volume. The statistical significance of interaction terms between day of the week and the variables: Fontaine score and type of procedure was evaluated using the Bayesian information criterion (BIC). The Kruskall-Wallis test was used to examine the association between covariates and the continuous outcome admission-to-intervention time.

Several sensitivity analyses were performed. The first repeated the analysis with a 7-day admission-to-intervention timeframe as the outcome. The second restricted the analysis to high-volume hospitals with more than 80% case ascertainment[238] and 100 or more endovascular procedures per year recorded in the NVR. All statistical tests were two-sided and a P-value of <0.05 was considered statistically significant. All analyses were

performed using STATA 15.1 (StataCorp, College Station, Texas, USA). Results are presented in accordance with the RECORD extension of the strengthening the reporting of observational studies in epidemiology (STROBE) Statement[312].

2.3 Results

A total of 13,149 revascularisation procedures performed during emergency admissions for CLTI between 2016 and 2019 were extracted from the NVR. Of these, day-cases (n=136), cases from non-arterial centres and hospitals with missing years of procedures (n=828), subsequent procedures in the same admission (n=476), cases with missing data (n=301) and with admission-to-intervention time of more than 100 days (n=10) were excluded. This left 11,398 cases for analysis, among whom there were similar proportions of open (n=5,973, 52.4%) and endovascular (n=5,425, 47.6%) procedures. Seventeen per cent of the open surgical procedures had an adjunct endovascular element (n=1,026). The open procedures were performed in 75 NHS Hospitals, while endovascular procedures were recorded in 50 of those; the remaining 25 did not submit data on endovascular procedures to the NVR.

The median age on admission was 72 years (IQR 64-80) and 68.7% (n=7,836) of patients were male (Table 7). Overall, 55.1% of patients had diabetes (n=6,283). Tissue loss was the most common reason for presentation (47.8%, n= 5,451) and 80.0% of the patients (n=9,124) had Fontaine IV on admission. The highest number of admissions occurred on Monday (18.4%, n=2,092) and the lowest on Sunday (5.8%, n=667).

2.3.1 Patient factors associated with delay to revascularisation

The median delay from admission to intervention was 5-days (IQR 2-9), and 88.2% of patients (n=10,055) had their revascularisation within the first two weeks of inpatient stay. However, only 50.6% of the patients with CLTI had revascularisation within 5-days from admission (n=5,771). In the multivariable model, a number of patient characteristics were associated with longer admission to intervention times. These included older age, a higher number of comorbidities other than diabetes (≥3 vs. 0-1), non-smoking status versus current smokers, Fontaine score IV versus III, and tissue loss and uncontrolled infection as presenting problem versus chronic ischaemia (Figure 4).

Table 7 – Characteristics of the 11,398 patients who underwent revascularisation for CLTI between January 2016 and December 2019 in UK NHS hospitals

Patient characteristics	Number of patients (%)	No. of patients (%) having open procedures (n=5,973, 52.4%)	No. of patients (%) having endovascular procedures (n=5,425, 47.6%)
Age (years)			
< 60	1,701 (14.9)	925 (15.5)	776 (14.3)
60-69	3,057 (26.8)	1,741 (29.2)	1,316 (24.2)
70-79	3,753 (32.9)	2,068 (34.6)	1,685 (31.1)
≥ 80	2,887 (25.4)	1,239 (20.7)	1,648 (30.4)
Male gender	7,836 (68.7)	4,190 (70.1)	3,646 (67.2)
Diabetes	6,283 (55.1)	2,717 (45.5)	3,566 (65.7)
Comorbidities			
0-1	8,127 (71.3)	4,353 (72.9)	3,774 (69.6)
2	2,343 (20.6)	1,196 (20.0)	1,147 (21.1)
≥ 3	928 (8.1)	424 (7.1)	504 (9.3)
Smoking status			
Current	3,648 (32.0)	2,424 (40.6)	1,224 (22.6)
Ex	5,842 (51.3)	2,957 (49.5)	2,885 (53.2)
Never	1,908 (16.7)	592 (9.9)	1,316 (24.2)
Fontaine score			
III	2,274 (20.0)	1,507 (25.2)	767 (14.1)
IV	9,124 (80.0)	4,466 (74.8)	4,658 (85.9)
Presenting problem			
Chronic ischaemia	5,188 (45.5)	2,867 (48.0)	2,321 (42.8)
Tissue loss	5,451 (47.8)	2,791 (46.7)	2,660 (49.0)
Uncontrolled infection	759 (6.7)	315 (5.3)	444 (8.2)
Day of admission			
Sunday	667 (5.8)	366 (6.1)	301 (5.5)
Monday	2,092 (18.4)	1,061 (17.8)	1,031 (19.0)
Tuesday	2,067 (18.1)	1,108 (18.5)	959 (17.7)
Wednesday	1,980 (17.4)	1,033 (17.3)	947 (17.5)
Thursday	1,979 (17.4)	1,016 (17.0)	963 (17.7)
Friday	1,894 (16.6)	993 (16.6)	901 (16.6)
Saturday	719 (6.3)	396 (6.6)	323 (6.0)
Hospital volume			
Low	3,585 (31.4)	1,807 (30.2)	1,778 (32.8)
Medium	3,882 (34.1)	2,102 (35.2)	1,780 (32.8)
High	3,931 (34.5)	2,064 (34.6)	1,867 (34.4)

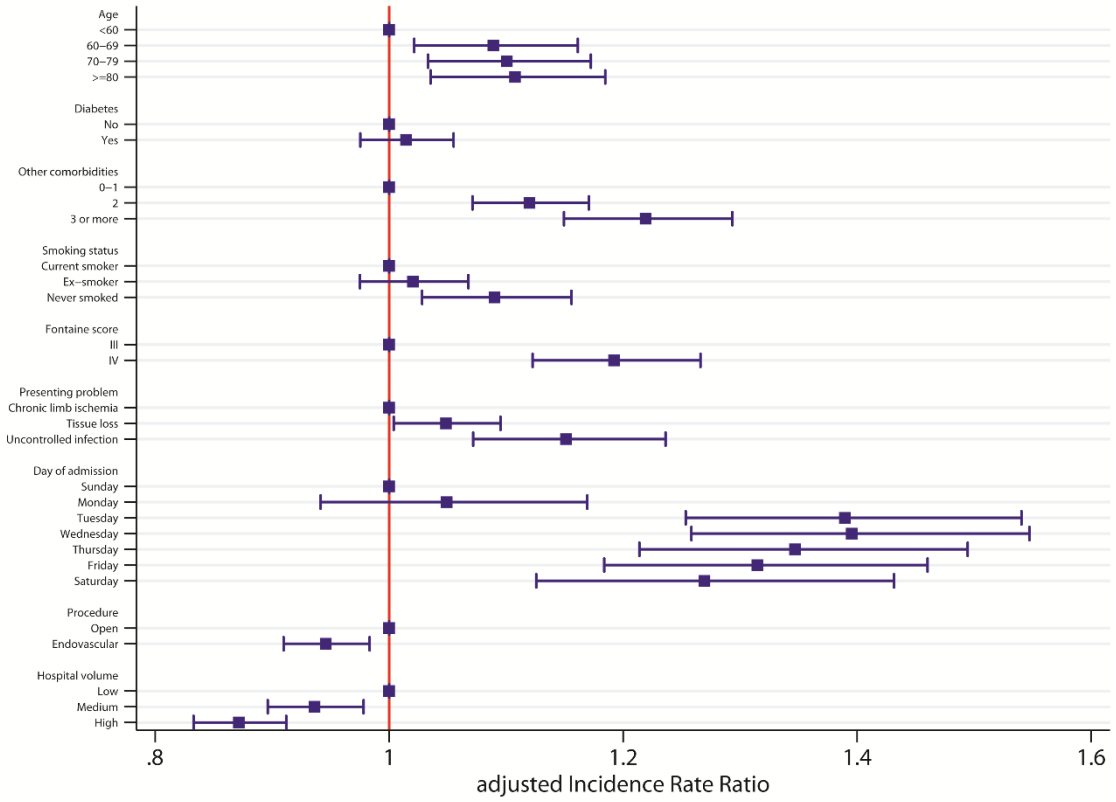

Figure 4 – Adjusted incidence rate ratios of waiting longer than 5 days from admission to revascularisation for various patient and admission factors and 95% confidence intervals

The same factors were significantly associated with delays in revascularisation in the univariable analysis (Table 8). The proportion of patients who had revascularisation within 5-days did not differ significantly by whether or not they had diabetes (p=0.474). The elevated incidence rate ratios for the patient characteristics were reflected in longer waiting times. The median delay from admission to intervention was 5-days (IQR 2-9) for patients with up to 1 comorbidity apart from diabetes, and increased to 6-days for 2 (IQR 3-11) and to 7-days for 3 or more (IQR 3-12) comorbidities (p<0.001). Similarly, it was 5-days (IQR 2-9) for patients less than 70 years old, and 6-days for patients 70 years or older (70-79; IQR 2-9, ≥ 80; IQR 3-10). The median time to revascularisation for patients with Fontaine III was 4-days (IQR 2-7), increasing to 6-days (IQR 3-10) for Fontaine IV (p<0.001). The model was not improved by the addition of interaction terms between day of the week and patient characteristics (Fontaine score, type of procedure).

Table 8 – Factors associated with waiting more than 5 days for revascularisation. Univariable and multivariable incidence rate rations (IRR) were estimated using Poisson regression

Variable	Waiting >5 days	Univariable analysis		Multivariable analysis	
	n (%)	IRR (95% CI)	p-value	aIRR (95% CI)	p-value
Age (years)			**<0.001**		**0.016**
< 60	754 (44.3)	1		1	
60-69	1,501 (49.1)	1.11 (1.04-1.18)		1.09 (1.02-1.16)	
70-79	1,889 (50.3)	1.14 (1.07-1.21)		1.10 (1.03-1.17)	
≥ 80	1,483 (51.4)	1.16 (1.09-1.24)		1.11 (1.04-1.19)	
Gender			0.138		**0.049**
Male	3,832 (48.9)	1		1	
Female	1,795 (50.4)	1.03 (0.99-1.07)		1.04 (1.00-1.08)	
Diabetes	3,169 (50.4)	1.05 (1.01-1.09)	**0.012**	1.01 (0.98-1.06)	0.474
Comorbidities			**<0.001**		**<0.001**
0-1	3,837 (47.2)	1		1	
2	1,248 (53.3)	1.13 (1.08-1.18)		1.12 (1.07-1.17)	
3 or more	542 (58.4)	1.24 (1.17-1.31)		1.22 (1.15-1.29)	
Smoking status			**<0.001**		**0.010**
Current smoker	1,710 (46.9)	1		1	
Ex-smoker	2,899 (49.6)	1.06 (1.01-1.11)		1.02 (0.97-1.07)	
Never smoked	1,018 (53.4)	1.14 (1.08-1.20)		1.09 (1.03-1.16)	
Fontaine score			**<0.001**		**<0.001**
III	935 (41.1)	1		1	
IV	4,692 (51.4)	1.25 (1.19-1.32)		1.19 (1.12-1.27)	
Presenting problem			**<0.001**		**<0.001**
Chronic ischaemia	2,374 (45.8)	1		1	
Tissue loss	2,830 (51.9)	1.13 (1.09-1.18)		1.05 (1.01-1.10)	
Uncontrol. infection	423 (55.7)	1.22 (1.14-1.31)		1.15 (1.07-1.24)	
Day of admission			**<0.001**		**<0.001**
Sunday	256 (38.4)	1		1	
Monday	841 (40.2)	1.05 (0.94-1.17)		1.05 (0.94-1.17)	
Tuesday	1,107 (53.6)	1.40 (1.26-1.55)		1.39 (1.25-1.54)	
Wednesday	1,068 (53.9)	1.41 (1.27-1.56)		1.40 (1.26-1.55)	
Thursday	1,037 (52.4)	1.37 (1.23-1.52)		1.35 (1.21-1.49)	
Friday	964 (50.9)	1.33 (1.19-1.47)		1.31 (1.18-1.46)	
Saturday	354 (49.2)	1.28 (1.14-1.45)		1.27 (1.13-1.43)	
Procedure			0.758		**0.005**
Open	2,957 (49.5)	1		1	
Endovascular	2,670 (49.2)	0.99 (0.96-1.03)		0.95 (0.91-0.98)	
Hospital volume			**<0.001**		**<0.001**
Low	1,910 (53.3)	1		1	
Medium	1,913 (49.3)	0.92 (0.88-0.97)		0.94 (0.90-0.98)	
High	1,804 (45.9)	0.86 (0.82-0.90)		0.87 (0.83-0.91)	

2.3.2 Admission factors associated with delay to revascularisation

The day of admission had a significant impact on the proportion of patients revascularised within 5-days. Approximately 61.6% of patients admitted on Sunday and 59.8% on Monday had a more timely intervention, but for patients admitted later in the week, the proportion dropped to 46.1-50.8%, with the lowest proportion occurring on Wednesday. The pattern of patient characteristics (as summarised by the Mahalanobis distance) across various days of the week did not suggest there was any substantial change in case-mix over the week (Figure 5). Adjusting for patient and admission characteristics, the incidence rate ratio (IRR) of waiting >5 days for revascularisation using Sunday as baseline was highest on Tuesday (IRR=1.39, 95% CI 1.25-1.54) and Wednesday (IRR=1.40, 95% CI 1.26-1.55), but was still higher for Thursday (IRR=1.35, 1.21-1.49), Friday (IRR=1.31, 1.18-1.46) and Saturday (IRR=1.27, 1.13-1.43) (Table 8).

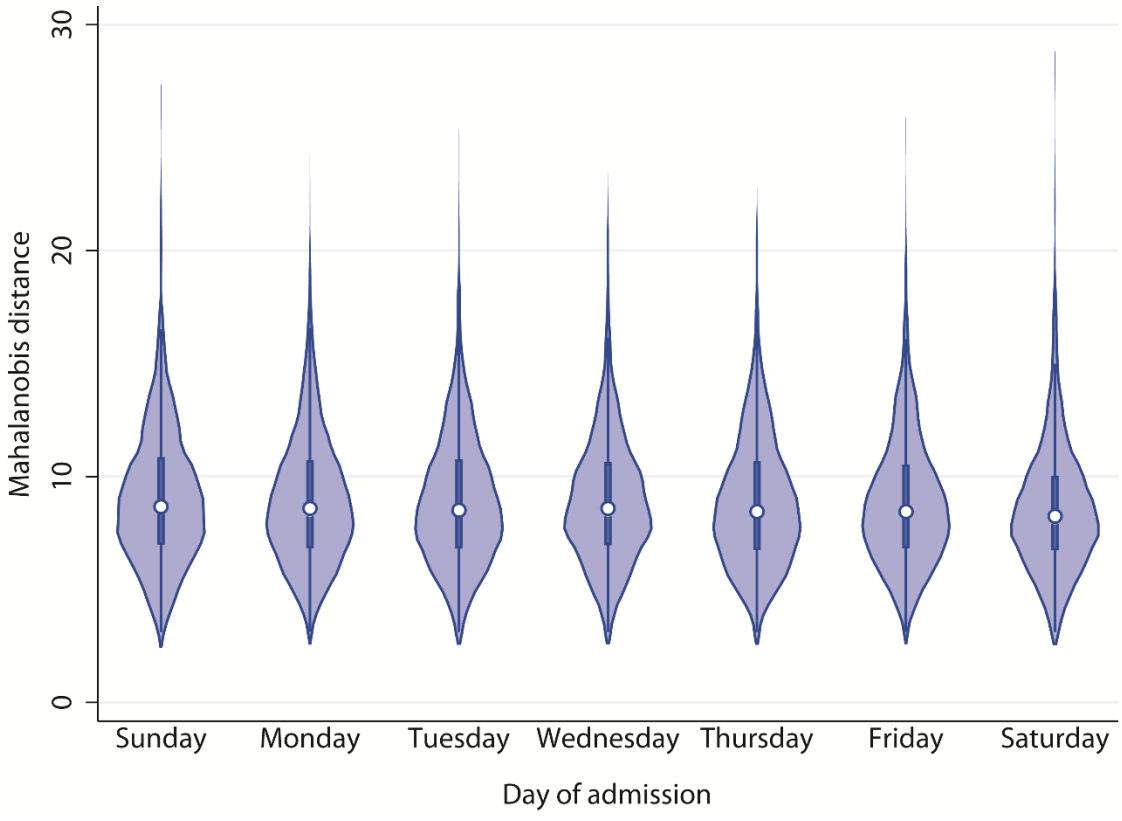

Figure 5 – Distribution of the Mahalanobis distance calculated from the explanatory variables in the Poisson regression model, stratified by day of admission. The figure shows the kernel-density estimate for the distribution together with a standard box plot.

Most patients admitted on Sunday had revascularisation during the same week, while a significant proportion of patients admitted later in the week were treated during the following week (Figure 6). Only 3.1% of procedures (n=358) were performed on the weekend. The cumulative percentage of undergoing revascularisation exhibited a bimodal pattern that indicated the effect of the day of admission was least prominent at 7 and 14 days after admission (Figure 7). Sensitivity analysis using a 7-day admission-to-intervention timeframe revealed that delays were still significantly affected by patient factors, but less so by the day of admission (Table 9).

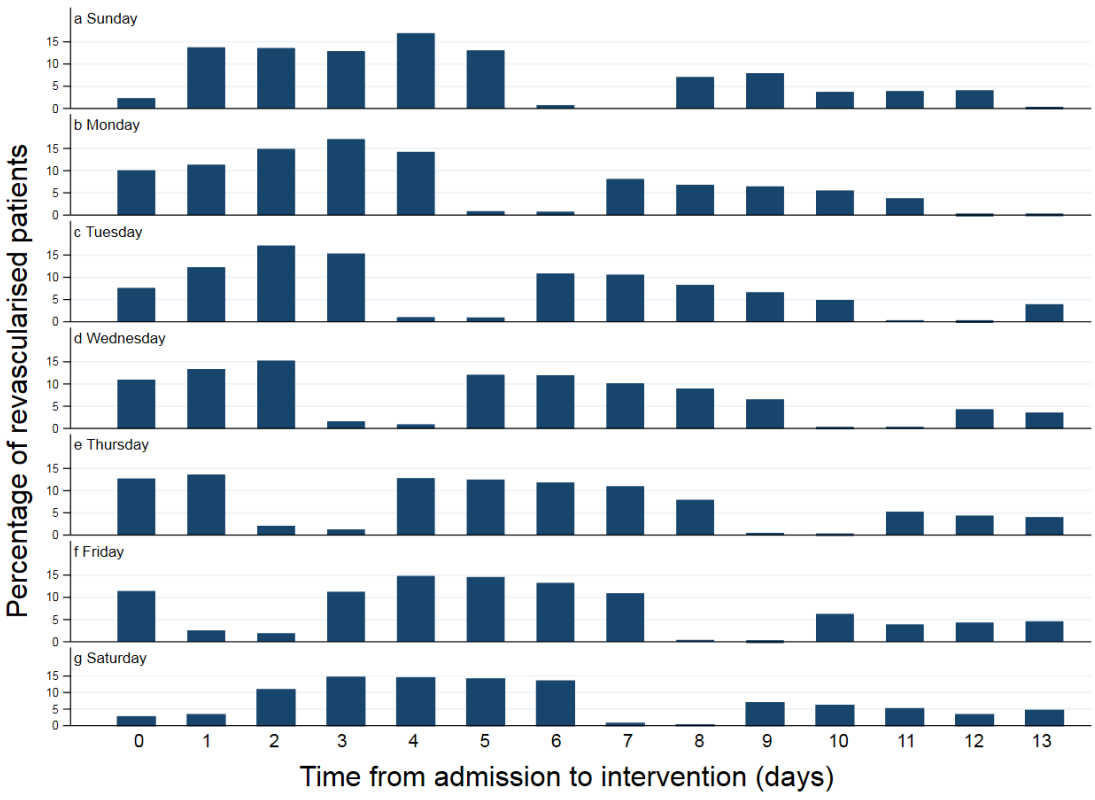

Figure 6 – Percentage of patients undergoing revascularization on specific days of pre-operative inpatient stay, by day of admission (population admitted on each day used as the denominator).

The procedure volume of the hospital where the intervention was performed was also associated with delay to revascularisation, with middle and high-volume hospitals associated with reduced risk of delay compared to low-volume centres (IRR 0.94, 95% CI 0.90-0.98 and IRR 0.87, 95% CI 0.83-0.91, respectively). Median time from admission-to-intervention was 6-days (IQR 3-11) for low-volume and 5-days (IQR 2-8) for high-volume hospitals. There was a slightly reduced risk of delay for patients having endovascular revascularisation procedures (IRR 0.95, 95% CI 0.91-0.98, p=0.005). A sensitivity analysis of 5,559 cases performed in hospitals with more than 80% case ascertainment for endovascular procedures produced similar results (Table 10 and 11).

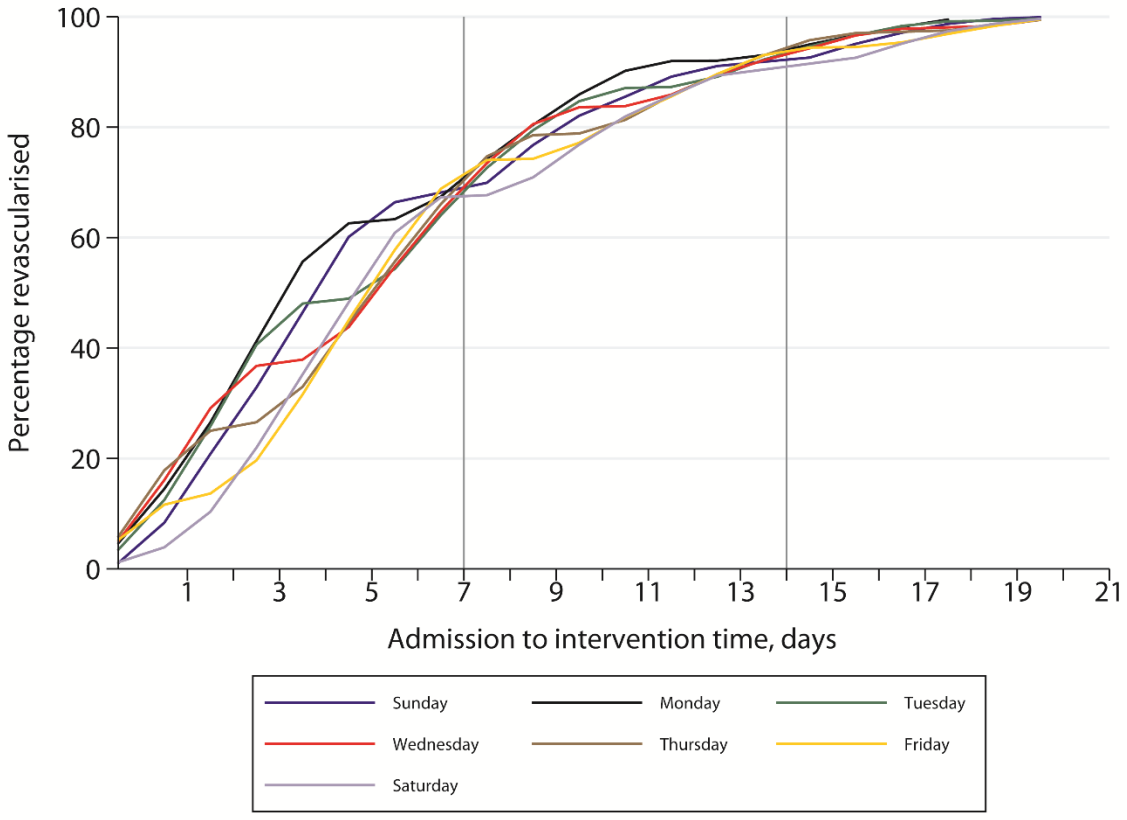

Figure 7 – Cumulative percentage of patients undergoing revascularization as length of pre-operative stay increases, by day of admission, for patients that were revascularised within 21 days.

Table 9 – Sensitivity analysis using 5-day vs. 7-day admission to intervention model. The adjusted incidence rate ratios (IRR), 95% CIs and p-values were estimated using multivariable Poisson regression analysis

	5-days		7-days	
	IRR (95% CI)	**p-value**	**IRR (95% CI)**	**p-value**
Age		**0.016**		0.107
< 60	1		1	
60-69	1.09 (1.02-1.16)		1.09 (1.01-1.19)	
70-79	1.10 (1.03-1.17)		1.06 (0.98-1.16)	
≥ 80	1.11 (1.04-1.19)		1.11 (1.02-1.22)	
Gender		**0.049**		0.126
Male	1		1	
Female	1.04 (0.99-1.08)		1.04 (0.99-1.10)	
Diabetes	1.01 (0.98-1.06)	0.474	1.03 (0.98-1.09)	0.239
Comorbidities		**<0.001**		**<0.001**
0-1	1		1	
2	1.12 (1.07-1.17)		1.20 (1.13-1.28)	
3 or more	1.22 (1.15-1.29)		1.37 (1.26-1.48)	
Smoking status		**0.010**		**0.022**
Current smoker	1		1	
Ex-smoker	1.02 (0.97-1.07)		1.01 (0.95-1.08)	
Never smoked	1.09 (1.03-1.16)		1.11 (1.02-1.20)	
Fontaine score		**<0.001**		**<0.001**
III	1		1	
IV	1.19 (1.12-1.27)		1.33 (1.22-1.45)	
Presenting problem		**<0.001**		**<0.001**
Chronic ischaemia	1		1	
Tissue loss	1.05 (1.01-1.10)		1.08 (1.02-1.15)	
Uncontrol. infection	1.15 (1.07-1.24)		1.29 (1.17-1.42)	
Day of admission		**<0.001**		**<0.001**
Sunday	1		1	
Monday	1.05 (0.94-1.17)		0.86 (0.77-0.97)	
Tuesday	1.39 (1.25-1.54)		0.93 (0.83-1.04)	
Wednesday	1.40 (1.26-1.55)		0.92 (0.82-1.03)	
Thursday	1.35 (1.21-1.49)		0.85 (0.75-0.95)	
Friday	1.31 (1.18-1.46)		0.78 (0.69-0.88)	
Saturday	1.27 (1.13-1.43)		0.97 (0.85-1.11)	
Procedure		**0.005**		0.122
Open	1		1	
Endovascular	0.95 (0.91-0.98)		0.96 (0.91-1.01)	
Hospital Volume		**<0.001**		**<0.001**
Low	1		1	
Medium	0.94 (0.90-0.98)		0.90 (0.85-0.96)	
High	0.87 (0.83-0.91)		0.80 (0.75-0.86)	

Table 10 – Characteristics of patients having endovascular procedures at hospitals with under 80% case ascertainment and 80% or more

Patient characteristics	No. of patients (%) in hospitals with < 80% case ascertainment (n=5,839)	No. of patients (%) in hospitals with ≥ 80% case ascertainment (n=5,559)
Age (years)		
< 60	896 (15.4)	805 (14.5)
60-69	1,636 (28.0)	1,421 (25.6)
70-79	1,945 (33.3)	1,808 (32.5)
≥ 80	1,362 (23.3)	1,525 (27.4)
Male gender	4,057 (69.5)	3,779 (68.0)
Diabetes	3,001 (51.4)	3,282 (59.0)
Comorbidities		
0-1	4,174 (71.5)	3,953 (71.1)
2	1,219 (20.9)	1,124 (20.2)
3 or more	446 (7.6)	482 (8.7)
Smoking status		
Current smoker	2,107 (36.1)	1,541 (27.7)
Ex-smoker	2,968 (50.8)	2,874 (51.7)
Never smoked	764 (13.1)	1,144 (20.6)
Fontaine score		
III	1,243 (21.3)	1,031 (18.5)
IV	4,596 (78.7)	4,528 (81.5)
Presenting problem		
Chronic ischaemia	2,601 (44.5)	2,587 (46.5)
Tissue loss	2,906 (49.8)	2,545 (45.8)
Uncontrolled infection	332 (5.7)	427 (7.7)
Procedure		
Open	4,154 (71.1)	1,819 (32.7)
Endovascular	1,685 (28.9)	3,740 (67.3)
Day of admission		
Sunday	346 (5.9)	321 (5.8)
Monday	1,011 (17.3)	1,081 (19.4)
Tuesday	1,108 (19.0)	959 (17.3)
Wednesday	1,028 (17.6)	952 (17.1)
Thursday	985 (16.9)	994 (17.9)
Friday	981 (16.8)	913 (16.4)
Saturday	380 (6.5)	339 (6.1)
Hospital volume		
Low	2,576 (44.1)	1,009 (18.1)
Medium	1,531 (26.2)	2,351 (42.3)
High	1,732 (29.7)	2,199 (39.6)

Table 11 – Analysis of NHS Hospitals with more than 80% case ascertainment for angioplasty and more than 100 procedures entered annually in the NVR (n= 5,559)

Variable	Waiting >5 days	Univariable analysis		Multivariable analysis	
	n (%)	aIRR (95% CI)	p-value	aIRR (95% CI)	p-value
Age			**0.022**		**0.039**
< 60	350 (43.5)	1		1	
60-69	706 (49.7)	1.14 (1.04-1.26)		1.14 (1.03-1.25)	
70-79	902 (49.9)	1.15 (1.05-1.26)		1.13 (1.03-1.24)	
≥ 80	747 (49.0)	1.13 (1.03-1.24)		1.09 (0.99-1.20)	
Gender			0.768		0.939
Male	1,844 (48.8)	1		1	
Female	861 (48.4)	0.99 (0.94-1.05)		1.00 (0.95-1.06)	
Diabetes	1,651 (50.3)	1.09 (1.03-1.15)	**0.004**	1.03 (0.97-1.09)	0.392
Comorbidities			**<0.001**		**0.002**
0-1	1,867 (47.2)	1		1	
2	571 (50.8)	1.08 (1.01-1.15)		1.07 (0.99-1.14)	
3 or more	267 (55.4)	1.17 (1.08-1.28)		1.16 (1.06-1.26)	
Smoking status			**<0.001**		**0.005**
Current smoker	696 (45.2)	1		1	
Ex-smoker	1,390 (48.4)	1.07 (1.01-1.14)		1.04 (0.97-1.12)	
Never smoked	619 (54.1)	1.20 (1.11-1.29)		1.14 (1.05-1.23)	
Fontaine score			**<0.001**		**0.001**
III	414 (40.2)	1		1	
IV	2,291 (50.6)	1.26 (1.16-1.36)		1.17 (1.07-1.28)	
Presenting problem			**<0.001**		**0.031**
Chronic ischaemia	1,160 (44.8)	1		1	
Tissue loss	1,311 (51.5)	1.15 (1.09-1.22)		1.07 (1.01-1.14)	
Uncontrol. infection	234 (54.8)	1.22 (1.11-1.35)		1.11 (1.01-1.23)	
Day of admission			**<0.001**		**<0.001**
Sunday	127 (39.6)	1		1	
Monday	404 (37.4)	0.94 (0.81-1.10)		0.94 (0.80-1.09)	
Tuesday	508 (53.0)	1.34 (1.15-1.55)		1.31 (1.13-1.51)	
Wednesday	508 (53.4)	1.35 (1.16-1.56)		1.31 (1.13-1.52)	
Thursday	524 (52.7)	1.33 (1.15-1.54)		1.29 (1.11-1.49)	
Friday	463 (50.7)	1.28 (1.10-1.49)		1.24 (1.07-1.44)	
Saturday	171 (50.4)	1.27 (1.07-1.51)		1.24 (1.05-1.47)	
Procedure			0.171		0.086
Open	861 (47.3)	1		1	
Endovascular	1,844 (49.3)	1.04 (0.98-1.10)		0.95 (0.89-1.01)	
Hospital volume			**<0.001**		**<0.001**
Low	579 (57.4)	1		1	
Medium	1,160 (49.3)	0.86 (0.80-0.92)		0.88 (0.82-0.94)	
High	966 (43.9)	0.77 (0.71-0.82)		0.78 (0.73-0.84)	

2.4 Discussion

This study found that only 50.6% of the patients with CLTI admitted to NHS arterial centres as emergencies between 2016 and 2019 underwent revascularisation within 5-days from admission. The comparatively low proportion of patients meeting the target set by the VSGBI is likely to reflect its recent introduction but it also reveals the magnitude of the task ahead.

The timing of revascularisation was associated with a number of patient characteristics, such as age, comorbidity burden, smoking status, Fontaine score and presenting problem. Whether or not a patient had diabetes was not associated with the time to revascularisation but there was a small effect associated with hospital volume, with a slightly higher proportion of patients being treated within 5 days of admission at hospitals with larger volumes. The results suggest that the type of procedure had a small impact on delay. There was also a strong association with the day of admission. The worst performance was observed midweek, with Tuesday and Wednesday being the days of admission with the lowest proportion of patients meeting the 5-day revascularisation target.

The finding that older age and multiple comorbidities were associated with an increased risk of waiting for a procedure longer than 5 days is similar to findings from other studies[313,314]. These delays may be attributed to the fact that comorbid patients require medical stabilisation and cardiorespiratory investigations (electrocardiograms, echocardiograms, pulmonary function tests) after admission to assess fitness for surgery. The waiting times for these tests vary between vascular units and they are often not available out-of-hours, prolonging the delay to the procedure. Clinical input from medical specialties may also be required to optimise these patients, and can further delay treatment.

Patients with more severe disease, indicated by higher Fontaine score and presentation with tissue loss also experienced longer delays to revascularisation. This finding is counterintuitive as these patients are at higher risk of limb loss, but it is possible that such cases have multilevel disease and require more complex decision-making about the

treatment options. The delays for patients presenting with uncontrolled infection may be due to antibiotic courses or other procedures performed to control the source of infection prior to revascularisation.

A slightly higher proportion of patients who had endovascular procedures were treated within the recommended 5-day standard compared to open revascularisation. This may be because endovascular procedures are less invasive than bypass surgery and are usually performed under local anaesthetic, so patients require fewer preoperative investigations. However, the case ascertainment for endovascular procedures in the NVR was substantially lower than for open surgical procedures, and this observation needs to be treated with caution. In the sensitivity analysis of hospitals with high case ascertainment for endovascular procedures, the difference in delays to revascularisation between procedure types became non-significant.

An association between increased hospital volume and better patient outcomes such as mortality and complication rates has been demonstrated in studies of vascular surgery[315–317]. This study also suggests there can be a relationship between delay to intervention and low hospital volume. This finding may reflect that larger vascular units are better able to manage patient flow, but is hard to interpret this result due to a lack of information on other unit-level factors, such as number of surgeons, theatre list availability and population coverage.

The relationship between the day of admission and the time-to-revascularisation is an important observation. There are mixed results about the importance of day of admission from studies exploring its effect on process indicators, such as time to intervention, and on patient outcomes[318,319]. Studies have reported that patients hospitalised on the weekend with stroke[320], acute myocardial infarction[321], upper gastrointestinal bleeding[322], gallstone pancreatitis[323] and spinal metastases[324] wait longer for invasive procedures compared to patients admitted during the week. In the USA, Orandi et al found that patients admitted non-electively with critical and acute limb ischaemia on the weekend had longer wait to revascularisation, lower likelihood of revascularisation, and higher odds of complications and major amputation than weekday admissions[325], but the effect of individual days of the week was not examined.

Variations in performance across the week have been observed in other settings. A study on hip fracture surgery found that patients admitted Thursday to Saturday experience the longest delays[326]. Complex patterns of temporal variation were also demonstrated in a study of acute stroke patients, where process outcomes, such as time to thrombolysis, varied both by admission day and time, indicating that the impact of the timing of admission is more intricate than the weekend effect implies[327].

The NVR dataset does not contain variables that would allow a study to explore the reasons behind the temporal variations in care. While some variation might reflect differences in disease severity[328,329], the distinct pattern of surgery illustrated by Figure 6 suggests that the variation in observed delays is more likely to be the effect of organisational factors, such as the limited availability of hospital resources and other care processes[313], especially during the weekend when there are typically lower staffing levels, reduced availability of diagnostic tests and limited access to operating or interventional theatres. Another reason for the delays could be the prioritisation of patients with other vascular conditions, such as carotid disease and aneurysms, due to incentives created by existing waiting time standards and previous quality improvement initiatives, such as the publication of surgeon-level outcomes for these procedures[330,331].

Nonetheless, while the variation in activity during the week is undesirable, a greater concern is that only 50.6% of the patients with CLTI had revascularisation within 5-days. It is unrealistic to expect all patients to be treated within this timeframe. While rapid revascularisation is important for patients with tissue loss, some individuals benefit from medical optimisation. One approach might be to agree a national standard based on the top performing vascular units as identified in the recent 2020 NVR Annual Report[238]. An alternative could be to revise the recommendation from 5-days to 7-days. However, such a change ideally requires information about how time to revascularisation affects limb salvage.

The adoption of 7-day urgent vascular services, with operating slots on the weekend as a way to expand capacity, has been recommended in the 2018 GIRFT Vascular Surgery report[236]. This model has improved waiting times in orthopaedic surgery[332]. Recent studies demonstrated the safety of aortic and lower limb procedures performed on the

weekend[333–335], even though there is significant heterogeneity of outcomes in the literature[336–338]. There may be lessons to learn from the centralisation of acute stroke services in London, which alleviated the effect of the day and time of admission on brain scanning and thrombolysis[339]. A strong relationship with the Radiology Department has been considered as one of the reasons for the success of this initiative[340] and increased access to imaging resources would also facilitate the quick progress of the CLTI patient through the diagnostic pathway, while redistribution of imaging as well as cardiorespiratory test slots to correlate with the variation in demand may alleviate this disparity in waiting times.

The development of 7-day services would come at significant cost to the NHS[341], which could be partially offset by the reduction in length of stay and complication rates thanks to early revascularisation. Prioritisation of patients with chronic limb-threatening ischaemia and reallocation of existing resources may be more attainable but their effectiveness should be evaluated. The study also suggests that further guidance on the 5-day recommendation and the role of medical optimisation is required. Without this advice, a range of local standards will probably develop.

Strengths and limitations

The main strength of this study is its population-based design and large size, which increases the generalisability of the findings. The detailed clinical information in the Registry also allowed adjustment for relevant confounding factors. To the best of the author's knowledge, this is the first study to report detailed day-to-day variation in time to intervention rather than focus on a weekend effect.

This study has several limitations. First, while the NVR has a high case-ascertainment for lower-limb bypass (90%), it only captures around 40% of all lower limb endovascular procedures[9]. The similarity of the patient characteristics from hospitals with low and high case-ascertainment (Table 10) and the results from the sensitivity analysis (Table 11) suggest that the estimated time to surgery for endovascular procedures are robust and have not unduly biased the estimated level of overall compliance. Similarly, there was no suggestion that data of endovascular procedures were more likely to be submitted on particular days of admission, which could have led to bias in the estimates

for each day of the week. Second, the NVR dataset does not record previous hospital admissions or outpatient reviews. Consequently, although the study was limited to emergency admissions documented as “non-elective” in the NVR system, some of the patients may have followed the outpatient pathway and may have been admitted for an expedited procedure, which would artificially increase the proportion of patients whose intervention was within the 5-day recommendation. Finally, the time of admission was not available. It was therefore not possible to assess the effect of in-hours versus out-of-hours presentation. It is hypothesised that, due to the timeframe for revascularisation being days rather than hours, the time of presentation does not substantially affect the time to intervention.

In conclusion, between 2016 and 2019, only 50.6% of patients admitted as emergencies with CLTI in UK vascular units received revascularisation within 5-days. The time from admission to revascularisation was associated with the day of admission among other factors. The adoption of a 5-day target has provided an explicit standard against which services can benchmark their performance and will hopefully motivate improvement.

Chapter 3. The association of timing of revascularisation with postoperative outcomes of patients with chronic limb-threatening ischaemia

3.1 Introduction

In patients with CLTI, there is a high risk of limb loss if blood flow is not restored promptly via open surgical or endovascular revascularisation. Delays to revascularisation can occur in various stages of the patient pathway from symptom onset to intervention and vary widely across the UK and internationally[236,240]. There is currently no evidence-based optimal timeframe for the revascularisation of patients with CLTI recommended by national[80] or international[3] guidelines.

In the UK, the VSGBI published a PAD Best Practice Framework in 2019, according to which revascularisation should be performed within 5 days from referral for patients admitted to the hospital urgently with severe disease[237]. This recommendation was based on clinical consensus and expert opinions, because there is limited evidence on the relationship between the timing of revascularisation and postoperative outcomes such as limb loss and death, even though the rates of major amputation and death after revascularisation and other factors that affect them have been explored extensively[230,234,342–345].

Shorter time to revascularisation is associated with increased probability of healing for ischaemic diabetic foot ulcers (HR 1.96, 95% CI 1.52-2.52), when the time from presentation to intervention was 8 weeks or less[307]. Additionally, the limb salvage rate was three times higher in patients with CLTI and diabetes, when they were revascularised within 2 weeks of referral (OR 3.1, 95% CI 1.4- 6.9)[308]. It is hypothesised that expedited revascularisation would also decrease the risk of limb loss and death in patients without diabetes. The aim of this study was to evaluate the association of timing of infrainguinal revascularisation with major amputation and mortality rates at 1-year for patients admitted to hospital as emergencies with CLTI.

3.2 Methods

3.2.1 Study cohort

Data were extracted from the Hospital Episode Statistics (HES) Admitted Patient Care (APC) database, the national administrative hospital database which captures information about all NHS hospital admissions in England[346]. The study cohort included all patients with a PAD-related diagnosis (Appendix 1) who underwent infrainguinal lower limb revascularisation procedures during emergency admissions to NHS hospitals in England between 1st January 2017 and 31st December 2019. The first admission of an individual patient with a revascularisation procedure during the study period was considered the index admission and the first revascularisation procedure was defined as the index procedure. Excluded were: patients younger than 50 years of age on the index admission, those that underwent major amputation on the same day as the index revascularisation procedure, patients who had undergone revascularisations or major amputations in the 3 years prior to the index admission, and patients with admission-to-revascularisation time longer than 30 days, as it was assumed that they were unsuitable for intervention in the short-term. Procedures performed in NHS Trusts with fewer than an average of 10 procedures per year and records with missing data on the covariates of interest (procedure date or side, deprivation status) were also excluded and a complete case analysis was performed.

3.2.2 Patient characteristics

Age on the date of the index admission was categorised into four groups (50-59, 60-69, 70-79, ≥ 80 years) for the analysis. Diagnostic information was recorded in HES using the International Classification of Diseases 10th revision (ICD-10)[347]. The presence of diabetes mellitus and PAD were determined by the presence of the relevant ICD-10 codes in any diagnostic field of the index admission and admissions in the 3 years prior to that (Appendix 1). Tissue loss was indicated by ICD-10 diagnosis codes for gangrene, ulcer and osteomyelitis on the index admission (Appendix 1).The patients' frailty status (not frail, mild, moderate, severe frailty) was derived from diagnostic codes of the index admission and admissions in the 3 years prior to that using the Secondary Care Administrative Records Frailty (SCARF) index[348]. As only 1.1% of patients (n=112) were

identified as “not frail”, these were grouped with the patients with mild frailty for the analysis. The burden of comorbidities was calculated using the Royal College of Surgeons Charlson Comorbidity Index (RCS CCI) and was categorised into zero, one, two, and three or more comorbidities[349]. PAD and diabetes mellitus were excluded from the calculation of the RCS CCI, as all patients had a PAD diagnosis, and diabetes was examined as a separate variable. The rest of the comorbidities included in the RCS CCI were identified from ICD-10 diagnostic codes in the index admission and admissions in the preceding 3 years. Socioeconomic status was determined using the Index of Multiple Deprivation (IMD) 2019 allocated to patients’ lower super output area of residence (LSOA) by the Office for National Statistics (ONS), and was divided into quintiles using the IMD rank of each area[350].

Revascularisation procedures were identified using relevant Office of Population Censuses and Surveys (OPCS) Classification of Surgical Operations and Procedures version 4.8 codes searching all procedure fields[351] (Appendix 2). These OPCS codes were used to categorise the index procedure type as endovascular or open (surgical). Hybrid procedures, which had both open and endovascular codes recorded on the index procedure date, were included in the open category. The level of the index infrainguinal revascularisation was defined as femoral, popliteal or crural using OPCS codes (Appendix 2), and reflected the outflow artery of a bypass or the vessel treated with an angioplasty or stent. When multiple arteries were treated during the index procedure, the most distal one was selected as the level of intervention. The side of the index procedure (right, left, bilateral) was also examined.

3.2.3 Outcomes

The primary outcome was mortality at 1-year after the index revascularisation procedure. Secondary outcomes were the 1-year ipsilateral major amputation rate, time to major amputation, and time to death. Mortality data were available from the ONS Death Registry, which records the date of death for all residents in England and Wales[352]. Major amputation was defined as any amputation proximal to the ankle joint and the side of amputation was taken into account, to capture only ipsilateral major amputations. The follow-up period was calculated from the index revascularisation date

to the date of death or the end of follow-up (31 December 2020), whichever happened first. All patients had at least one year of follow-up.

3.2.4 Statistical analysis

Categorical variables of patients' demographic characteristics were summarised as frequencies and proportions, and differences between patient groups were examined using the chi squared test. The median and IQR statistics were used to summarise the distributions of time from admission to revascularisation in days, time from revascularisation to major amputation, and time from revascularisation to death. The difference in medians between groups was examined using quantile regression[353].

The time from admission to revascularisation had a different relationship with 1-year mortality depending on the presence of tissue loss, and therefore separate logistic regression models were fitted for patients who presented with and without tissue loss. In addition to time from admission to revascularisation, the models included: age group, gender, presence of diabetes, comorbidity burden, frailty status, presence of gangrene (tissue loss group only), type of procedure and level of revascularisation. For similar reasons, two separate multinomial logistic regression models were used to evaluate the association between 1-year major amputation and time-to-revascularisation for patients with and without tissue loss. The second outcome in the multinomial model was 1-year mortality, and this enabled the competing risk of death to be incorporated. The models contained the previous explanatory variables plus social deprivation. Interaction terms between variables for which relationships were likely based on clinical reasoning were evaluated for statistical significance using the Bayesian information criterion. The Kaplan–Meier estimator was used to investigate the timing of occurrence of major amputation and death in the year after revascularisation.

A sensitivity analysis was also performed including only patients that had revascularisation procedures during admissions to hospital from 1 January 2017 to 31 December 2018, so that the 1-year follow-up period was complete before January 2020, after which mortality may have been higher due to the coronavirus-19 (COVID-19) pandemic. All statistical tests were two-sided and p-values less than 0.05 were considered statistically significant. All analyses were performed in STATA 17.0

(StataCorp, College Station, TX, USA). The study was conducted and reported according to the RECORD extension of the STROBE statement for observational studies[312].

3.3 Results

HES records were available for 13,497 patients who underwent infrainguinal lower limb revascularisation procedures for PAD during emergency admissions between 1st January 2017 and 31st December 2019. Excluded were 422 patients younger than 50 years of age, 1,597 patients who had a revascularisation or major amputation 3 years prior to the study period, 55 with major amputation on the same day as the index revascularisation, 244 patients with admission-to-index revascularisation time longer than 30 days, 381 in low-volume trusts, and 615 patients with missing information on the variables included in the analysis. After the exclusion criteria were applied, 10,183 patients were included in the analysis (Figure 8).

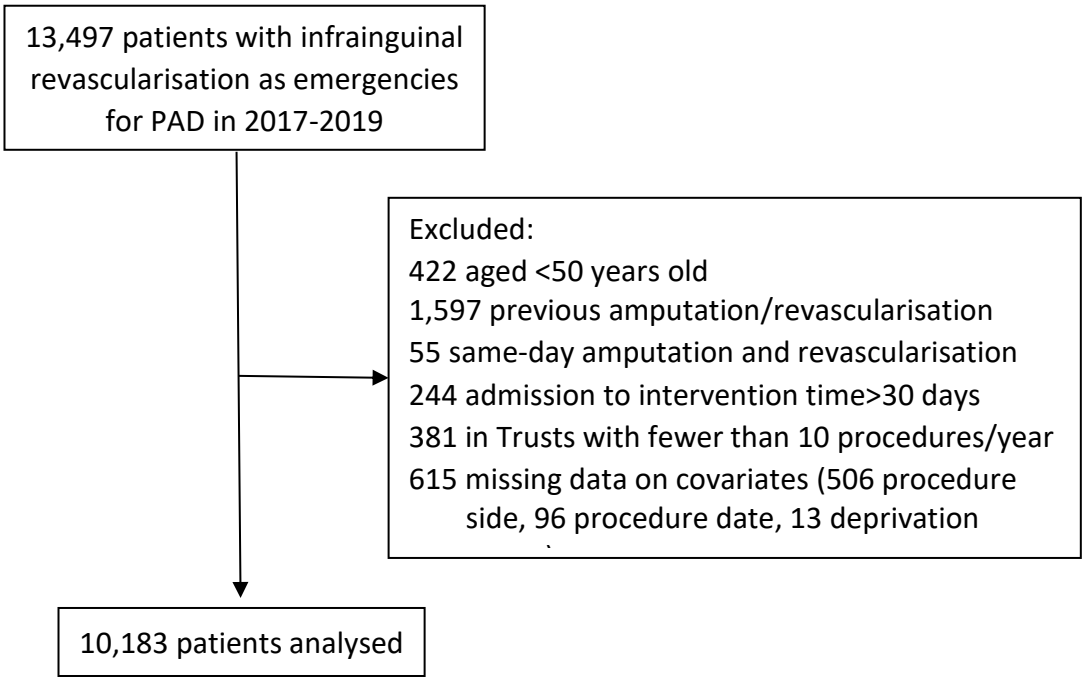

Figure 8 – Flow chart of study population

3.3.1 Baseline demographics

Men comprised 67.1% (n=6,831) of the study population and median age was 75 years (IQR 66-82). More than half of the patients had diabetes mellitus (n=5,863, 57.6%) and 73.2% (n=7,458) had tissue loss. Of the patients with tissue loss, 30.3% (n=2,259) had diagnostic codes for ulcer only, 26.5% (n=1,980) for gangrene only and 42.2% (n=3,145) for both, with a further 1.0% (n=74) having osteomyelitis. Two thirds of patients were severely frail based on the SCARF index (65.8%,n=6,696). There were more endovascular procedures compared to open (68.2%, n=6,946 vs 31.8%, n=3,237). The most common site of intervention was the femoral arteries (48.6%, n=4,944), followed by the crural arteries (29.2%, n=2,975) (Table 12).

Overall, 54.5% of patients (n=5,546) were revascularised within 5 days, and the median admission-to-revascularisation time was 5 days (IQR 2-9). There was a greater proportion of younger patients, those without a diagnosis of diabetes or other comorbidities, less frail and less deprived patients among those who had their procedure within five days compared to those waiting longer than 5 days (Table 12). Patients with tissue loss waited longer for revascularisation (median 6 days, IQR 3-10) compared to patients without tissue loss (median 2 days, IQR 1-5) (Figure 9). Seven percent of patients without tissue loss (n-=190) and 22.2% with tissue loss (n=1,657) waited longer than 10 days for a revascularisation procedure. A greater proportion of procedures performed within 5 days from admission were open revascularisations (36.4% vs 26.3%) and fewer involved crural arteries (26.7% vs 32.2%) compared to those performed after 5 days (Table 12).

Table 12 – Baseline patient characteristics presented as frequencies (%), divided into groups according to time from admission to revascularisation. P-values are derived using the chi squared test for the difference between the two groups.

		Time to revascularisation		
	Total (n=10,183)	**<=5 days (n=5,546)**	**>5 days (n=4,637)**	**p-value**
Age group				
50-59	1,207 (11.9)	741 (13.4)	466 (10.0)	<0.001
60-69	2,241 (22.0)	1,239 (22.3)	1,002 (21.6)	
70-79	3,218 (31.6)	1,717 (31.0)	1,501 (32.4)	
≥80	3,517 (34.5)	1,849 (33.3)	1,668 (36.0)	
Gender				0.282
Male	6,831 (67.1)	3,695 (66.6)	3,136 (67.6)	
Female	3,352 (32.9)	1,851 (33.4)	1,501 (32.4)	
Diabetes mellitus	5,863 (57.6)	2,875 (51.8)	2,988 (64.4)	<0.001
RCS Charlson Comorbidity Index				<0.001
0	2,858 (28.1)	1,753 (31.6)	1,105 (23.8)	
1	2,775 (27.2)	1,592 (28.7)	1,183 (25.5)	
2	2,042 (20.1)	1,059 (19.1)	983 (21.2)	
3 or more	2,508 (24.6)	1,142 (20.6)	1,366 (29.5)	
Scarf frailty index				<0.001
Mild frailty	888 (8.7)	649 (11.7)	239 (5.2)	
Moderate frailty	2,599 (25.5)	1,651 (29.8)	948 (20.4)	
Severe frailty	6,696 (65.8)	3,246 (58.5)	3,450 (74.4)	
Deprivation				<0.001
Q1 (least deprived)	1,522 (14.9)	852 (15.4)	670 (14.4)	
Q2	1,790 (17.6)	996 (18.0)	794 (17.1)	
Q3	2,032 (20.0)	1,167 (21.0)	865 (18.7)	
Q4	2,227 (21.9)	1,187 (21.4)	1,040 (22.4)	
Q5 (most deprived)	2,612 (25.6)	1,344 (24.2)	1,268 (27.4)	
Tissue loss	7,458 (73.2)	3,464 (62.5)	3,994 (86.1)	<0.001
Gangrene	5,125 (50.3)	2,378 (42.9)	2,747 (59.2)	<0.001
Procedure type				<0.001
Endovascular	6,946 (68.2)	3,527 (63.6)	3,419 (73.7)	
Open	3,237 (31.8)	2,019 (36.4)	1,218 (26.3)	
Level of intervention				<0.001
Femoral	4,944 (48.6)	2,803 (50.5)	2,141 (46.2)	
Popliteal	2,264 (22.2)	1,263 (22.8)	1,001 (21.6)	
Crural	2,975 (29.2)	1,480 (26.7)	1,495 (32.2)	

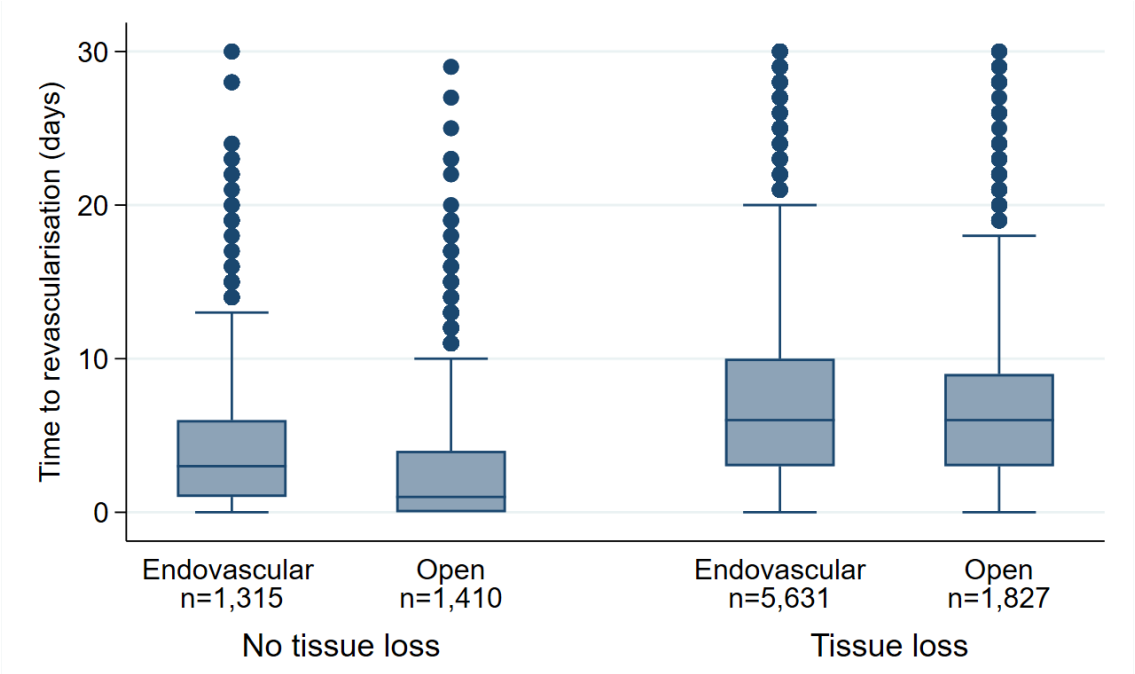

Figure 9 – Boxplots illustrating the association between time-to-revascularisation in days and presence of tissue loss by procedure type

3.3.2 Delay and mortality risk

Overall 1-year mortality after lower limb revascularisation was 27.3% (n=2,776). The unadjusted mortality was 30.0% (95% CI 28.9-31.0%) in patients with tissue loss and 19.9% (95% CI 18.4-21.4%) in patients without. The relationship between time-to-revascularisation and mortality in patients with and without tissue loss is depicted in Figure 10. In patients without tissue loss, 1-year mortality was not associated with the timing of intervention (aOR 1.00, 95% CI 0.98-1.03, p=0.706), after adjustment for age, gender, diabetes, comorbidity burden, frailty, procedure type and level of intervention. However, in patients with tissue loss, for every one-day increase in time-to-revascularisation, the odds of 1-year mortality increased by 3% (aOR 1.03, 95% CI 1.02 to 1.04, p<0.001), after adjustment for the previous patient factors and the presence of gangrene (Table 13).

Gangrene was an independent risk factor for 1-year mortality (aOR 1.37, 95% CI 1.22-1.54) compared to other forms of tissue loss. Other factors significantly associated with 1-year mortality were older age, higher number of comorbidities, severe frailty, and

more proximal interventions, irrespective of tissue loss status (Table 13, Figure 11). There was no evidence of an association between mortality and gender, presence of diabetes or deprivation in either group.

The population attributable risk suggests that if everyone with tissue loss had a delay of no more than 5 days from admission to revascularisation, the mortality rate after one year would be 27.7% (95% CI 26.5-28.8%), which is 2.3% lower (95% CI 1.63-2.95%) than the current mortality rate of 30.0% (95% CI 29.0-30.9%), based on the current distribution of delays. No change in mortality would be expected in patients without tissue loss, if the time to revascularisation was 5 days or less for all patients.

Table 13 – Adjusted odds ratio and 95% Confidence intervals for 1-year mortality in patients with and without tissue loss

	No tissue loss	**Tissue loss**
Time-to-revascularisation	1.00 (0.98-1.03)	1.03 (1.02-1.04)
Age group		
50-59	0.43 (0.28-0.66)	0.52 (0.42-0.65)
60-69	0.58 (0.43-0.78)	0.70 (0.59-0.82)
70-79	1	1
≥80	1.69 (1.34-2.13)	2.10 (1.85-2.38)
Female gender	0.97 (0.79-1.19)	1.04 (0.93-1.17)
Diabetes mellitus	1.03 (0.83-1.28)	1.05 (0.93-1.18)
Severe frailty	1.80 (1.40-2.31)	1.42 (1.21-1.67)
Gangrene	-	1.37 (1.22-1.54)
RCS Charlson Comorbidity index		
0	1	1
1	1.57 (1.16-2.12)	1.41 (1.18-1.67)
2	2.09 (1.49-2.91)	1.99 (1.66-2.39)
3 or more	2.96 (2.10-4.17)	3.19 (2.67-3.81)
Procedure type		
Endovascular	1	1
Open	1.17 (0.95-1.44)	0.86 (0.75-0.98)
Level of intervention		
Femoral	1	1
Popliteal	0.75 (0.58-0.96)	0.86 (0.75-1.00)
Crural	0.72 (0.55-0.95)	0.78 (0.69-0.88)

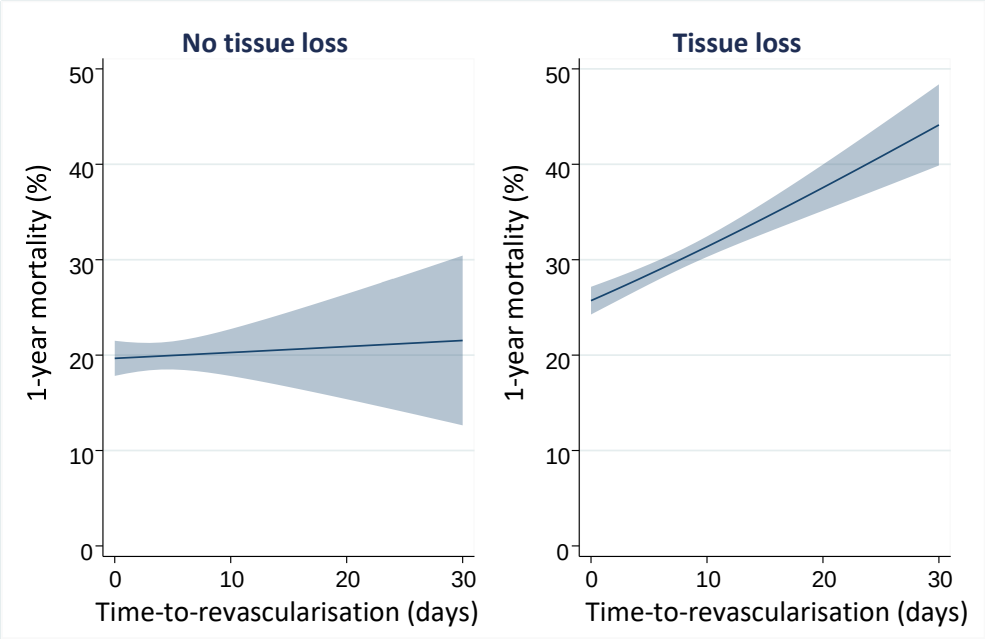

Figure 10 – Estimated 1-year mortality by time to revascularisation and presence of tissue loss

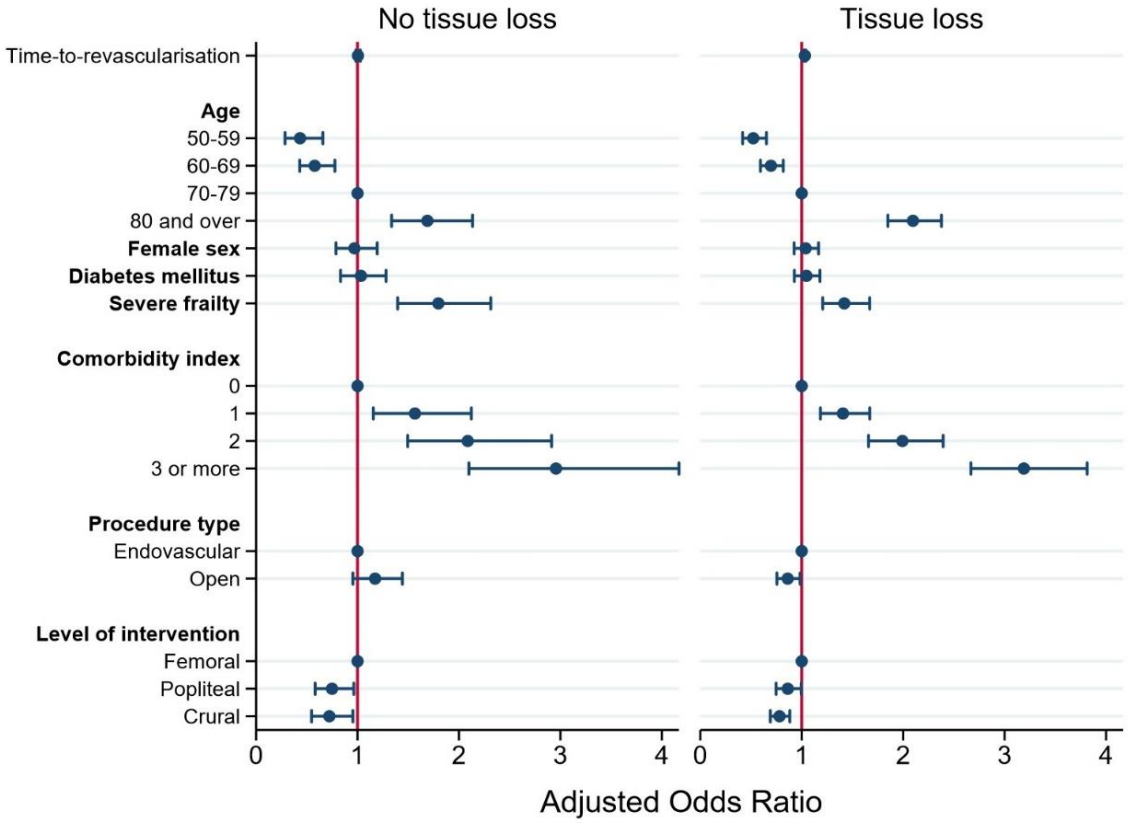

Figure 11 – Coefficients plot indicating the adjusted odds ratio and 95% Confidence Intervals for mortality at 1-year from separate multivariable logistic regression models in patients with and without tissue loss

3.3.3 Delay and risk of amputation

At 1-year after revascularisation, 6,215 patients (61.0%) were alive and amputation-free, 1,599 (15.7%) had undergone an ipsilateral major amputation and 2,369 (23.3%) had died without an amputation. The median time-to-revascularisation was 4 days (IQR 2-8) for those who were alive and amputation-free at 1-year, 5 days (IQR 2-8) for patients with a major amputation and 6 days (3-11) for those who died ($p<0.001$).

There was no significant association between the time from admission to revascularisation in days and the risk of ipsilateral major amputation at 1-year, after controlling for patient and admission factors and taking into account the competing risk of death (Table 14, Figure 12). Estimated 1-year amputation rate was 16.4% for patients with tissue loss (95% CI 15.5-17.2%) and 13.9% (95% CI 12.6-15.1%) for patients without tissue loss. The relationship between time-to-revascularisation and estimated 1-year major amputation rate is shown in Figure 12. There was a trend towards an increase in the risk major amputation as the time to revascularisation increased in patients without tissue loss, that did not reach significance (adjusted Relative Risk Ratio [aRRR] 1.02, 95% CI 0.99-1.05). Conversely, the adjusted relative risk of 1-year major amputation for every one-day increase in time-to-revascularisation for patients with tissue loss was 0.999 (95% CI 0.99-1.01), which was also not statistically significant.

Different factors were associated with increased risk of 1-year major amputation depending on whether the patient had tissue loss or not, apart from severe deprivation, which was a significant factor in both groups (aRRR 1.36, 95% CI 1.06-1.75 in no tissue loss group; 1.22, 95% CI 1.06-1.41 in tissue loss group) (Table 14). In patients without tissue loss, intervention on the crural vessels was also independently associated with increased risk of 1-year major amputation (aRRR 2.74, 95% CI 2.09-3.59 vs. femoral). In patients with tissue loss, significant factors included multiple comorbidities (aRRR 1.42, 95% CI 1.15-1.75 for 3 or more comorbidities vs none), severe frailty (aRRR 1.25, 95% CI 1.05-1.49 vs mild frailty), and presence of gangrene (aRRR 2.02, 95% CI 1.73-2.35). On the other hand, women and people over 80 years old were significantly less likely to have a major amputation at 1-year in the tissue loss group (aRRR 0.83, 95% CI 0.72-0.96 for women vs men; aRRR 0.75, 95% CI 0.63-0.89 for ≥80 vs. 70-79 age group) (Figure 13).

Table 14 – Adjusted relative risk ratio and 95% Confidence intervals for 1-year ipsilateral major amputation, taking into account the competing risk of death in patients with and without tissue loss

	No tissue loss	Tissue loss
Time-to-revascularisation	1.02 (0.99-1.05)	1.00 (0.99-1.01)
Age group		
50-59	1.08 (0.77-1.51)	1.08 (0.88-1.32)
60-69	0.92 (0.69-1.24)	1.08 (0.91-1.28)
70-79	1	1
≥80	0.74 (0.54-1.01)	0.75 (0.63-0.89)
Female gender	0.95 (0.75-1.22)	0.83 (0.72-0.96)
Diabetes mellitus	1.11 (0.86-1.42)	1.14 (0.98-1.32)
Severe frailty	1.14 (0.86-1.52)	1.25 (1.05-1.49)
Most deprived	1.36 (1.06-1.75)	1.22 (1.06-1.41)
Gangrene	-	2.02 (1.73-2.35)
RCS Charlson Comorbidity index		
0	1	1
1	1.19 (0.89-1.58)	1.09 (0.90-1.31)
2	1.10 (0.76-1.58)	1.09 (0.88-1.35)
3 or more	1.20 (0.81-1.80)	1.42 (1.15-1.75)
Procedure type		
Endovascular	1	1
Open	1.09 (0.86-1.38)	1.13 (0.96-1.32)
Level of intervention		
Femoral	1	1
Popliteal	1.28 (0.96-1.70)	1.03 (0.86-1.22)
Crural	2.74 (2.09-3.59)	1.04 (0.89-1.20)

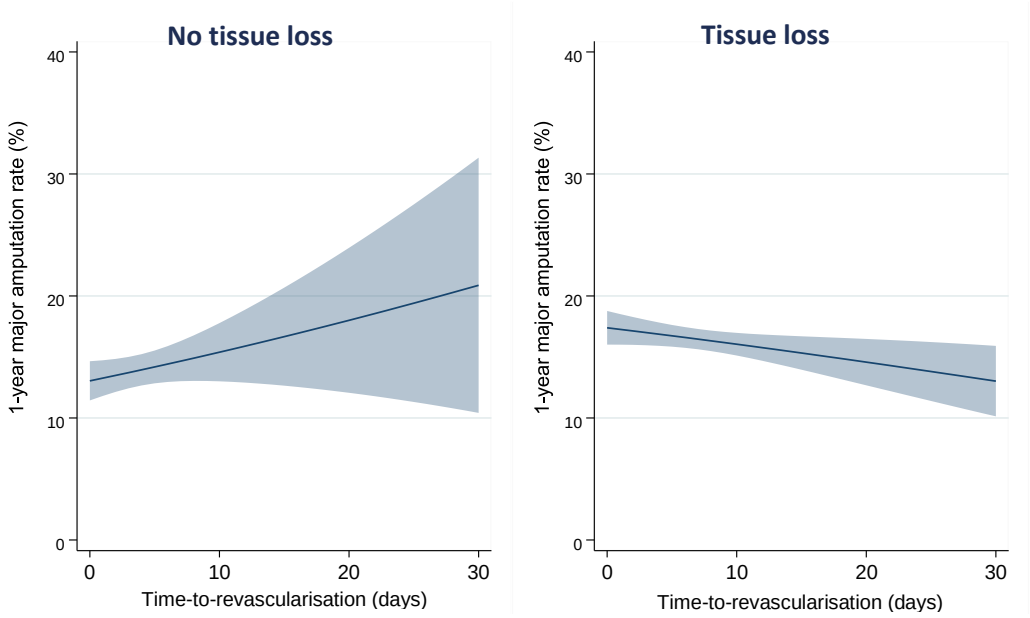

Figure 12 – Estimated probability of 1-year ipsilateral major amputation by admission-to-revascularisation time in days in patients with and without tissue loss

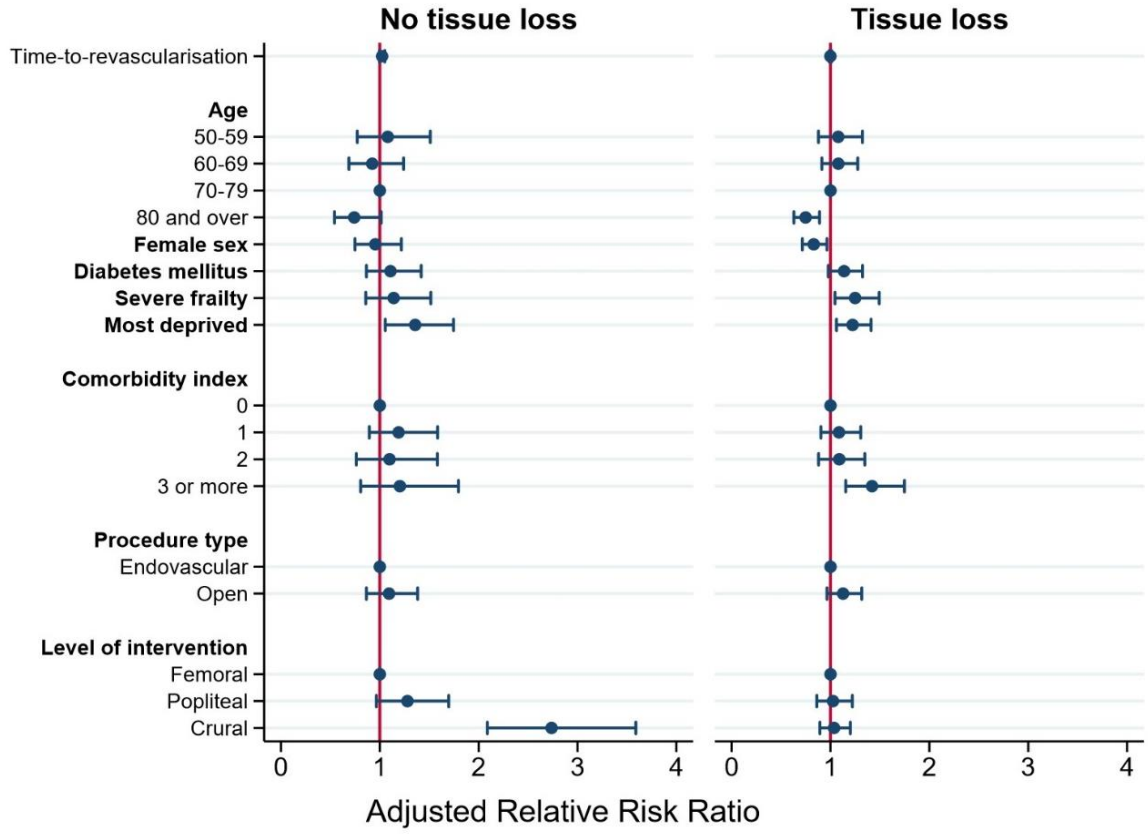

Figure 13 – Adjusted relative risk ratio and 95% CI for ipsilateral major amputation at 1-year for various patient and admission factors by presence of tissue loss

3.3.4 Delay and time to first event (major amputation or death)

Kaplan-Meier curves were drawn to examine the impact of revascularisation delays on survival during the 12 months of follow-up. Longer time from admission to revascularisation was associated with higher mortality, with the difference becoming more prominent over time, especially in the tissue loss group (Figure 14).

Regarding the occurrence of the amputation and death throughout the 1st year after revascularisation, the incidence of major amputations increased sharply in the first 2 months and continued to increase at a lower rate from 6 months onwards, whereas mortality increased at a steady rate over time (Figure 14). For those patients who had an amputation in the first year after revascularisation, median time to major amputation was 35 days (IQR 10-98), with the 30-day major amputation rate being 7.4% (n=752).

A sensitivity analysis that included only 6,843 patients treated in 2017 and 2018, whose follow-up period did not include 2020, had similar results. One-year overall mortality was 27.9% (n=1,910), only slightly higher compared to the whole cohort which was 27.3%. Additionally, the 1-year ipsilateral major amputation was the same (15.7%) and 1-year amputation-free survival very similar in both analyses (60.5% in sensitivity vs 61.0% in full cohort). The association of delay to revascularisation with outcomes was also the same. This indicated that the overall mortality was unlikely to have been influenced by the COVID-19 pandemic.

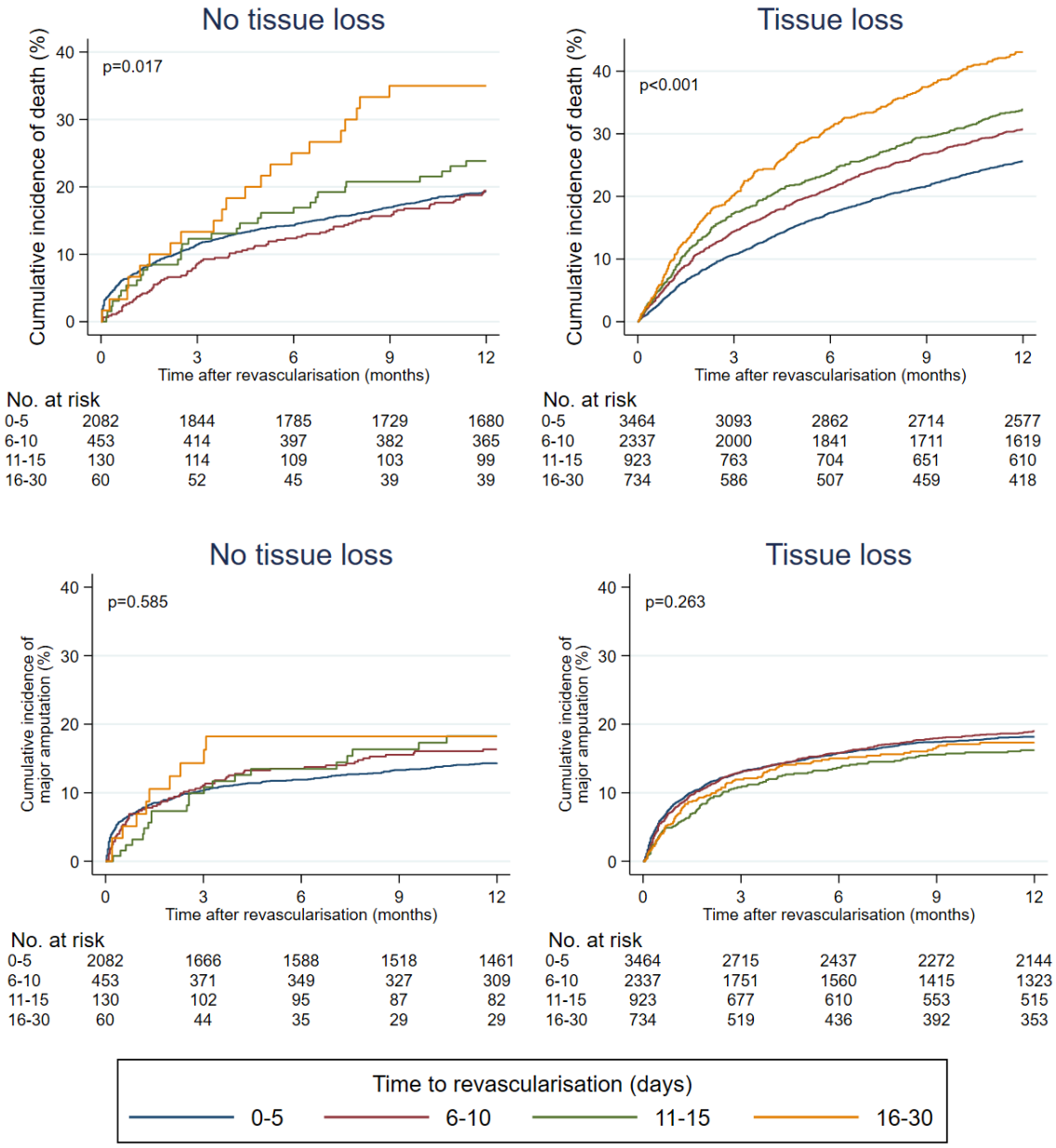

Figure 14 – Kaplan–Meier estimates of incidence of death (top row) and ipsilateral major amputation (bottom row) for different delays to intervention in days in patients with and without tissue loss

3.4 Discussion

In this study of 10,183 patients with CLTI undergoing infrainguinal revascularisation during emergency admissions in England between 2017 and 2019, overall 1-year mortality rate was 27.3% and 1-year ipsilateral major amputation rate was 15.7%, with most amputations occurring in the first few months after revascularisation. The mortality rate was similar to the reported 28% in a German cohort study of 199,953 patients hospitalised with CLTI, 63% of which underwent revascularisation in the index admission[62]. However, it was higher than previously reported rates of 12-24% in two meta-analyses of patients undergoing revascularisation for CLTI[227,342] and rates of 11-13% in English cohort studies using the same dataset[194,228]. The difference in mortality between these studies and our findings may be due to the fact that we limited our cohort to emergency admissions, with high proportion of tissue loss and a third of the patients being 80 years or older, all of which are associated with higher mortality. In the study by Gray et al, only 24% of patients were admitted as emergencies to hospital and other studies also included non-emergency patients without specifying their proprotion[194]. Additionally, 73% of patients in our study had tissue loss, which is much higher than the study by Heikkila with 21%[228]. The RCTs reported in the meta-analyses often excluded high risk and very elderly patients which are included in real-world studies such as ours and have higher mortality risk. One-year major amputation rate after revascularisation in patients with CLTI ranges from 8% to 24%, and our reported rate of 15.7% falls within this range[44,233,342]. It was not possible to compare our outcome rates with large RCTs such as the BEST CLI or BASIL, as they reported outcomes over the follow-up period and not specifically at 1-year[185,189].

The median admission-to-revascularisation time was 5 days (IQR 2-8), therefore only half of the patients achieved the recommended timeframe to revascularisation according to the VSGBI Best Practice guidance[237]. However this is not surprising, as the guidance was published in April 2019 and most of the revascularisation procedures in this study were performed prior to that date. Time to revascularisation was longer for patients with tissue loss compared to those without, indicating that patients with more severe presentation waited longer for revascularisation. This finding is congruent with other studies that have identified the increased severity of PAD at presentation as a

factor associated with delays to revascularisation in this patient cohort[241,354]. Reasons for delays in the presence of tissue loss may include the need for pharmacological treatment such as antibiotics or other procedures such as debridement to control foot sepsis. It is also possible that these patients have more complex disease and require additional imaging and cardiovascular investigations or medical optimisation prior to the revascularisation procedure. Other factors contributing to delays include older age, greater burden of comorbidities, the procedure volume of the hospital, the type of revascularisation procedure, presentation in a hub or spoke hospital and the weekday of admission[241,354]. In our study, the delays were similar for endovascular and open procedures in the tissue loss group, but longer for endovascular procedures when revascularisation was performed for indications other than tissue loss. This is in contrast to the BEST-CLI trial, which reported a shorter median time to index procedure for endovascular interventions compared to surgical procedures (1 day, IQR 0-7; vs. 4 days, IQR 1-11)[189]. This difference may be attributed to the health system disparities and vascular service configuration in England and the United States.

The association between mortality and delay to operative management has been demonstrated in patients with hip fractures[355] and those undergoing major amputation[356] but to our knowledge it has not been explored in patients undergoing revascularisation for CLTI[240]. We found that longer time from emergency admission to revascularisation in patients with tissue loss was independently and significantly associated with increased 1-year mortality, while there was no evidence of such a relationship in the absence of tissue loss. We determined that if all patients with tissue loss were revascularised within 5 days, the 1-year mortality rate would be reduced by 2.3%. The more prominent negative association of delays in patients with tissue loss may have been related to their physiological state, which was likely worse compared to patients with less severe presentations, so they may have decompensated while waiting for a procedure in the hospital. Even though the results were adjusted for the patients' comorbidities and frailty, physiological measurements such as blood pressure and heart rate or biochemical markers that have influenced these outcomes in other studies were not available[235].

Patients with tissue loss had higher mortality in our study compared to patients revascularised in the absence of tissue loss. These findings are supported by a large cohort study of 38,470 from the US Vascular Quality initiative, which reported 50% higher 2-year mortality in the tissue loss group (HR 1.5, 95% CI 1.2-1.9)[230]. Similarly, Vierthaler et al. found that patients with rest pain had 13% mortality at 1-year, compared to 20% in patients with tissue loss[232].

It was hypothesised that longer time from admission to revascularisation would be associated with higher risk of major amputation. A delay of more than 2 weeks from referral to revascularisation has been associated with 3-fold increased risk of major amputation in patients with diabetes and CLTI, but not in patients without diabetes[308]. A further study of 478 patients with ischaemic diabetic foot ulcers demonstrated that shorter time from presentation to revascularisation (≤8 weeks) was associated with increased probability of healing (HR 1.96, 95% CI 1.52-2.52)[307]. There was, however, no association between time to revascularisation and 1-year ipsilateral major amputation in our current study. This may be due to the fact that delays were measured from the day of admission rather than the onset of symptoms, therefore the time prior to presentation was not taken into account and may have varied considerably[240]. However, it was considered that patients with disease so severe that required immediate intervention as inpatients would seek healthcare advice relatively quickly after symptom onset.

Even though longer time from admission to revascularisation was not significantly associated with higher risk of 1-year major amputation, we identified several factors that were. Such factors in patients with tissue loss included male gender, high comorbidity burden, severe frailty and living in a high deprivation area, as well as presence of gangrene. The association of male gender with increased risk of major amputation has been previously reported, but is yet unexplained[44,232,357]. Additionally, the presence of tissue loss is a well-documented risk factor for major amputation, as these patients tend to have more advanced disease compared to patients with rest pain or claudication[228,232,233]. On the other hand, octogenarians with tissue loss had lower risk of major amputation in our study compared to younger patients, after adjustment for comorbidities, frailty, and other patient factors. This finding was also demonstrated in

four studies summarised in a meta-analysis, with pooled OR of 0.61 (95% CI 0.39-0.96) for patients 80 years and over compared to <80 years, but the quality of evidence was deemed very low, and in other studies such a trend was observed but did not reach significance[358]. It is worth highlighting that the reported lower risk of major amputation refers to patients who have undergone a revascularisation attempt rather than primary amputation, and therefore it may indicate a better functional status or a reluctance of clinicians to offer or of patients to undergo further procedures. In agreement with a larger meta-analysis and the BEST-CLI trial, we did not find a significant difference in this outcome between open and endovascular procedures[189,193]. These factors are not modifiable, therefore further research is required to identify modifiable factors associated with major amputation following revascularisation and potential effective interventions.

Our study has several strengths. It included a large population cohort extracted from the HES administrative database covering all admissions in NHS hospitals in England, and follow-up information was available for all patients for at least a year after the index procedure. Therefore, there is low risk of selection bias or loss to follow-up. Additionally, we only included major amputations performed on the same side as the revascularisation procedure. Therefore our findings are more likely to be associated with the condition for which the revascularisation procedure was performed compared to studies that do not limit the reporting of outcomes on ipsilateral-only amputations. Moreover, we reported on the risk of amputation separately from the risk of death, instead of the composite outcome amputation-free survival, and the competing risk of death was taken into account when reporting the estimated risk of ipsilateral major amputation. Finally, the results are unlikely to have been influenced by the COVID-19 pandemic, as a sensitivity analysis excluding that time-period had similar results.

This study also has various limitations. Firstly, the data source was an administrative database that does not optimally collect the severity of PAD. Our previous study demonstrated that combining the ICD-10 diagnostic codes for PAD with the mode of emergency admission was highly specific (91.7%) for CLTI but not sensitive (67.1%)[229]. Therefore, some patients with emergency CLTI admission may have been excluded from the study. The HES database is also prone to errors, such as omission of clinical

information or inaccurate coding, but overall the discharge coding has been deemed sufficiently robust for use in research[359,360]. Secondly, the results were adjusted for many patient and admission characteristics that have been associated with mortality or major amputation in previous studies, but there may have been residual confounding factors that were unaccounted for and may have influenced the outcome, such as smoking, atherosclerotic burden, operative technique (vein vs prosthetic bypass graft, plain balloon angioplasty vs stenting)[342], and biochemical markers[235]. Thirdly, only the first revascularisation of an admission was taken into account when determining the type of procedure performed, so staged approaches or the number of re-interventions or failed procedures were not explored, due to the limitations of the available data.

In conclusion, patients undergoing infrainguinal revascularisation for CLTI during emergency admissions had high 1-year major amputation and mortality rates in this study. Longer time from admission to revascularisation was independently associated with higher mortality in patients with tissue loss but not in those with less severe forms of PAD. There was no evidence of an association between delay to revascularisation and major amputation, after adjustment for patient and admission factors.

Chapter 4. Implementation and short-term outcomes of the Peripheral Arterial Disease Quality Improvement Programme

4.1 Introduction

CLTI is a vascular condition with high morbidity and mortality, and management options include medications, revascularisation procedures or primary amputation. As discussed in previous chapters, the NCEPOD report and the NHS Improvement GIRFT report on vascular surgery highlighted deficiencies in the management of patients with CLTI in the NHS, which varied widely across the country[206,236]. This variation included inconsistencies in the choice of open surgical or endovascular treatment, involvement of a multidisciplinary team in the decision-making, availability of pre-operative anaesthetic assessment, and the timeliness of assessment and treatment[236]. For this reason, the GIRFT report recommended the creation of a pathway to achieve faster referral to treatment times, to eliminate variation and improve outcomes for patients.

In response to the recommendation, the VSGBI published the "Best Practice Clinical Care Pathway for Peripheral Arterial Disease" in March 2019[237]. This document described a Quality Improvement Framework (PAD QIF) with specific guidance for the management of patients with peripheral arterial disease and short timelines from referral to treatment for CLTI. However, it is unknown whether these timelines are achievable, taking into account the limited resources and high service demand in most UK vascular units. Additionally, there is a paucity of evidence regarding the changes required in vascular services to achieve these timelines and whether these changes improve patient outcomes.

The Peripheral Arterial Disease Quality Improvement Programme (PAD QIP) was designed to evaluate the implementation and clinical effectiveness of the PAD QIF in practice, using the Institute of Healthcare Improvement Breakthrough Series Collaborative approach[301]. A Quality Improvement Collaborative (QIC) is an organised structured process that includes multidisciplinary teams from multiple healthcare sites supported by a team of experts to address a specific healthcare problem by applying

improvement methods, reporting results and sharing best practice and data on service performance[300,304]. QICs are an effective way to help clinicians improve the quality of care delivered to patients[299]. The QIC approach has been used once in the UK vascular surgery setting, during the Abdominal Aortic Aneurysm Quality Improvement Programme (AAA QIP)[330], and due to the success of other collaborative projects in UK surgical contexts[361,362], it was adopted for this programme. An additional reason for choosing the QIC approach was the lack of evidence on specific interventions that would be suitable for adoption; therefore collaborative work, brainstorming, sharing of practice and trials in multiple contexts would expedite the generation of evidence for effective interventions.

The aim of this study was to assess the impact of the implementation of changes in UK vascular services through the PAD QIP on revascularisation times and the management of patients with CLTI in line with the recommendations outlined in the PAD QIF document.

4.2 Methods

This was an implementation study carried out in England from January 2020 to December 2022. The PAD QIP took place from May 2020 to May 2022 and formed the implementation strategy, while the participating NHS Trusts introduced specific interventions to their vascular service. The study is reported according to the standards for reporting implementation studies (STARI) checklist[247] and the interventions are described in detail using the template for intervention description and replication (TIDieR) checklist[272]. The quantitative outcomes are reported according to the STROBE statement for observational studies[363]. The implementation strategy and the programme delivery are described in the methods section, the local interventions and quantitative evaluation in the results section, while the qualitative evaluation is reported in the next chapter.

4.2.1 Participating sites

All UK vascular centres were invited to participate in the PAD QIP through a newsletter disseminated via email to all members of the VSGBI in June 2019. The newsletter called

for expressions of interest to be involved in the early adoption and implementation of the PAD QIF, by coming together and discussing current patient pathways and sharing ideas and good practice to improve timelines to limb salvage and patient outcomes. Centres were selected based on the following criteria: performance of a sufficient number of vascular arterial procedures per year (>50); presence of a vascular surgeon willing to lead the local implementation team; a commitment/willingness to make changes to the vascular service delivery; and approval by the Clinical Director. Eleven vascular centres in NHS Trusts applied and were accepted into the programme, as they satisfied all selection criteria. All participating centres were located in England and their location is depicted in Figure 15.

The Participating NHS Trusts and their arterial centres were the following:

1. Cambridge University Hospitals NHS Foundation Trust (Addenbrookes' Hospital)
2. Gloucestershire Hospitals NHS Foundation Trust (Cheltenham General Hospital, Gloucestershire Royal Hospital)
3. Hull University Teaching Hospitals NHS Trust (Hull Royal Infirmary)
4. Liverpool University Hospitals NHS Foundation Trust (Royal Liverpool University Hospital)
5. North Bristol NHS Trust (Southmead Hospital)
6. St George's University Hospitals NHS Foundation Trust (St George's Hospital)
7. The Dudley Group NHS Foundation Trust (Russells Hall Hospital) and Royal Wolverhampton NHS Trust (New Cross Hospital) – Black Country vascular network
8. University Hospitals Dorset NHS Foundation Trust (Royal Bournemouth Hospital)
9. University Hospitals Birmingham NHS Foundation Trust (Queen Elizabeth Hospital, Heartlands Hospital)
10. University Hospitals of Leicester NHS Trust (Glenfield Hospitals)
11. York Teaching Hospital NHS Foundation Trust (York Hospital)

The participating NHS Trusts had varying sizes, number of network hospitals, procedure volume, number of surgeons and interventional radiologists (IR), and geographic location. Site characteristics (personnel, resources, catchment population) are displayed in Table 15. Information about the number of network hospitals, vascular surgeons and

interventional radiologists (Full-time equivalent – FTE) was obtained from the organisational survey published in the 2022 Annual NVR report[164], the catchment population and number of beds from Public Health England dashboards[364] and the average annual number of lower limb revascularisation procedures from the 2020 NVR Annual report[238].

Two more NHS Trusts joined the programme in May 2021, Manchester University Hospitals NHS Foundation Trust and University Hospital of North Midlands NHS Trust, but as they did not participate for the full duration of the programme, they are not included in this analysis.

Figure 15 – Map of PAD QIP participating centres in red

Table 15 – Characteristics of PAD QIP participating centres

NHS Trust of arterial centre	Arterial centre	Active network hospitals	Referring network hospitals	Catchment population	Arterial centre beds	Trust beds (per 10,000 people)	Vascular Surgeons (FTE)	Vascular IR Cons. (FTE)	Revascular. procedures/ year*
University Hospitals Dorset	Royal Bournemouth Hospital	2	3	975,000	723	10	10	6	77
York and Scarborough Teaching Hospitals	York Hospital	0	6	693,000	700	17	7	5	563
Liverpool University Hospitals	Royal Liverpool University Hospital	3	4	1,069,000	850	14	12	4	188
Cambridge University Hospitals	Addenbrookes' Hospital	2	4	1,322,000	1,100	16	8	7	258
St George's University Hospitals	St George's Hospital	6	6	1,861,000	860	15	9	6	273
The Dudley Group	Russells Hall Hospital	1	2	1,004,000	650	21	8	9	503
University Hospitals Birmingham	Queen Elizabeth Hospital	1	5	1,600,000	1215	11	11	4	573
Gloucestershire Hospitals	Gloucestershire Royal Hospital	1	2	942,000	683	16	6.5	6	102
North Bristol	Southmead Hospital	0	3	1,685,000	996	17	11	6	336
Hull University Teaching Hospitals	Hull Royal Infirmary	0	4	896,000	700	19	7	7.5	361
University Hospitals of Leicester	Leicester Royal Infirmary	0	2	948,000	890	16	7.5	5.5	92

*Average number of lower limb revascularisation procedures per year is based on 2017-2019 data from the 2020 NVR Annual report. This may not reflect the true number of procedures in NHS Trusts with low case ascertainment for angioplasty procedures, such as University Hospitals Dorset.

The target population was patients with CLTI admitted to hospital as emergencies, who underwent a revascularisation procedure (open, endovascular or hybrid). These patients had the most severe form of PAD and it was decided to focus on improving their management.

4.2.2 Context

All the participating centres were located in England, therefore they had common contextual factors, such as the social, economic and policy background[365,366]. Apart from the PAD QIF document, there was no other national or international guidance specifying a specific timeframe for treatment of patients with CLTI[3,80]. Additionally, there were no financial incentives or penalties for Trusts to follow the recommendations, such as the 4-hour targets in A&E departments or the 2-week rule for cancer referrals.

However, the most important contextual factor that affected the study was the arrival of the coronavirus disease (COVID-19), an infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 was associated with high transmission rate, morbidity and mortality and was declared as a pandemic in January 2020 by the World Health Organisation (WHO)[367]. It arrived in the UK in early 2020 and led to multiple national lockdowns in 2020 and 2021. There was a major disruption to the delivery of surgical services as well as access to hospital care in general[114]. A subsequent chapter details the effect of the COVID-19 pandemic on UK lower limb revascularisation procedures[368].

4.2.3 Implementation strategy

The PAD-QIP was designed and delivered by the central PAD-QIP team, which I led and which consisted of 12 clinicians, statisticians, health services researchers, and qualitative researchers, based at the Clinical Effectiveness Unit of the Royal College of Surgeons of England and Hull York Medical School. After the 11 participating vascular centres were selected, the first formal event of the Collaborative was the pre-launch meeting in October 2019, where the PAD QIP team and representatives from the centres agreed on the aim and focus of the collaborative, identified common barriers to change and suggested methods for improvement. Based on these discussions and after a literature review of QIC projects, Quality Improvement guidance[294] and Implementation Science

principles[267], the protocol for the PAD QIP was developed and shared with the participating centres in April 2020. The programme planned to launch in May 2020, with an 18-month implementation period until November 2021, which was subsequently extended by 6 months (Figure 16). It consisted of four components:

- QI training and online resources, including data analysis tools and QI materials;
- collaborative events, in the form of face-to-face meetings and webinars;
- data collection in the National Vascular Registry audit, to understand the size of the problem and monitor progress; and
- 4-monthly comparative performance reports, to feed back on progress.

The expert team set the outcomes and measurement strategies, provided quality improvement resources and organised the collaborative activities.

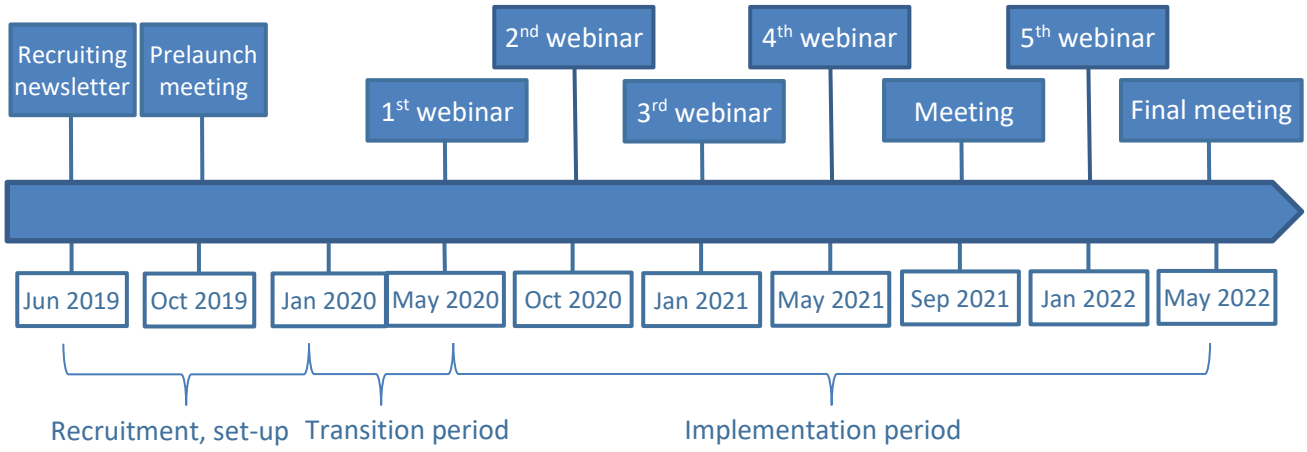

Figure 16 – PAD QIP timeline as implemented

QI training and online resources

The same set of QI interventions were not suitable across all participating centres due to local variation in referral pathways and processes for the management of patients with CLTI. Therefore, individual centre support was provided to generate change ideas and test interventions tailored to their local context, using common elements outlined in a driver diagram (Figure 17). The driver diagram described the primary and secondary drivers to consider whilst developing the interventions to achieve the desired outcome. This and other Quality Improvement tools, such as the Model for Improvement and

process mapping, were introduced to the participants during the introductory webinar in May 2020.

Online Quality Improvement resources were available on the VSQIP website, including a guide describing how centres could analyse their own data and monitor their performance in real time[369], and QI training materials from reputable sources such as the Health Foundation, NHS Improvement, and the Institute of Healthcare Improvement[370]. A webpage was created with information about the programme, collaborative events and the protocol (https://www.vsqip.org.uk/resources/quality-improvement/vsgbi-pad-quality-improvement -programme), and a twitter account was set up to promote the project, raise awareness and serve as a platform of communication between the central and the local teams (@VSQIP_news). The local teams were supported to analyse their own data and monitor their progress, by demonstrating how to download centre-specific data from the NVR during the first webinar. They could also contact the central PAD QIP team via email or telephone to submit enquiries or seek support.

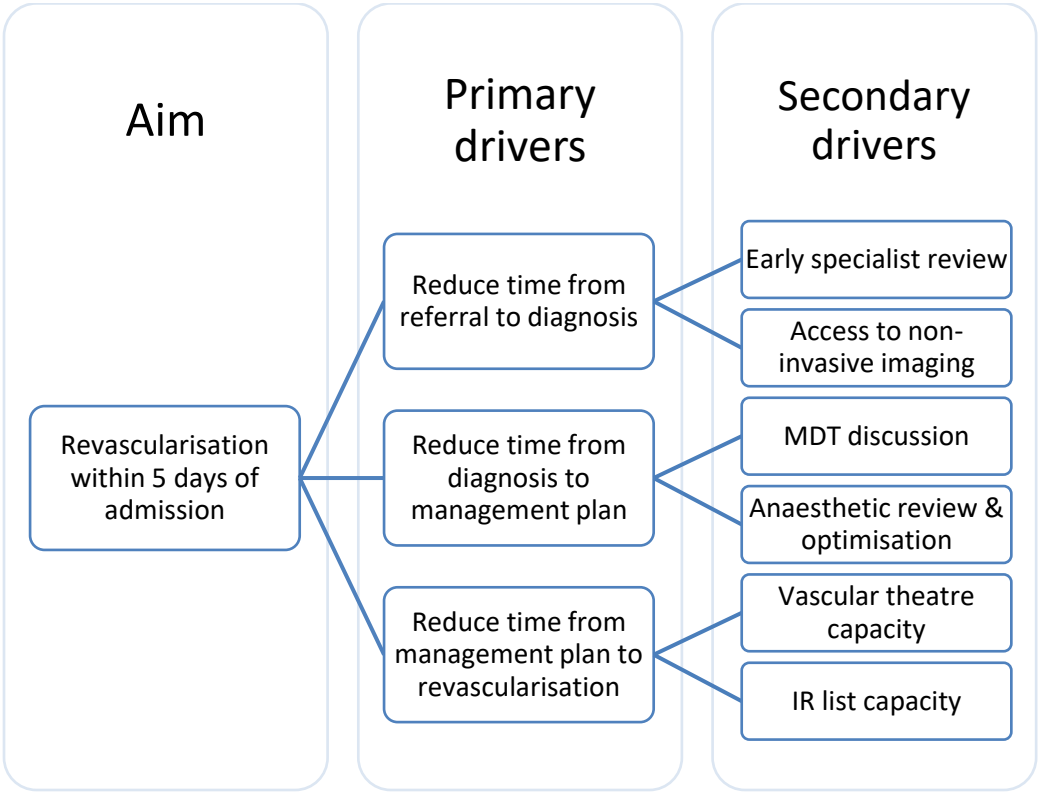

Figure 17 – Driver diagram for PAD QIP

Collaborative events

Meetings were organised by the PAD QIP team every 4 months (Figure 16). Their purpose was to facilitate the sharing of progress and exchange of ideas between the participating teams. During these learning sessions, the central team presented quantitative results on process indicators, while the local teams reported on successes, barriers to change and lessons learned. These also contributed to maintaining the momentum, and offered an opportunity to discuss issues that arose and reinforce the community aspect of the collaborative. Webinars lasted 60-120 minutes, whereas the in-person and hybrid meetings lasted the whole day.

The introductory webinar in May 2020 was the formal starting point of the PAD QIP, where final details were discussed regarding the collaborative structure and activities, and from which time point change in practice was measured. Presented at this webinar were the four components of the programme, individual centre baseline performance figures against the process measures from 2018 and 2019, a guide to analysing their own data to monitor progress and outcomes, and an introduction to the use of QI tools. Additionally, the impact of COVID-19 on vascular services was explored through a real-time online questionnaire that the attendees answered. All attendees stated that they continued to operate on CLTI patients and were running CLTI clinics. The following requests were made of the participating teams after the webinar:

- Produce a description of their patient pathway from emergency admission under vascular services to revascularisation using process mapping, and identify priority areas to implement changes. Process mapping allowed teams to assess their current practice and decide what changes to implement in their local context. Development of the interventions by the local teams increases engagement, as the teams take ownership of the proposed changes and try harder to adhere to them[245].
- Recruit team members. Centre leads were asked to form a multidisciplinary local implementation team, consisting of vascular surgeons, interventional radiologists, anaesthetists, vascular scientists, vascular specialist nurses and service co-ordinators, and nominate a contact person that would communicate with the PAD

QIP team. Involvement of trainee doctors and patients with the project was encouraged.

- Engage with stakeholders in their organisation and gain support from the senior team in their department, division or Trust. The engagement and support of senior leaders in the participating organisations is a key condition for a QI collaborative to be successful[283]. The centres were therefore advised to discuss the collaborative with the divisional operations managers and underline the link with the GIRFT recommendations, so that the level of support could be formally agreed and documented.
- Register the project with the Audit Department in their hospital.
- Hold meetings to raise awareness of the project in their department and discuss the aims, baseline data, local challenges and ideas for improvement.

The webinar was also an opportunity to collect information from the participating teams on their implementation plans. Using a real-time online questionnaire, the participants were asked about the level of leadership they were planning to approach to seek support for the project. Representatives from five units planned to approach divisional directors, one to discuss at Trust Board level and five to have inter-departmental discussions only. Regarding the start of the implementation phase, two mentioned they were ready to start immediately, and six within 3-months. In a question about further training on the QI tools mentioned in the webinar, twelve participants answered that they would be keen for further training through online resources, four through another webinar, and two did not wish to have further training. Regarding further webinars, most felt that 1-hour webinars would be enough.

The subsequent webinars and the meeting in September 2021 included presentations by the PAD QIP leads of the 11 participating centres about the changes they had implemented and their overall progress, and presentation of graphs with the 3-monthly progress of each centre and the overall cohort by the central team (Table 16).

Table 16 – Details of collaborative meetings

Date	Platform	Duration	Topics discussed
May 2020	Online (GoToWebinar)	60 mins	Impact of COVID-19 on vascular services PAD QIP protocol & QI tools Data on baseline performance
Oct 2020	Online (MS Teams)	60 mins	Graphs of 3-monthly outcomes Proposal for new QI database Presentations of local implementation plans
Jan 2021	Online (MS Teams)	80 mins	Graphs of 3-monthly outcomes Presentations of local implementation progress Management of CLTI during COVID-19
May 2021	Online (MS Teams)	90 mins	Graphs of 3-monthly outcomes Presentation from Birmingham team Presentations of local implementation progress
Sep 2021	In-person RCS England London	6 hours	Graphs of 3-monthly outcomes, Group discussions Presentations of local implementation progress Talks on the National Wound Care strategy programme and on Sustaining QI changes
Jan 2022	Online (MS Teams)	90 mins	Graphs of 3-monthly outcomes REDCap database demonstration Primary care referrals in participating centres
May 2022	In-person RCS England Manchester	6 hours	Presentation of final quantitative-qualitative data Evidence for effectiveness of QICs Round table discussions on experience of PAD QIP Talk on sustainability and next steps

Data collection system

Patient-level data on procedures performed at the participating centres were prospectively collected in the National Vascular Registry (NVR)[371]. The NVR collects information on major vascular procedures performed in NHS hospitals, including open and endovascular lower limb revascularisation procedures, and is commissioned by the Healthcare Quality Improvement Partnership (HQIP).

Key data items collected in the NVR were patient characteristics (age, gender, presence of diabetes mellitus, ischaemic heart disease, chronic respiratory disease, chronic kidney disease, smoking status, presenting problem, Fontaine score) and admission details (admission date, mode of admission, procedure date, procedure type, discharge date,

discharge status, further unplanned lower limb surgery, complications). The date of referral to the vascular service was only collected for open but not endovascular revascularisation procedures, therefore, the date of admission was selected as the starting time point of the patient pathway. Local teams were asked to ensure that their data were submitted to the NVR in a prospective manner for the duration of the programme. Data completeness was derived by comparing the number of procedures submitted in the NVR with those recorded in Hospital Episode Statistics (HES), an administrative database of all procedures performed in NHS Trusts in England.

Performance reports

Four-monthly cumulative performance data for each participating centre and the whole cohort were analysed and shared with centre leads in the form of run charts and a comparative dashboard prior to each collaborative meeting. The dashboard included information on the proportion of patients with CLTI undergoing open or endovascular revascularisation within 5 days from emergency admission and on time-to-revascularisation. The baseline performance of the participating Trusts for these outcomes was also provided and was estimated using NVR data from 1st January to 31st December 2019. The frequent reporting aimed to provide feedback to the local teams in the participating centres on their improvement efforts and illustrate how their unit's performance compared against peers. The teams were also able to analyse their own data and monitor their progress using a guide provided by the NVR team.

Programme theory

The programme theory or Theory of Change of the PAD QIP describes how and why its components are expected to lead to the intended outcomes by outlining the assumptions about the mechanisms that link the inputs with its activities and outcomes[269]. The theory of change supporting QICs is that by benchmarking and working together, teams are motivated to make changes which improve services and patient outcomes, spread innovations, and create long-term learning networks, based on the Partnership Synergy Theory and the Diffusion of Innovations theory[285,299,302]. Additionally, participants can learn from experts, develop inter-organisational

relationships and gain experience in QI processes that can be used in subsequent projects.

The relationships between the required inputs, planned activities, expected outputs and desired outcomes are depicted graphically in the form of a Logic Model, which was intended for use during the planning, implementation and evaluation phase[372] (Figure 18). It can be articulated in a series of if-then statements, e.g. if the material and staff resources, time, committed people and leadership support are available, then they will collect data, monitor performance, identify causes of delays and areas for improvement, act on feedback, and share good practice, some effect will be generated, which will then lead to an increase in the proportion of patients treated within five days from admission, which is expected to then reduce the time from admission to treatment, the length of stay, readmissions and amputation rates in the long term.

INPUTS	ACTIVITIES	OUTPUTS	OUTCOMES
Resources (Clinic, imaging, theatre slots) Time Healthcare teams Leadership support	Collect data, monitor performance and act on feedback Share good practice and discuss problems and solutions Identify causes of delays and areas for improvement	Make changes to vascular services Increase % of patients treated within 5 days from admission	Reduced time from admission to treatment Reduced length of stay Reduced readmissions Reduced amputation rates

Figure 18 – Logic model for PAD QIP

4.2.4 Evaluation

Firstly, a controlled interrupted time series study was undertaken at the end of the implementation period to evaluate the outcomes of the participating centres compared to their baseline and using vascular units in the UK not participating in the collaborative as controls, and is described in detail in the next section[373–375].

Secondly, a qualitative documentary analysis of materials produced during the study was performed to obtain information on interventions implemented in each centre. These included slides presented by centre representatives during the webinars; video

recordings of webinars; notes from in-person meetings; participant feedback from the webinars and meetings; and online questionnaire results from the 1st webinar regarding services during COVID, audit of current practice for CLTI patients, leadership engagement for QIP, QI training, capacity for additional data collection, and future webinar organisation.

Thirdly, each centre's engagement with the programme and adherence to the implementation strategy were assessed by measuring the number of participants attending collaborative meetings, the number of implemented service changes and the completeness of data collection for each participating centre, as the proportion of eligible procedures entered in the data collection system based on NVR data.

Finally, a mixed methods study consisting of semi-structured interviews and an online survey with clinicians from the participating centres was performed. That study is presented in chapter 5 of this thesis.

4.2.5 Statistical analysis

All lower limb revascularisation procedures for CLTI performed in NHS Trusts in the UK during emergency hospital admissions from 1st January 2019 to 30th April 2022 were extracted from the NVR. NHS Trusts that did not participate in the programme comprised the control group. The period from 1st January to 31st December 2019 was considered the baseline period (baseline), while that from 1st June 2020 to 30th April 2022 was the implementation period. The period from 1st January to 31st May 2020 was considered a transition period and was excluded from the analysis. Also excluded were data from the two centres that joined the programme in May 2021 and from non-arterial centres, day-case procedures and procedures with admission-to-revascularisation time longer than 30 days, as these patients were likely to be unsuitable for an operation on admission. Records with missing data on important variables (age, comorbidities, discharge date) were also excluded, and a complete case analysis was performed. The first revascularisation procedure of the hospital admission was considered the index procedure and was used to calculate the admission-to-revascularisation time.

The primary outcome measure was the proportion of patients admitted as emergencies with CLTI who underwent revascularisation within 5 days from admission. Secondary outcomes were the time from admission to revascularisation, overall length of stay (LOS), postoperative LOS, and in-hospital mortality. Balancing measures included the cardiac, respiratory, renal, and limb complication rates, re-intervention rate, and 30-day readmission rate. Balancing measures are used in QI programmes to monitor for unintended consequences in other parts of the system not directly related to the intended goal of improvement[376]. The time from admission to revascularisation, overall LOS and postoperative LOS were measured in days and explored as continuous variables. The median and IQR statistics were used to summarise their distributions and the difference in medians between groups was examined using quantile regression.

Patient characteristics included in the analysis were gender (man/woman), age (<60 years, 60-69, 70-79, ≥80 years), smoking status, presence of comorbidities (diabetes mellitus, ischaemic heart disease, chronic lung disease, and chronic kidney disease), Fontaine score on admission (III-rest pain or IV- tissue loss), type of index revascularisation procedure (open, endovascular or hybrid) and level of intervention (supra-inguinal, femoral, popliteal, crural). Categorical variables of patients' demographic characteristics were summarised as frequencies and proportions, and differences between groups were examined using the chi squared test.

Outcomes in the PAD QIP centres during the implementation period were compared to their baseline period and the control group using interrupted time series and difference-in-difference (DID) analysis[377]. In this analysis, both the group in which each centre belonged (PAD QIP group vs. control group) and the time period (baseline vs. implementation) were taken into account. Therefore, it was possible to control for secular trends and the effect of external factors such as the COVID-19 pandemic. Time-to-revascularisation, LOS and postoperative LOS were modelled by fitting separate negative binomial regression models, which were preferred to Poisson as they allowed for overdispersion[378,379]. The rate of revascularisations within 5-days, 30-day readmissions, re-interventions, and complications was modelled using separate Poisson regression models with robust standard errors. These were preferred to logistic regression, because the odds ratios deriving from logistic regression overestimate the

risk ratio for common outcomes (>10%)[311]. Logistic regression was used to model in-hospital mortality. The change in the primary outcome over time was illustrated using a Shewhart SPC chart, with the upper and lower control limits calculated at 3 standard deviations from the mean[380,381].

A sensitivity analysis was performed to compare the centres' performance between 2019 and 2021, considering the period from 1st January to 31st December 2020 as the transition period. Subgroup analysis was also performed for the outcome referral-to-revascularisation for the patients that referral date was captured. All analyses were undertaken in STATA 17.0 (StataCorp, College Station, Texas, USA). P-values <0.05 were considered statistically significant.

4.2.6 Ethical considerations

This implementation study was designed as a service evaluation and therefore ethics committee approval was not required for participation in the collaborative or the implementation of changes at local level. Verbal consent was gained from the participants for video recording of the collaborative webinars and meetings for the purposes of the study and not for public dissemination. The mixed-methods evaluation study of the survey and clinician interviews received Ethics Approval by the Hull York Medical School Ethics committee (Ref. number 21 35, approval date 23/06/2021).

Patient consent for data collection in the NVR is sought prior to elective procedures by the treating clinicians. The NVR also has approval from the Confidentiality Advisory Board to process healthcare information for emergency procedures without patient consent, under section 251 (reference number: CAG 5-07(f)/2013). Additionally, patient-level data collection in the NVR is legally permitted under articles 6(1)(e) and 9(2)(i) of the UK General Data Protection Regulation (GDPR) as "data needed to carry out a task in the public interest to ensure high standards of quality and safety of healthcare", as well as under Schedule 1(1)(3) 'public health' of the UK Data Protection Act 2018. The data were de-identified and no patient identifiers were available after data were extracted for analysis. Ethics committee approval was not required for the secondary analysis of existing pseudo-anonymised data in this study.

4.3 Results

4.3.1 Programme delivery

The programme was mostly delivered as it was initially designed, including the programme components, the performance indicators, and the measurement strategies. However, a number of adaptations were made to address the restrictions posed by the COVID-19 pandemic. Firstly, the duration of the programme was extended for 6 months, with the implementation period ending on 30th April 2022 instead of 30th November 2021 (Figure 16). Additionally, the majority of the collaborative meetings were held online via webinars and teleconferences instead of in-person due to the restrictions imposed by the British government to limit the spread of the disease. Therefore, only two in-person meetings were organised in September 2021 and May 2022, with five more events held online. Finally, two site visits to each participating centre were initially planned, one at the beginning and one at the end of the implementation period, to allow data collection for the process evaluation and assessment of how the programme was implemented in each Trust. These site visits were cancelled, as there were travel restrictions in place and limited access to hospitals, due to the risk of spreading the COVID-19 disease.

4.3.2 Programme adherence and local interventions

The local implementation teams consisted of vascular surgeons, interventional radiologists, vascular specialist nurses, quality improvement specialists and service managers. After local teams were formed, they explored the patient pathway in their centre, audited their practice and identified areas where improvements could be made. They provided updates on the changes they had implemented during collaborative events. The number of attendees from each centre at the collaborative events varied from zero to six (Table 17).

Based on the documentary review of materials from the programme, most centres focused on expediting vascular review following referral by securing dedicated CLTI slots in existing clinics or by setting up urgent CLTI clinics with imaging capacity, such as Duplex or CTA slots, so that patients could be investigated fully in one visit. Another

intervention adopted by six centres was the allocation of one individual responsible for triaging the incoming referrals daily, so that patients referred with CLTI could be recognised and prioritised for urgent clinic review. A further six centres employed acute care coordinators or other administrative staff to keep track of patients throughout their journey and to ensure timely review of results, MDT discussion, and intervention if appropriate. The changes implemented in the PAD QIP participating centres are summarised in Table 18 and Table 19. Adherence to the programme for each centre in terms of participation in collaborative events, implementation of changes, and completeness of data collection is shown in Table 20.

The participating vascular departments did not receive additional funding from their NHS Trust, and there was no commitment from the organisational leadership to allow staff time to participate in the programme or allocate project management resources.

Table 17 – Number of attendees from each centre at the collaborative events, in descending order of attendance

Centre	Webinar 1	Webinar 2	Webinar 3	Webinar 4	Meeting Sep 2021	Webinar 5	Meeting May 2022	Total
Black Country	1	4	2	3	2	3	1	16
Leicester	6	1	3	2	0	2	1	15
Hull	4	3	2	2	1	1	1	14
Dorset	4	1	2	2	2	2	0	13
Cambridge	1	2	2	2	3	1	1	12
Birmingham	1	2	2	2	1	1	0	9
York	1	1	0	2	2	1	2	9
Gloucester	2	0	1	2	0	0	2	7
St Georges	0	2	1	1	2	0	0	6
North Bristol	0	4	1	1	0	0	0	6
Liverpool	1	1	0	1	0	0	0	3
Total	21	21	16	23	17	14	11	123

Table 18 – PAD QIP Centres and the local interventions implemented in each one, in order of increasing number of interventions

Centre	Interventions
Dorset	CLTI clinic 5/week with Duplex and CTA
Cambridge	Daily triage of referrals CLTI clinic 4/week with Duplex
Gloucester	CLTI clinic x3/week with Duplex and CTA CLTI coordinator
St Georges	CLTI clinic with Duplex and CTA Dedicated vascular IR sessions
Liverpool	Daily triage of referrals Hot slots in all clinics (CLTI clinic 08/20-04/21 – stopped) CLTI coordinator
Birmingham	Daily triage of referrals Hot slots in all clinics Dedicated vascular IR sessions Daily anaesthetic inpatient assessment
Black Country	Rapid access system (RAS) for GP referrals Availability of arterial duplex in vascular clinic Fast-tracked CTA/MRA booking CLTI coordinator
North Bristol	Daily triage of referrals CLTI clinic 5/week with Duplex and CTA Daily MDT Admin support
York	Triage by Consultants and Podiatry Hot slots in all clinics Virtual ward for outpatients Daily urgent vascular theatre list
Hull	Daily referral triage by Consultant of the Week CLTI clinic 3/week with Duplex + CTA Daily MDT Daily urgent vascular theatre list Acute care coordinator
Leicester	Open-door policy for referrals Dedicated CLTI clinic with Duplex Daily MDT Dedicated vascular IR slots CLTI coordinator

Table 19 – Common interventions and centres that implemented them

Centre	Daily triage of referrals	Other referral/ triage intervention	Urgent CLTI clinics (with Duplex +/- CTA)	Dedicated CLTI slots in existing clinics	Other imaging intervention	Daily MDT with vascular & IR	Urgent vascular surgical lists	Dedicated IR sessions	Acute care coordinator/ admin support
Dorset			✓						
Cambridge	✓		✓						
Gloucester			✓						✓
St Georges			✓					✓	
Liverpool	✓			✓					✓
Birmingham	✓			✓				✓	
Black Country		RAS		✓	Expedited CTA/MRA				✓
North Bristol	✓		✓			✓			✓
York	✓			✓	Virtual ward		✓		
Hull	✓		✓			✓	✓		✓
Leicester		Open door	✓			✓		✓	✓

RAS=Rapid Access System

Table 20 – Adherence of participating centres to the PAD QIP components

Centre	No. of meeting participants	No. of interventions	% of eligible procedures collected in NVR
Dorset	13	1	<70%
Cambridge	12	2	<70%
Gloucester	7	2	<70%
St Georges	6	2	≥70%
Liverpool	3	3	≥70%
Birmingham	9	4	≥70%
Black Country	16	4	<70%
North Bristol	6	4	≥70%
York	9	4	≥70%
Hull	14	5	≥70%
Leicester	15	5	<70%

4.3.3 Quantitative results

Of the 12,592 patients with CLTI admitted as emergencies for revascularisation in the UK during the study period, 2,984 were excluded from the analysis for the following reasons:

- 727 were in two centres that joined the programme late
- 235 were from non-arterial centres
- 1,382 were performed during the transition period
- 114 were performed as day-cases
- 158 revascularisations occurred more than 30 days after admission
- 367 had missing data on variables of interest (age, diabetes status, discharge date).

Therefore, 9,608 patients with CLTI admitted as emergencies for revascularisation were included in this analysis. Of these, 2,966 (30.9%) were in PAD QIP centres and 1,929 (20.1%) were during the implementation period.

Table 21 summarises the patient characteristics by group and time-period of admission. There were significant differences between the PAD QIP and control groups for age, presence of diabetes and ischaemic heart disease (IHD), smoking status, Fontaine score, type of procedure, and level of intervention. The proportion of hybrid procedures increased significantly during the implementation period compared to the baseline in both PAD QIP (14.7% during vs 9.3% before, $p<0.001$) and control centres (14.4% vs 8.9%, $p<0.001$). There was also a significant proportional increase in procedures performed in current smokers during the implementation period compared to the baseline in all centres, while a significant decrease in patients with IHD during implementation was observed in control centres. When the PAD QIP centres were compared to the control centres during both periods, the PAD QIP centres had significantly higher proportion of procedures performed by endovascular approach (58.1% vs 44.9%, $p<0.001$) and in crural vessels (44.7% vs 36.1%, $p<0.001$). Similarly, PAD QIP centres treated significantly higher proportion of patients with diabetes (59.6% vs 57.1%, $p=0.023$) and with tissue loss (82.4% vs 79.0%, $p<0.001$) compared to the control group in both baseline and implementation periods, while the control centres treated more current smokers (34.8% vs 31.5%, $p=0.002$).

Table 21 – Patient characteristics by group and time-period of admission

	PAD QIP		Control		Difference
	Baseline (n=1,037)	**Implement.** (n=1,929)	**Baseline** (n=2,214)	**Implement.** (n=4,428)	
Age group					* ‡
< 60	156 (15.0)	323 (16.7)	317 (14.3)	762 (17.2)	
60-69	272 (26.2)	512 (26.5)	628 (28.4)	1,247 (28.2)	
70-79	336 (32.4)	629 (32.6)	760 (34.3)	1,448 (32.7)	
≥ 80	273 (26.3)	465 (24.1)	509 (23.0)	971 (21.9)	
Men	736 (71.0)	1,367 (70.9)	1,546 (69.8)	3,094 (69.9)	
Diabetes	634 (61.1)	1,133 (58.7)	1,250 (56.5)	2,542 (57.4)	‡
Ischaemic heart disease	371 (35.8)	702 (36.4)	824 (37.2)	1,492 (33.7)	*
Chronic lung disease	220 (21.2)	433 (22.5)	501 (22.6)	986 (22.3)	
CKD	203 (19.6)	376 (19.5)	439 (19.8)	798 (18.0)	
Current smoker	301 (29.0)	634 (32.9)	734 (33.2)	1,577 (35.6)	§ * ‡
Fontaine score					‡
Rest pain	194 (18.7)	327 (17.0)	458 (20.7)	937 (21.2)	
Tissue loss	843 (81.3)	1,602 (83.1)	1,756 (79.3)	3,491 (78.8)	
Procedure type					§ * ‡
Endovascular	645 (62.2)	1,079 (55.9)	1,051 (47.5)	1,930 (43.6)	
Open	296 (28.5)	566 (29.3)	965 (43.6)	1,862 (42.1)	
Hybrid	96 (9.3)	284 (14.7)	198 (8.9)	636 (14.4)	
Level of intervention (distal)†					‡
Iliac/Femoral	339 (33.1)	617 (32.7)	794 (36.2)	1,578 (36.2)	
Popliteal	244 (23.9)	410 (21.7)	618 (28.2)	1,196 (27.4)	
Crural	440 (43.0)	859 (45.6)	782 (35.6)	1,584 (36.4)	

† 128 procedures were related to grafts and 19 had missing level of intervention

§ indicates statistically significant difference between baseline and implementation periods at PAD QIP centres

* indicates statistically significant difference between baseline and implementation periods at control centres

‡ indicates statistically significant differences between PAD QIP and control centres throughout the whole study period (baseline and implementation periods combined)

Change in proportion of patients revascularised within 5 days

The outcomes of patients treated in the PAD QIP and the control centres at baseline and during the implementation period are summarised in Table 22. There was a significant increase in the proportion of patients revascularised within 5-days during the implementation compared to the baseline in PAD QIP centres (63.8% vs 56.9%), which was also observed in the control group (53.1% vs 48.6%). This represents a relative change of 1.12 (95% CI 1.05-1.19) in PAD QIP centres, compared to 1.09 (95% CI 1.04-1.15) in the control group. When the improvement in PAD QIP centres was compared with the control centres, the increase observed in PAD QIP centres was not statistically significantly higher (IRR 1.03, 95% CI 0.95-1.11) (Table 23). Therefore the PAD QIP centres improved, but not significantly more than the national trend. Despite the lack of significant improvement, the PAD QIP centres revascularised significantly higher proportion of patients within 5-days during both periods. The change in the proportion of patients revascularised within 5-days over time is depicted in Figure 19.

Change in time-to-revascularisation and LOS

The PAD-QIP centres decreased the time-to-revascularisation from 5 to 4 days ($p<0.001$) (Table 22). Again, this decrease was not statistically significantly higher than that observed in control centres (IRR 0.96, 95% CI 0.89-1.04) (Table 23). There was also a statistically significant reduction in LOS (from 13 to 11 days, $p<0.001$) and postoperative LOS (from 7 to 6 days, $p<0.001$) among participating centres during the implementation period compared to their baseline. This reduction was significantly greater than the trend observed in the control centres, where both LOS and postop LOS were unchanged (15 days and 8 days, respectively) (Tables 22 and 23).

Change in complications

There was a significant increase in occurrence of limb ischaemia post-revascularisation in PAD QIP centres in the implementation period compared to the baseline (5.2% vs 3.6%, $p=0.044$), which was not statistically significantly higher than that found in other UK centres (IRR 1.40, 95% CI 0.92-2.13). Other complication rates were unchanged in PAD QIP centres, while the control centres had increased respiratory complications in the implementation period compared to their baseline (4.5 vs 3.2%, $p=0.015$)(Table 22).

Table 22 – Outcomes by group (PAD QIP vs. control) and time-period of admission (baseline vs. implementation period)

	PAD QIP		Control		Difference
	Baseline (n=1,037)	**Implement.** (n=1,929)	**Baseline** (n=2,214)	**Implement.** (n=4,428)	
Time-to-revascularisation	5 (2 - 8)	4 (2 - 7)	6 (3 - 9)	5 (2 - 8)	§ * ‡
Length of stay (LOS)	13 (7 - 24)	11 (6 - 20)	15 (9 - 27)	15 (8 - 25)	§ ‡
Postoperative LOS	7 (3 - 15)	6 (3 - 13)	8 (4 - 17)	8 (4 - 17)	§ ‡
Revascularised in 5-days	590 (56.9)	1,231 (63.8)	1,076 (48.6)	2,352 (53.1)	§ * ‡
Complications					
Cardiac	23 (2.2)	35 (1.9)	74 (3.4)	114 (2.6)	‡
Respiratory	27 (2.6)	40 (2.1)	71 (3.2)	197 (4.5)	* ‡
Renal	15 (1.5)	22 (1.2)	35 (1.6)	57 (1.3)	
Limb ischaemia	37 (3.6)	98 (5.2)	139 (6.3)	289 (6.6)	§ ‡
Re-interventions (during index admission)					
Open surgical	32 (3.1)	70 (3.7)	79 (3.6)	171 (3.9)	
Endovascular	51 (4.9)	98 (5.1)	97 (4.4)	217 (4.9)	
Minor amputation	79 (7.6)	93 (4.9)	172 (7.8)	371 (8.4)	§ ‡
Major amputation	43 (4.2)	94 (5.0)	117 (5.3)	252 (5.7)	
30-day major amputation	55 (5.3)	107 (5.6)	121 (5.5)	255 (5.8)	
Mortality	40 (3.9)	76 (3.9)	87 (3.9)	182 (4.1)	
30-day readmission	164 (16.4)	228 (12.5)	352 (16.8)	717 (17.1)	§ ‡

Time-to-revascularisation and LOS are presented as median (interquartile range) in days. Other outcomes are presented as n (%)

§ indicates statistically significant difference between baseline and implementation periods at PAD QIP centres

* indicates statistically significant difference between baseline and implementation periods at control centres

‡ indicates statistically significant differences between PAD QIP and control centres throughout the whole study period (baseline and implementation periods combined)

Table 23 – Association of implementation group, time-period of admission and their combination with outcomes

	PAD QIP centres (vs. control)	Implementation (vs. baseline)	PADQIP # Implementation
% revasc. in 5-days	1.17 (1.09-1.25)	1.09 (1.04-1.15)	1.03 (0.95-1.11)
Time-to-revascularisation	0.87 (0.81-0.92)	0.92 (0.88-0.96)	0.96 (0.89-1.04)
Length of stay (LOS)	0.90 (0.85-0.95)	0.95 (0.91-0.98)	0.92 (0.86-0.98)
Postoperative LOS	0.91 (0.85-0.98)	0.96 (0.92-1.01)	0.91 (0.84-0.99)
Mortality	0.98 (0.67-1.44)	1.05 (0.81-1.36)	0.98 (0.61-1.56)
30-day readmission	0.98 (0.83-1.16)	1.02 (0.91-1.14)	0.74 (0.60-0.93)
Limb ischaemia	0.57 (0.40-0.81)	1.04 (0.86-1.27)	1.40 (0.92-2.13)
Minor amputation	0.98 (0.76-1.26)	1.08 (0.91-1.28)	0.60 (0.43-0.84)

Outcomes are presented as incidence rate ratios (95% confidence intervals), apart from mortality, which is presented as odds ratio.

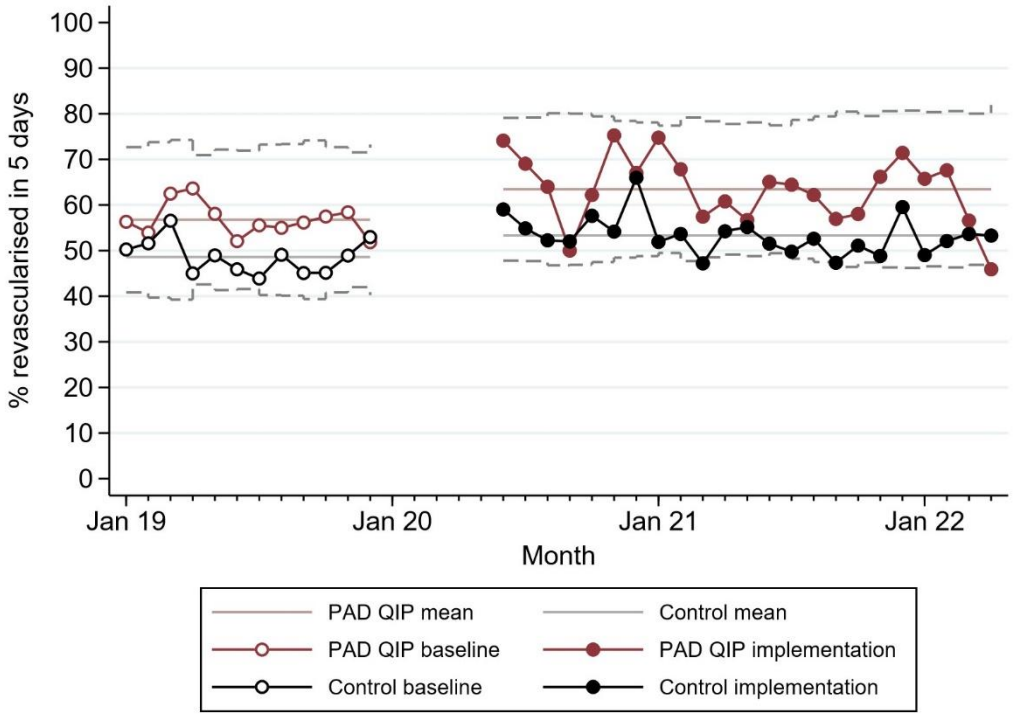

Figure 19 – Statistical process control chart depicting the percentage of patients with CLTI revascularised within 5-days from emergency admission in the PAD QIP and the control centres in baseline and implementation periods.

Change in re-interventions and 30-day readmission rate

There was a statistically significant reduction in subsequent minor amputations (4.9% vs. 7.6%, p=0.003) and 30-day readmission rate (12.5% vs 16.4%, p=0.004) during the implementation period compared to the baseline in PAD QIP centres (Table 22). The change was statistically significantly greater than in the control centres, where a slight increase in these metrics was observed (Table 23). There was no difference in postoperative mortality and 30-day major amputation rate between baseline and implementation period in either of the groups.

Individual centre performance

Examining each PAD QIP participating centre individually, two achieved a significant increase in the proportion of patients revascularised within 5-days compared to their baseline, with Birmingham improving by 43% and Liverpool by 54% (Table 24). The improvement in Birmingham remained significant even after comparison with the temporal trend observed in the control centres (Table 24). Seven more centres also improved, but this was not statistically significant when compared to their baseline. Overall, there was a wide variation in the primary outcome during the baseline and implementation periods across participating centres, with the proportion of patients revascularised in 5-days varying from 26.0% to 73.1% at baseline and from 40.2% to 75.5% during the implementation period.

Figure 20 depicts the ranking of PAD QIP centres for the 5-day revascularisation target compared to all UK centres during the baseline and implementation periods. Six centres improved their ranking, one remained in the same position, and four had a lower ranking among UK arterial centres. One centre in particular moved up by 26 places (site 1, Birmingham, from 44th to 18th).

Table 24 – Individual centre 5-day revascularisation rates in the PAD QIP and control groups, in descending order of improvement

	Procedure volume		% revascularised in 5-days		Relative change from baseline	Relative change adjusted for control group
	Baseline	Implement.	Baseline	Implement.		
Control	2,214	4,428	48.6	53.1	1.09 (1.04-1.15)	-
PAD QIP	1,037	1,929	56.9	63.8	1.12 (1.05-1.19)	1.03 (0.95-1.11)
Birmingham	231	426	45.9	65.7	1.43 (1.23-1.67)*	1.31 (1.11-1.54)*
Liverpool	73	239	26.0	40.2	1.54 (1.02-2.34)*	1.41 (0.93-2.15)
St Georges	81	115	53.1	67.0	1.26 (0.99-1.61)	1.15 (0.90-1.48)
Leicester	42	203	54.8	64.0	1.17 (0.87-1.57)	1.07 (0.79-1.44)
N. Bristol	124	188	62.1	68.1	1.10 (0.93-1.30)	1.00 (0.84-1.20)
Cambridge	89	59	50.6	54.2	1.07 (0.78-1.47)	0.98 (0.72-1.35)
York	104	212	73.1	75.5	1.03 (0.90-1.19)	0.94 (0.81-1.10)
Black Country	156	182	68.6	69.2	1.01 (0.87-1.17)	0.92 (0.79-1.08)
Gloucester	31	79	67.7	68.4	1.01 (0.76-1.34)	0.92 (0.69-1.23)
Hull	93	205	68.8	67.3	0.98 (0.83-1.16)	0.90 (0.75-1.07)
Dorset	13	21	69.2	47.6	0.69 (0.38-1.24)	0.63 (0.35-1.12)

The relative change in the percentage of patients revascularised within 5-days is presented as incidence rate ratio (IRR). Values in parentheses are 95% confidence intervals.

The asterisk indicates statistically significant difference ($p<0.05$).

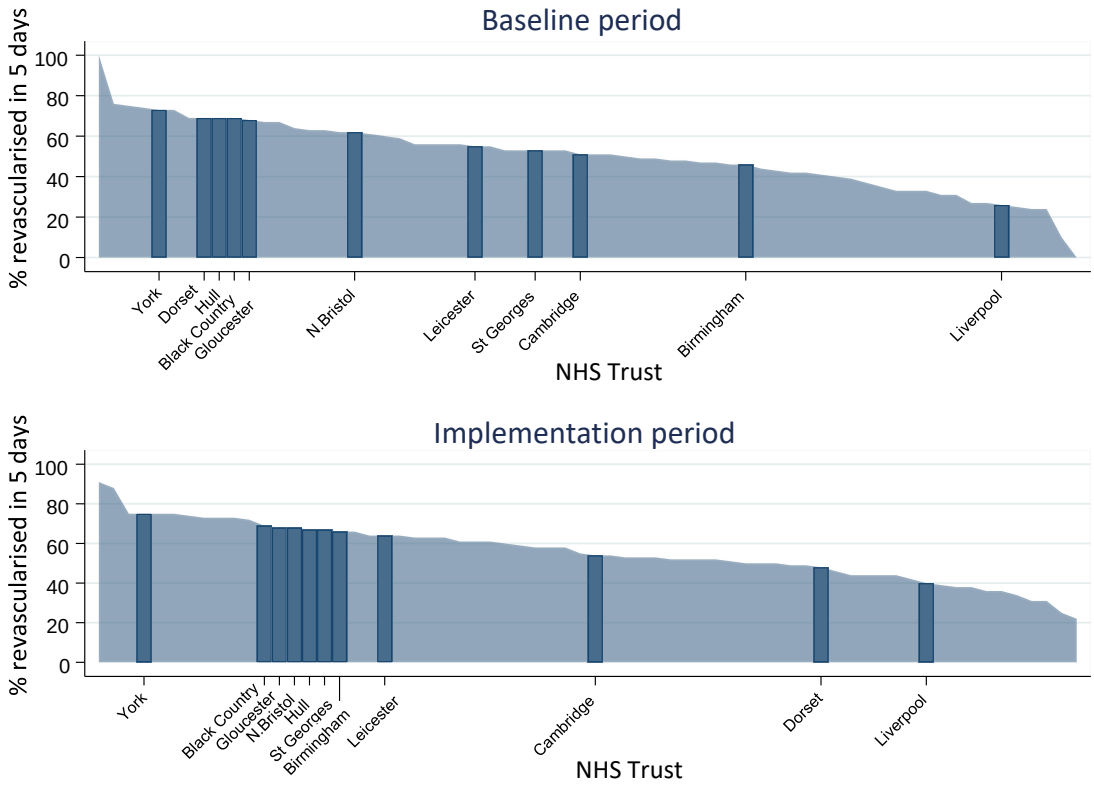

Figure 20 – Ranking of PAD QIP centres (bars) compared to all centres in the UK (light blue area) by the percentage of patients revascularised within 5-days from admission in the baseline (top graph) and implementation (bottom graph) periods.

Sensitivity analysis without 2020

A sensitivity analysis examined the association of the time period and implementation group with outcomes when the baseline period of 2019 was compared to the period from January 2021 to April 2022, excluding January-December 2020 as a transition period. This analysis included 7,744 admission records, 2,374 in PAD QIP centres (30.7%) and 5,370 in the control centres (69.3%). The outcomes remained mostly unchanged (Table 25). During the implementation period, 62.7% of patients were revascularised in 5-days in PAD QIP centres and 51.8% in control centres. The difference between PAD QIP and control centres was maintained across all outcomes, but the improvement during the implementation period compared to the baseline was less prominent.

Table 25 – Association of implementation group (PAD QIP vs. control), time period and their combination with outcomes, excluding the period January-December 2020

	PAD QIP centres (vs. control)	Implementation (vs. baseline)	PADQIP # Implementation
% revasc. in 5-days	1.17 (1.09-1.25)	1.07 (1.01-1.13)	1.03 (0.95-1.13)
Time-to-revascularisation	0.87 (0.81-0.92)	0.94 (0.90-0.98)	0.98 (0.90-1.06)
Length of stay	0.90 (0.85-0.95)	0.97 (0.93-1.01)	0.91 (0.84-0.97)
Postop. LOS	0.91 (0.85-0.98)	0.99 (0.94-1.04)	0.88 (0.80-0.97)
Mortality	0.98 (0.67-1.44)	1.01 (0.76-1.33)	0.98 (0.59-1.63)

Time-to-revascularisation and length of stay (LOS) are presented as median (interquartile range) in days

Referral to revascularisation

A subgroup analysis assessed whether the outcome referral-to-revascularisation time in days changed during the programme. Only procedures in the "Bypass" dataset were considered, as the referral date was not captured in the "Angioplasty dataset". Procedures with a referral-to-revascularisation time longer than 180 days were excluded (n=52). Of the 4,429 remaining procedures, 338 were performed in PAD QIP centres before and 737 during the implementation period, while 1,092 were performed in control centres before and 2,262 during the implementation period. Median referral-to-procedure time was 7 days (IQR 4-12).

The PAD QIP centres tended to have significantly shorter referral-to-procedure time (IRR 0.85, 95% CI 0.80-0.90) compared to the control group, but they did not make an improvement during the implementation period compared to their baseline (IRR 1.12, 95% CI 0.99-1.26). The findings were similar when the referral-to-procedure time was examined as a binary variable (≤5 days, >5 days), with PAD QIP centres being significantly more likely to achieve the 5-day target compared to control centres (IRR 1.18, 95% CI 1.09-1.28) but no improvement was observed compared to their baseline (IRR 0.97, 95% CI 0.84-1.12).

4.4 Discussion

The PAD QIP aimed to evaluate the implementation and clinical effectiveness of the 5-day admission-to-revascularisation target in patients with CLTI. The programme was successfully delivered, with the COVID-19 pandemic necessitating some adaptations. The participating centres implemented various interventions in an attempt to reduce delays to revascularisation and were successful in increasing the proportion of patients revascularised within 5-days. The extent to which this was due to the QIC is unclear, because a similar improvement on this metric was observed in the rest of the UK arterial centres, and it might be that both PAD QIP and control centres were responding to the best practice guidance published by the VSGBI. PAD QIP centres also reduced the length of hospital stay and readmission rate during the implementation period, while the other UK centres did not achieve a reduction in these metrics. These are notable findings considering the current bed crisis in NHS hospitals, and may contribute to financial gains, increased capacity, and falling waiting lists for NHS Trusts.

The design of the programme was based on a systematic review of QI Collaboratives, and findings from the AAA QIP and CholeQuIC programmes[299,330,382]. For example, the PAD QIP was supported by professional societies, such as the VSGBI and BSIR, the interventions were adaptable to the local context of each vascular centre, and performance data were shared with the teams regularly to help them benchmark and obtain organisational resources, all of which were highlighted as factors facilitating change in previous surgical QICs[362,382–385]. However, the QIC could not be delivered as planned. It was not possible to hold regional events, which encourage engagement of local commissioning groups and opinion leaders, due to the social distancing measures that were in place during the COVID-19 pandemic[330]. Site visits were cancelled for the same reason, despite the favourable opinion on them in other programmes[382]. Additionally, even though the creation of a team with at least 3 members in each unit was recommended, this did not occur in some of the centres. Indeed, the participating centres had different levels of engagement with the programme. Only three centres had team members attending all collaborative events, while four centres did not have representation in three or more of the seven collaborative events. One site had limited engagement, with no new interventions implemented and incomplete local data, as

endovascular procedures were not collected. Based on these observations, future iterations of the programme should endeavour to include site visits and more in-person events, support from a quality improvement expert, closer engagement and support by Trust leadership, and dedicated time for QI in clinician job plans.

Additionally, the PAD QIP participating centres implemented interventions at a different pace. Some had urgent CLTI clinics in place prior to the programme, such as Dorset, North Bristol, and Leicester. The Leicester team in particular had set up a Vascular Limb Salvage (VaLS) service with positive outcomes prior to their participation, so their main role in the collaborative was to share their experience and support others with the same goal[242]. Others implemented changes in the first 3 months, as indicated by their presentations in the second webinar, while a minority only adopted interventions in the second year of the programme. Some interventions were adopted by multiple centres, such as the introduction of urgent CLTI clinics or dedicated CLTI slots in existing clinics, daily triage of referrals, and employment of coordinators that ensured patients moved expeditiously along the set pathway. These changes were successfully introduced in the different contexts of the participating centres, indicating their adaptability and likely generalisability to other UK centres.

The improvement in the 5-day target observed in both PAD QIP and control centres might reflect the best practice guidance published by the VSGBI and the COVID-19 pandemic. National guidelines with specific waiting time targets had already been in place for the management of carotid disease since 2008 and abdominal aortic aneurysms since 2013, so vascular units allocated substantial resources and created pathways for these conditions perhaps at the expense of patients with CLTI[386,387]. The publication of the PAD QIF document in March 2019 brought PAD and especially CLTI to the attention of vascular teams in the UK and for the first time set specific timelines to be achieved for this patient group[237]. Therefore, non-participating vascular units may also have implemented changes in response to this guidance.

The COVID-19 pandemic was an important contextual factor that affected the implementation of changes. In the UK, a national lockdown was implemented from March to June 2020, followed by two additional lockdowns between November 2020

and February 2021[388]. COVID-19 caused a significant disruption in vascular services during the first year of the programme, with national guidance recommending the deferral of elective surgery and consideration of therapeutic options with minimal need for postoperative critical care[389], while the service was in the recovery phase during the second year[114,390]. The pause in elective activity may have benefited patients with CLTI, as it freed up theatre lists to perform urgent revascularisation procedures. Simultaneously, hospital pathways were modified and every effort was made to reduce patient exposure to hospital, which may have contributed to a shorter length of stay.

The centres participating in the PAD QIP had better performance in most outcomes at baseline compared to the control centres. Five of the eleven were already revascularising more than 60% of the eligible patients in 5-days prior to the start of the programme, while the national average at the time was 51.3%, and only two centres were performing below that. The higher performance of PAD QIP centres during the baseline period is likely a consequence of the recruitment method, as centres that volunteered to participate already had an interest in CLTI patients. However, this may have affected their potential to improve, as centres that were already performing well had less room for improvement, known as the ceiling effect[391]. The difference observed in individual centre improvement during implementation may be partly explained by this effect, as the only two centres that displayed a significant improvement were the ones that performed below the national average at baseline. For example, Birmingham improved from revascularising 45.9% of patients with CLTI within 5-days at baseline, to 65.7% during the implementation period, a relative change of 43% that was higher than the national improvement trend. On the other hand in York, 73.1% of patients were already treated within 5-days in 2019, which improved to 75.5% during the programme, representing a relative change of 3.3%. As some of the patients admitted urgently to the hospital with CLTI have other medical problems that require treatment or optimisation prior to surgery, it is empirically believed that it is not possible to apply the 5-day target to 10-20% of the patients, making the performance of the York team very close to optimal.

The implementation of changes during a QI programme occasionally has unintended consequences, known as balancing measures[392]. For example, strict adherence to

antibiotic and diabetes guidance may be associated with overtreatment[393,394], or efforts to reduce the length of hospital stay could result in increased readmission rates[395]. In this study, there was no increase in the postoperative complication, re-intervention, and mortality rate in the index admission, and there was a reduction both in LOS and readmission rate in participating centres. The increase in limb ischaemia complications was comparable in PAD QIP and control centres, and it may have been related to the COVID-19 pandemic, as thrombotic complications have been reported in other studies[396,397].

The main strength of this study was its controlled cohort design, which allowed us to account for the temporal trend of improvement observed in the non-participating UK arterial centres. The use of registry data also facilitated the comparison with historical data from 2019, collected prospectively in the NVR before the start of this study. However, this study also has some limitations. Firstly, some revascularisation procedures performed during the study period were not captured in the NVR. This is more likely the case for endovascular procedures, which have a case ascertainment in the NVR of approximately 48%, compared to 86% for open surgical procedures[164]. However, there is no evidence to suggest that the centres preferentially captured procedures with shorter time-to-revascularisation that would alter the results, and indeed many of the missing endovascular procedures may represent day-cases, excluded in this analysis. Additionally, the NVR dataset does not record previous hospital admissions or outpatient reviews, therefore some of the cases may represent scheduled urgent procedures with minimal preoperative stay, which would artificially increase the proportion of patients revascularised within the 5-day recommendation. Again, this would be expected to affect participating and non-participating Trusts during both baseline and implementation periods, so it is unlikely to have introduced significant bias. Moreover, changes to the vascular services were introduced throughout the duration of the programme, not all at the start, and it was not possible to identify the exact time specific interventions were adopted in each centre. Due to this limitation, it is not possible to evaluate how each intervention affected the outcomes, and whether some were more effective than others. Finally, due to the short follow-up time in this study, it was not possible to explore the effect of the programme on longer term outcomes, such

as readmission, re-intervention and major amputation rates one year after revascularisation. Further studies should assess the impact of the programme on long-term patient outcomes and the sustainability of the changes over time.

In conclusion, the changes to the CLTI patient pathway implemented in vascular centres participating in the PAD QIP significantly reduced delays to revascularisation and length of hospital stay, with improvement in the latter being higher than the national trend. The interventions introduced in the participating centres can be adopted by any vascular unit seeking to expedite the revascularisation of patients with CLTI. Further research is required to ascertain the long-term effects of the programme on patient outcomes.

Chapter 5. Factors that affected the implementation of the Peripheral Arterial Disease Quality Improvement Programme: a mixed methods study

5.1 Introduction

The development and components of the Peripheral Arterial Disease Quality Improvement Programme have been described in the previous chapter of the thesis, and consist of an implementation strategy, namely the "method used to enhance the adoption, implementation, and sustainability of a clinical practice or program"[252], and local interventions. In summary, the implementation strategy consisted of four components; a data collection system, quarterly performance reports, collaborative networking events, in the form of face-to-face meetings and webinars, and online QI resources, including data analysis tools and QI training materials. As each of the 11 participating vascular centres had different referral pathways and local processes for management of the patients with CLTI, the local improvement interventions were tailored to the context of each centre guided by data from ongoing evaluation activity and by the Model for Improvement[398]. The programme launched in May 2020 and was concluded in May 2022. A quantitative analysis of the performance of the participating centres was undertaken at the end of the programme, to evaluate the progress of the units compared to their baseline and the rest of the vascular units in the UK, which was presented in the previous chapter.

A mixed methods study that included semi-structured interviews and an online survey with clinicians from the participating centres was also performed during the implementation period and is presented in this chapter. The aims of this study were; a) to explore in depth the perceptions of the participants about the components of the programme, b) to understand the service changes that were introduced in each centre in relation to the programme, c) to describe how these changes were implemented, and d) to identify the factors that facilitated or hindered the implementation of service changes in the vascular surgery setting. This information will allow us to improve the next cycles of the programme by removing elements that were not useful, and will guide

future studies on this domain, as there are few quality improvement programmes conducted in vascular surgery.

5.2 Methods

5.2.1 Mixed methods approach and research paradigm

The study followed an effectiveness-implementation hybrid design[251,252], with the effectiveness evaluated in the previous chapter. The selection of a particular research method was complicated by the unique challenges that implementation science studies pose[399]:

- There was a need to balance the speed of analysis with the achievement of rigour and methodological integrity.
- Different kinds of insider and outsider expertise was required to support implementation.
- There was a variety of existing frameworks to choose from, to examine the mechanisms and associations of factors that influence implementation.
- The intended audiences were particularly diverse.
- There were resource constraints (staff, time, funding)
- Access to relevant participants was difficult

Based on these considerations, a mixed methods study design was followed, as it was considered that the combination of qualitative and quantitative approaches would provide a better understanding of the research topic[400]. The mixed methods approach adopted for the evaluation of the implementation allowed us to discover and document the *context(s)* and the *environment(s)* where implementation occurs, the *process* that occurs during implementation, the effectiveness of our chosen *implementation strategy ,* and the relationship(s) between *theorized* and *actual change*[401]. The two studies were conducted in the same time period, with the qualitative method used to analyse the semi-structured interviews viewed as dominant and the quantitative method used for the online survey as secondary (QUAL + quant)[400]. The purpose of using a mixed methods design was: a) convergence or triangulation, namely one study was used to validate the findings from the other, and b) expansion, where the qualitative study explained more in-depth the findings of the quantitative study[251].

The qualitative study followed the theory-informed framework method based on the Consolidated Framework for Implementation Research (CFIR)[274] and using a pragmatic approach, "strategically combining and borrowing from established qualitative approaches to meet the needs of a given implementation study, with the guidance from an IS framework and with clear research and practice change goals"[399]. This approach satisfied the need to conduct a time-bound study, which engaged with theories and frameworks, could be applied in practice and spoke to a diverse audience. The pragmatic approach involved combining inductive and deductive analytical processes, using a balance of insider/outsider orientation, following flexible coding and producing practice-focused, actionable findings[399].

In terms of ontological stance about the nature of reality, this study is based on critical realism, according to which there is a social reality beyond ourselves, but understanding this reality is dependent on the construction of a plausible account using subjective judgement[402]. Therefore, we postulate that the information collected in this study is socially influenced and viewed through the lens of the study participants, providing only partial knowledge of reality and the phenomenon we explore. Epistemologically, I leaned towards contextualism, where knowledge is perceived as emerging from contexts and reflecting the researcher's and participants' position. This indicates that the study findings may not be universally generalizable, but they will be valid in certain contexts, similar to the ones in the programme, namely vascular surgery setting. Thirdly, this is an experiential piece of work, as I documented peoples' experiences of their participation in the programme, but I also tried to draw out the influencing factors of the decisions they made.

The study received Ethics Approval by the Hull York Medical School Ethics committee (Ref. number 21 35, approval date 23/06/2021). The methods and results of the online survey are reported according to the Consensus-Based Checklist for Reporting of Survey Studies (CROSS)[403], while those of the qualitative interviews are presented according to the Standards for Reporting Qualitative Research (SRQR) checklist[404], ensuring that all consolidated criteria for reporting qualitative studies (COREQ)[405] are covered.

5.2.2 Researcher characteristics and reflexivity

I designed the study, conducted and analysed the interviews and wrote this chapter, supported by supervisors with training and experience in qualitative and quantitative research methodology. My supervisory team comprised of two senior lecturers in qualitative research methods who had expertise in framework analysis and implementation science (LS, EG), a professor of health services research (DAC), a professor of academic surgery and experienced mixed-methods researcher (ICC), and an academic surgeon (JB).

In qualitative research, the researchers background, beliefs and biases, can influence the analysis and interpretation of the findings[406]. Therefore, prior to the onset and during the study I considered my positionality and how this may have affected my conclusions through a reflexive practice, debrief notes and the upkeep of a research journal[407]. Positionality refers to both the world view and the stance of the researcher towards the research project, but as my ontological and epistemological assumptions have already been examined above, I further expand on my position towards the subject of the research, the study participants and the process.

As I am a vascular surgery trainee and did not have experience in qualitative research before undertaking the PhD, a significant portion of my time in preparation for the interviews was spent exploring the principles and methodology of qualitative research and I undertook a postgraduate module on “Qualitative Research Methods”, in order to further familiarise myself with the topic. Despite my limited knowledge on qualitative research, I had in-depth knowledge of the research topic and shared a common language with the study participants, having spent 5 years in training in vascular surgery in the United Kingdom. As such, I was able to understand terms they used and the situations they described.

I also had contextual knowledge, due to my previous clinical experience as healthcare professional and working within NHS and the vascular service. This provided me with a level of understanding that was important for the findings and the recommendations derived from this qualitative analysis. I can be considered ‘embedded’ within the healthcare service area being researched. This embeddedness provided me with useful

insights in the relevance and meaning of the study findings. For example, I could understand the acronyms used by the participants and the role of other healthcare professionals in the multidisciplinary team. However, it may have unconsciously influenced data interpretation, as I viewed the interviewees' personal accounts through the lens of my own experiences of the vascular service[408].

I developed the protocol for the programme and lead its implementation for the first 2 years, therefore my personal investment on the programme may have been a source of bias. As I conducted the interviews, the participants may have been reluctant to directly criticise the components of the programme. However, my familiarity with the participants, with whom I had been interacting throughout the project during webinars and through emails, is expected to have created a more relaxed environment during the interviews, as rapport has already been developed. Additionally, I believe I was perceived as an "insider", based on my identity as doctor and vascular surgery trainee. However, there were also elements of a power imbalance, as surgery as a discipline has rather strict hierarchy and the study participants were more senior than me in the clinical setting.

5.2.3 Data collection

Instrument design

Data were collected through semi-structured interviews and an online survey. The CFIR framework (Appendix 3) was used to inform the development of the interview topic guide (Appendix 4) and the survey questions (Appendix 5). The CFIR is a determinant framework developed by Damschroder et al, which includes constructs across five domains of factors that influence implementation[274]. The constructs of this framework were used for the design of the study tools (interview guide and survey questionnaire), as well as the coding, analysis of the qualitative data and reporting of the findings. The CFIR was chosen due to the comprehensive and systematic inclusion of factors that influence the implementation of complex health care interventions in multi-level contexts, and has been used in a large number of implementation studies in healthcare[257]. It has five domains (intervention characteristics, outer setting, inner setting, characteristics of individuals and process), and 41 constructs (Appendix 3).

The interview guide was designed based on the online CFIR Interview Guide Tool[409], to ensure agreement with the framework, but other areas raised by the participants could also be discussed and this was encouraged. The interview guide and the corresponding CFIR constructs covered by each question are presented in Appendix 4. The topics that we wished to capture during the interviews were the following:

- Role of the participant in the local implementation team and the organization
- Opinion of the participant about the recommendations that we try to implement in practice (perceived value, benefit)
- Opinion of the participant about the usefulness of the components of the Peripheral Arterial Disease Quality Improvement Programme (webinars, as a way of communication with colleagues from other centres and sharing knowledge and practice, online resources, electronic data collection system, quarterly performance reports)
- Changes in vascular service delivery that were implemented as part of the programme in the participant's organization
- Involvement of stakeholders on the decision of what changes to introduce and opinions of other team members on the implemented changes
- Factors that facilitated or hindered implementation of the changes in the participant's organization, such as availability of resources, support at senior organizational level, perceptions of colleagues outside the implementation team about the changes, factors arising from circumstances outside the control of the department

The rationale behind the data collection instrument design was to focus on the most important constructs of the CFIR framework, related to the research question and the topics of interest that could be covered during a 30-45 minute interview. Based on the experience of the research team, 15-20 open-ended questions would be appropriate, and prompts were noted as a memory aid in case the interviewee did not expand on the questions. The instrument was reviewed and agreed upon by all members of the research team.

The researcher who conducted the interviews (PB) had received training in qualitative research methods and interviewing. A mock interview was conducted with another member of the research team, who was also one of the implementation team members in a participating centre, in order to pilot test the interview guide and practice interview skills, as this was the first semi-structured interview the investigator had conducted.

The interview guide was modified after the mock interview, with one question about the effects of coronavirus disease 2019 (COVID-19) (positive or negative) on the implementation efforts added. Due to this addition, it was decided to remove a question about sustainability, especially because some centres had not implemented changes based on the discussions during collaborative meetings, so the question would not be applicable to all participants. Additionally, the question "what was done well in your centre" was originally included in the interview guide before the question about things that could be improved, but the question was not congruent with the flow of the conversation, and after it was not asked in the first 4 interviews, it was removed from the interview guide. Most questions were asked to all participants and when a question was not asked, this was because the participants had already answered as part of a previous question.

The questions of the online survey were also based on the CFIR Interview Guide Tool[14], to ensure agreement with the CFIR framework (Appendix 5). The online survey was designed and distributed using the Jisc online surveys software, provided by the University of Hull. Jisc is a secure, GDPR-compliant, web-based software platform for designing and conducting surveys and therefore it ensured the security of the data. The survey contained 4 questions about the participant's characteristics (occupation, specialty, organisation and stage of implementation), 4 questions about the programme, and 45 questions about factors affecting implementation based on the CFIR domains. The "stage of implementation" question was used to divide the survey into 2 pathways, depending on whether changes had been implemented in their unit (past tense in the wording of questions) or not (future tense). The questions about the implementation factors were formed as positive statements and rated on a 5-point Likert scale ranging from 1 (Completely disagree) to 5 (Completely agree). The questions

about the programme components were rated as “very useful”, “moderately useful”, “not useful” and “did not use/attend”.

Interview sampling strategy, sample size and participant characteristics

The study followed purposive sampling, and specifically criterion and maximum variation sampling[410,411]. Purposive sampling is a technique used to select “information-rich cases to study, cases that by their nature and substance will illuminate the inquiry question being investigated”[410], because they have knowledge about or have experienced the phenomenon of interest. Criterion sampling includes all cases that meet a specific criterion, which in our study was the involvement with the programme, while maximum variation sampling involves “purposefully picking a wide range of cases, to get variation on dimensions of interest”, which are described further in the sampling framework (Table 26). The initial study protocol also included snowball sampling, a method where participants recommend other people in their network, as the centre leads were asked to suggest individuals suitable for an interview in their organisation. However, this did not occur during the study, as none of the email recipients made suggestions for other colleagues, but volunteered to participate in the interview themselves.

The target sample size was 15 to 20 interviews with healthcare professionals in the local teams implementing the intervention. This was based on our critical realist approach, for which we required enough data to identify patterns across the data. Various studies have explored saturation as related to the emergence of new themes during thematic analysis[412,413] and most indicate that 12-16 interviews of a homogenous population are enough to explore the topic[413–418]. We considered that our participants had a relatively homogeneous background, as they were all treating vascular surgery patients with a specific condition (CLTI), albeit in different sites. Thus we aimed to interview at least one individual from each site, in order to collect adequate data to address the research question[419].

The sampling framework for the semi-structured interviews was developed as part of the study protocol (Table 26). As each centre implemented the intervention differently, representation from all centres with at least one interviewee was important to the

study. The centre leads were all vascular surgeons, but variety was sought in participant occupation (doctors, nurses, administrators) and specialty (vascular surgery, interventional radiology). Additionally, the vascular centres' catchment area and size were taken into account for the selection of interview participants. The rationale behind the sampling technique was to include "key stakeholders", people who have the most knowledge about, played a role in or were impacted by the implementation effort[420]. This approach was pragmatic, taking into account available resources in terms of researcher time as well as researcher numbers, availability and experience. Balanced representation from centres that had made a lot of and little progress in implementation during the programme was desirable, but as the final results of the programme were not available during the qualitative fieldwork stage, this criterion was not considered in the sampling framework.

Table 26 – Criteria of the theoretical sampling framework

Axis of diversity	**Operationalised Selection Criteria**
Role in implementation	Team Leader Team member
Occupation	Doctor Specialist nurse Administrative staff
Specialty of participant	Vascular Surgery Interventional Radiology
Size of organisation	<800 beds >800 beds
Catchment area	< 1 million population > 1 million population
Organisation	A B C D E F G H I J K

The clinical leads of the 11 participating vascular units were contacted via email and were asked to nominate the most appropriate representative from their centre for an interview. The email included a consent form and the participant information leaflet, which described the purpose of the study, what was required of them, how the collected data would be used (including how to view the results if published), contact details for the investigators, and how their confidentiality and anonymity would be protected. Most of the centre leads volunteered to participate in the interviews. Reminder emails were sent every 2 weeks to centre leads that had not responded. Even though it may be considered that the recurring emails put pressure on the recipients, previous feedback from them indicated that they often welcomed the reminder due to their heavy clinical workload and the emails were carefully phrased to indicate that any response (to accept or decline the invitation to interview) was sought.

As none of the centre leads suggested other members of their team for interviews, emails were also sent to other healthcare professionals in the participating centres, who had previously engaged with the programme and had agreed for their contact information to be retained and used for communications about the programme as per GDPR[421]. More specifically, emails were sent to three Interventional Radiology Consultants, two specialist nurses and one administrator, to ensure that a variety of occupations and specialties were represented. All participants were known to the researchers prior to the qualitative study, as they had participated in collaborative webinars and in-person meetings. People that were invited to interview via email and declined to participate included a clinician, who did not have availability for an interview due to time pressures, a specialist nurse who was retired and a QI coordinator, who did not give a reason.

During the interviews with the centre leads, the involvement of other team members in the implementation process was discussed, and it transpired that in some centres only one or two individuals were sufficiently engaged with the programme to be able to answer the interview questions. Therefore, the population eligible for interviews was much more limited than initially estimated, but all groups of healthcare professionals apart from administrative staff and all organisations were represented.

Interview process

The semi-structured interviews were conducted online and were recorded using Microsoft Teams software. Microsoft Teams was chosen as it is considered a secure platform, used by NHS organisations for discussion of sensitive patient data, and the participants were familiar with it. The interviews were conducted between 27 July 2021 and 26 October 2021 and they took place between 9am-5pm. The need for online interviews was necessitated by the social distancing rules and travel restrictions during the COVID-19 pandemic.

All the interviewees received the information leaflet and an electronic consent form prior to the interview. They signed and dated the consent form and returned it to the study team via email. They were asked to re-consent at the beginning and at the end of the interview and confirm that they were willing for their data to be analysed. They were also offered the opportunity to ask questions and they were advised of their right to withdraw from the study at any time after their interview.

Minimal field notes were taken during the interview, in order to maintain eye contact and interaction with the participants, but a debrief note was kept after the completion of each interview. The debrief note included observations about the overall impression that the interviewee made to the interviewer, the participant's surroundings, self-presentation and non-verbal communication (body language, tone of voice, mood, openness to questions), audio and video quality, interruptions during the interview, notes about prompt questions that were asked or questions that not asked and the reasons, important features of the participant's responses, ideas for data analysis and additional questions to ask in subsequent interviews or areas for the interviewer to work on regarding interview technique. Particular care was taken not to interrupt the participants and let them expand on the questions.

Online survey

All healthcare professionals in the 11 NHS Trusts participating in the PAD QIP, who had been involved in the implementation of the programme were invited to complete the survey via email. The clinical leads of the 11 vascular units were asked to distribute the online survey link to the other members of their team, including the information leaflet

about the study. Consent for participation in the online survey was gained at the beginning of the survey, by agreeing with the statement "I consent to take part in this survey and agree with how my data will be managed". If the participant did not confirm the statement, the survey was automatically stopped. The responses were anonymous.

The online survey opened on 1st July 2021 and closed on 30th October 2021, therefore was conducting concurrently with the interviews. The initial target sample size was 33 responses, 3 from each centre, but during the interviews it transpired that some clinical leads had not involved many other colleagues in the implementation effort, as previously discussed, so the survey closed before reaching this number.

5.2.4 Data Analysis

Development of the implementation score

After the conclusion of the programme in May 2022, an implementation score was developed, to categorise the centres as high or low implementation, in a similar method as described in previous implementation evaluation papers[422–425]. Centres are represented by a randomly generated capital letter for anonymisation purposes. Participation in collaborative meetings, number of changes implemented and engagement with data collection were used to create a 3-point implementation score, indicating the degree of programme implementation for each participating centre. For each of these characteristics, a cut-off point was decided, that would equally divide the centres into 2 categories and would be given 0 or 1 point. For example, a centre was given 0 points if it was represented by 9 or fewer participants in the meetings overall, and 1 point if represented by more than 9, resulting in 6 centres with 0 points and 5 centres with 1 point. Similar approach was followed for the number of interventions implemented (0 points if 3 or fewer, 1 point if 4 or 5) and proportion of eligible procedures entered in the data collection system (0 points if less than 70%, 1 point if 70% or more). The points were then added up and the participating centres were divided into high implementation if their score was 2 or 3 and low if it was 0 or 1 (Table 27). Therefore, centres were considered high implementation if they fulfilled 2 or more of the following criteria:

- they were at the top 50% of the cohort for meeting participation,
- at the top 50% for change implementation
- had more than 70% case ascertainment for lower limb procedures in 2020 and 2021.

Table 27 – Participating centres and their implementation score

Centre	Meeting Participation		Interventions		Data collection		Implementation score	
	No. of participants	Score	No. of changes	Score	Case ascertainment	Score		
F	7	0	2	0	<70%	0	0	Low
K	13	1	1	0	<70%	0	1	Low
D	12	1	2	0	<70%	0	1	Low
G	3	0	3	0	≥70%	1	1	Low
J	6	0	2	0	≥70%	1	1	Low
A	6	0	4	1	≥70%	1	2	**High**
E	9	0	4	1	≥70%	1	2	**High**
C	9	0	4	1	≥70%	1	2	**High**
H	16	1	4	1	<70%	0	2	**High**
I	15	1	5	1	<70%	0	2	**High**
B	14	1	5	1	≥70%	1	3	**High**

Interview analysis method

The purpose of the analysis was to move from the raw transcribed data to codes, then themes and finally theory and conclusions. The analytical method was chosen to provide timely evaluation of the intervention using limited resources but being scientifically rigorous. Several methods of rapid qualitative evaluations have been described in the literature[426,427]. It was decided by the research team that the traditional Framework Analysis was the most suitable for use in this study, as it is structured and systematic, therefore relatively easy to follow for those with no previous experience in qualitative research[428,429].

The Computer Assisted Qualitative Data Analysis Software (CAQDAS) QSR NVivo 12 Pro[430] was used for data management and analysis. The use of CAQDAS has been used widely in qualitative research and has a number of advantages and limitations[431]. Its main advantage is the ability to organise and manage large amounts of data effectively,

facilitate visualisation and summarisation, and maintain an audit trail that increases the transparency of the analysis process[432]. Its main drawbacks are the time required to learn how to use the software and the limited ability to view all the data at once, due to the screen size constraints[433]. It is important to underline that the software did not analyse the data, it just aided the analysis process, especially the charting or summarisation step as described below.

Framework analysis (FA) consists of the following steps[434]:

1. Transcription
2. Familiarisation with the interview, where the researchers view the recorded interview and read the transcript and the reflective notes.
3. Coding, which involves reading the transcript line by line and applying a code that captures the message of that excerpt. A code is defined as a word or phrase used as a label (descriptive or conceptual) and assigned to excerpts of data.
4. Developing a working analytical framework
5. Applying the analytical framework (indexing), where the coding structure is applied to the whole dataset.
6. Charting, where the data are summarised and entered into the framework matrix
7. Interpretation, during which patterns within and between cases are identified and the relationships across and between codes are explored. Data is synthesised using tables or diagrams.

Transcription

Software-assisted transcription of the interviews was performed. The transcription function of Microsoft Teams was activated during the interview and a transcript was produced after the interview was completed. This was used to facilitate the transcription of the interviews but required considerable amendments by the researcher. Verbatim transcripts were produced using this process but edited for clarity. Word or phrase repetitions were deleted and words such as “you know” and “like”, and utterances such as “um” and “yeah” were removed. Instances when the interviewee repeated the words of a third person were put in double quotes. Punctuation was added to improve readability of the written text.

Familiarisation

The familiarisation process occurred throughout the data collection process, from the creation of the interview guide, interview process, transcription, coding and analysis of the transcripts.

Coding

After the interview transcripts were de-identified and imported into the software, Framework-guided analysis was performed using deductive and inductive line-by-line coding methods[435]. The codebook was based on a rich set of deductive CFIR constructs and inductive codes that were relevant to the evaluation but not included in the CFIR framework. This is often called template analysis, as it involves a codebook which is based on a framework, but is then adapted to the study context[436].

Developing a working analytical framework

The CFIR framework was modified in a number of ways, to fit the research question, the resources and generally the context of the study, as in previous studies[437]. Initially, all 41 CFIR constructs were included as codes and new constructs were also added to the existing ones, to capture factors influencing the implementation.

To capture elements of the context in more detail, the CFIR "Inner Setting" domain was divided into team-level and organisational-level determinants, based on the work by Rogers et al.[281]. This was necessitated by the fact that contextual factors are of particular interest in this study and even though the CFIR framework has been shown to capture these well compared to other frameworks[280], it does not separate them into team and organisation. Rogers et al. describe a coding framework based on CFIR and supported by organisational theory, where system-level, organisational-level, team-level, and individual-level determinants are used to capture context[281]. In our study, the system-level determinants were captured by the CFIR "Outer setting" constructs, organisational-level by the "Inner setting – Organisation" constructs and the individual-level by the "Characteristics of Individuals" constructs. For the team-level determinants, a new set of constructs was created under the domain "Inner setting – Team", which

included “team structure”, “teamwork”, “team culture”, “team compatibility”, “team resources”, “local leadership engagement” and “team efficacy”. This change was decided during the design stage of the study and prior to the interview process, and has been reported in other studies evaluating complex interventions[438,439]. These 48 codes formed the initial nodes in the NVivo software before coding was attempted.

The initial codebook was used to code the first three interviews. During this coding process, the codebook was modified, with inductive codes created to capture interview content not covered by the CFIR constructs. This has again be common practice in other studies, especially ones evaluating large programmes rather than discrete interventions[437]. For example, two codes were created to capture the effects of the COVID-19 pandemic on the implementation efforts (“COVID positive effects”, “COVID negative effects”). The code “Team beliefs” was added to the “Inner setting – Team” domain, to capture opinions, feelings and perceptions of the team members about the changes implemented in the service.

Additionally, six codes were created under the “Design Quality and Packaging” CFIR construct, to capture opinions about the resources provided by the programme (“NVR data collection”, “Online QI resources”, “Performance reports”, “Meetings”) and about the programme overall (“PAD QIP overall”, “PAD QIP suggestions”).

Two codes were also used to capture barriers and facilitators, labelled “Main facilitating factor” and “Main difficulty”, with a sub-code “Other difficulties”. This approach helped with summarisation and has been used in other published studies of complex interventions[437].

A code was also developed inductively to capture how the intervention was implemented locally (“Local changes”) and another one for local plans going forward (“Local future plans”), as the participants were at various stages of the implementation journey when the interviews were conducted (Question 17 of interview guide, Appendix 4). This was different from the “Planning” construct in CFIR, which referred to the process of planning changes that were already implemented.

The code “Data collection” was developed to capture the methods used by the participants to collect data relevant to the programme. It was known prior to the interviews through the webinars that some organisations maintained local databases whereas others used the National Vascular Registry as data collection tool. Local databases contained more detailed information about the patient pathway and indicated that the participants devoted more resources to data collection in their centre. This code was also used to capture information about the presence of data coordinators/data clerks in each centre, who were responsible for collecting data.

Finally, the “Culture” and “Learning climate” constructs of the “Inner setting” domain were merged during analysis of the second interview, as their definitions were very similar and discriminating between the two would not add value to this particular analysis. The amendments resulted in 61 inductive and deductive codes in total.

Applying the analytical framework

After the first three interviews were coded and the codebook updated, the remaining interviews were coded. No new inductive codes were created at this stage. However, the definitions and inclusion criteria of some CFIR constructs were modified, to reflect the specific needs of our programme (Appendix 6, notes in italics), as in other evaluation studies[437,438]. This enabled all members of the research team to have a common understanding of the constructs. The first three interviews were re-analysed in the end and their coding was modified to reflect the changes made to the definition of codes.

The first three transcripts were also analysed independently by another member of the team with experience in qualitative research and implementation science (LS). These transcripts had broad use of codes and included inducted new codes, providing a good opportunity to test the deductive and inductive processes and appropriateness of the framework. This process also allowed analyst triangulation through a consensual qualitative research approach, assessment of inter-rater agreement and evaluation of individual bias.

Charting data into the framework matrix

At the end of the coding process, the CFIR constructs that were not used in the analysis were removed. These were: “Trialability”, “Individual identification with organisation”, “Other personal attributes”, “Goals and feedback”, “Readiness for implementation”, “Compatibility”, “Access to knowledge and information”, “Organisational incentives and rewards”, “Team resources”, “Team efficacy”, and “Local Leadership Engagement”. Additionally, the six constructs related to “Engaging” in the “Process” domain were included in a single “Engaging” code. Finally, the constructs “Complexity” and “Culture” of the Inner setting domain, were only discussed in 2 interviews and therefore were not considered in the analysis due to insufficient data. The above changes resulted in 42 codes and are reflected in the final version of the codebook (Appendix 6).

After all the interviews were coded, the data were summarised in a matrix, each code in a column and each participant as a row. Matrices are considered to “streamline the process of noting simultaneously and systematically similarities, differences, and trends in responses across groups of informants”[440]. Data for each participant and code were summarised and inserted into the corresponding cell in the matrix. The summaries were created by paraphrasing the answers and were brief but thorough, keeping the general sense of what was discussed. This was a minimally interpretative process. However, our aim was to analyse the vascular centres participating in the programme as cases because they were the context of the implementation and the participants belonged in the same team. Therefore, when there were more than one interviewees representing a centre, their data were combined, providing a composite picture. This approach allowed us to interpret the data at a team and organisational level. NVivo was very useful at this stage, as it enabled the easy retrieval of indexed data for specific codes within each transcript. References to potentially interesting quotes were highlighted within the cells of the matrix using Q or QQ/QQQ depending on how illustrative the quote was.

Ratings were also provided for each cell in the matrix on a scale of -2 to +2, based on valence and strength (weak or strong influence on implementation) (according to the CFIR rating rules)[422,424,441]. Valence was indicated by the + or – sign and representing the construct’s positive or negative influence on implementation. Zero represented no

influence on implementation (neutral), M represented mixed influences (positive and negative) and X indicated that no statements were coded in that construct. Strength of the influence on implementation was indicated by the number 1 or 2, which was determined by the strength of language and the use of examples by the interviewee. Constructs were evaluated and rated one at a time across all interviews, to allow estimation of the strength of influence and consistent rating across a construct[423,425].

The influence of COVID-19 was given an overall rating, depending on whether there were more comments about the positive or the negative effect of the COVID-19 pandemic by each interviewee, while seven of the 44 codes ("Data collection", "Local changes", "Local future plans", "PAD QIP suggestions", "Main facilitating factor", "Main difficulty" and "Other difficulties") were not rated. This information was collected to get a more complete picture of the local interventions, and to inform future iterations of the programme.

Interpreting the data

After the coding of the interview transcripts against the CFIR constructs, analysis sessions in the form of peer debriefing were carried out between me and my qualitative supervisor Dr Laura Sheard, where we thematically categorised the CFIR constructs. Themes "describe or explain aspects of the data, which are the final output of the analysis"[434]. We wished to move away from descriptive themes, defined as simple summaries of data separated into domains, and towards conceptual themes, as "patterns of shared meaning underpinned by a central organising concept"[442]. For this reason, we developed our own conceptual themes, which captured the messages from the interviews better than the CFIR domains, because some key messages could be found in constructs from different domains. For example, the importance of the programme for patients and the patient benefits from the programme were captured in the "Intervention – Relative Advantage", "Outer setting – Patient needs", "Inner setting (Organisation) – Tension for change", "Inner setting – Team beliefs", and "Individual – Beliefs and Knowledge about the intervention" constructs, and all these constructs supported the concept of "Patient Benefit", which was the resulting theme.

After the themes were defined, the coded data extracts were reviewed again to determine whether they were coherent with the overarching theme. The theme names were purposefully kept short, but give an immediate idea of the theme's content[443]. Four codes could not be integrated in the main themes, and they were kept under a miscellaneous theme[429].

Additionally, a construct analysis was performed to identify CFIR constructs that were associated with facilities with high and low implementation success, based on their implementation score (Table 27)[441]. The valence and strength ratings for each construct were entered in a matrix, with the high and low performing units as columns and the constructs as rows and a graph was also created. This visual representation and comparison of codes within and between cases allowed the identification of constructs that distinguished between high and low implementation units (difference in valence and/or magnitude), and constructs that had an overall positive or overall negative effect on implementation. Distinguishing constructs were subsequently characterised as barriers or facilitators of implementation using the valence rating and summary text[425]. The organised assembly of information in tables and graphs allowed conclusions to be drawn and suggestions for improvement to be made[444].

Survey response analysis

The two pathways that were created based on whether changes had been implemented in a vascular unit (past tense in the wording of questions) or not (future tense), were combined for the analysis, as they were addressing the same factors. The survey responses about the CFIR implementation factors, which were rated on a 5-point Likert scale from "Completely disagree" to "Completely agree", were recoded to follow the rating for valence and strength according to CFIR rating rules, with "Completely disagree" corresponding to -2, "Disagree" -1, "Neutral" 0, "Agree" +1 and "Completely agree" +2. These were quantitatively analysed and the mean score and standard deviation for each item was calculated. Higher mean score indicated agreement with the positive statements, and therefore presence of the factors explored.

Data integration

The results from the semi-structured interviews and the online survey were examined concurrently, to explore their convergence, complementarity and dissonance through triangulation, with the aim of increasing the validity of the research, using a similar method as Farmer et al[445]. In summary, the findings related to each CFIR construct from the two data collection methods were compared, with respect to their prominence and positive or negative effect on implementation. Based on the comparison, it was decided if there was agreement, partial agreement, silence or dissonance. The main findings of each theme are presented, supported by verbatim quotations from the interviewees, and compared with the survey findings.

5.2.5 Integrity measures

The scientific integrity of the findings was assessed by evaluating the rigor, reliability, validity, and generalisability of the data[446]. For a qualitative study to be rigorous, both criteria of validity and reliability should be met. Reliability refers to the consistency and dependability of the project's processes, that would allow the same results to be obtained if the project was repeated. This can be established primarily by developing a coding system and assessing interrater agreement, but also by presenting the theory and framework that informed the study design, the researcher's background and the data collection and analysis in sufficient detail[446]. The reliability of coding of the interview content to the framework constructs was explored at the end of the coding process, by re-coding the first three interviews after all the interviews had been coded[257]. Additionally, to assess interrater agreement, another member of the research team coded the first three interviews independently[447,448]. The same themes were generated through this process, ensuring good interrater agreement and that no important concepts were missed. A reflective journal was also kept throughout the data collection and analysis process, and a detailed audit trail of all important decisions about data collection and analysis was maintained.

Validity is defined as the "degree to which inferences made in a study are accurate and well-founded"[449], or "how well the research represents the actual phenomenon"[446], the accuracy of data and findings. This can generally be demonstrated by providing a clear

description of the methods of data collection and analysis and of the study context, clarifying researcher bias through reflexivity[450], using more than one data collection method (triangulation), developing a coding system and checking interrater reliability, and performing negative case analysis[446]. In this study, we employed methodological triangulation, which involved the use of more than one data collection technique, to examine if there were commonalities or differences in the collected data. We also used an established coding system (CFIR) and checked interrater reliability by having more than one researcher analyse a sample of the interviews. To minimise the risk of bias that arose from my involvement in the QI programme design and the conduct of the interviews, field notes and debrief notes were kept, which became part of the analysis to demonstrate my personal and epistemological reflexivity[451]. An audit trail was also kept in the form of a research journal that described the decisions that were made and the steps that were taken from the beginning of the project to the reporting of results.

Generalisability refers to the application or extension of findings to other contexts, settings or organisations. We believe that this study is generalizable to vascular surgery settings, similar to the ones described in this study. To achieve this, we described the context of the study, the characteristics of the participants and participating units, as well as the research assumptions that informed the study design and analysis.

Therefore, this work fulfils the eight criteria highlighted by Tracy as representative of high quality qualitative research[452]:

- a relevant, timely and significant topic, highlighted by recent national reports,
- rich rigor, achieved by using appropriate theory, sample, data collection and analysis process,
- credibility, through detailed description of events and triangulation,
- sincerity, by using self-reflexivity of the researcher and transparency of methods and findings,
- resonance, as it may interest readers through the transferability of findings to surgical settings,
- significant contribution, as it adds knowledge to a field where little information exists,

- ethics, as it follows all the ethical considerations and gained approval by an Ethics Committee, and
- meaningful coherence, through using methods that support the research question and connects the findings with the existing literature.

5.2.6 Data management

All electronic records, including the consent forms, interview recordings, transcripts and debrief notes were stored on secure servers of the Royal College of Surgeons (RCS) of England, which are encrypted and allow access through a two-factor authentication system only to members of the research team that have been granted permission. The interview recording video files were uploaded on the RCS servers immediately after the interview. The transcript record was also anonymised immediately and saved in that format. Anonymised quotations were extracted from transcripts during the analysis.

5.3 Results

5.3.1 Participant characteristics

Sixteen semi-structured interviews were conducted with representatives from 11 vascular units, which lasted from 35 to 50 minutes. The participant characteristics are presented in Table 28, based on the axes of diversity of the sampling matrix. According to the field notes, most of the participants joined the interview from a private space at their place of work (hospital), while one was in a shared office, one was in a theatre suite (therefore they had no privacy), and two of them were at home (home-working during COVID-19). Two of the participants did not have a camera on their computer, so it was not possible to see their facial expressions and other non-verbal communication, or their surroundings. Overall, the remote online nature of the interview made eye contact through the camera and interpretation of body language difficult. There were interruptions during five of the interviews, which consisted of phone calls to the interviewees, some of which were answered, people entering the room, and one interruption on the interviewer's part, but none of the participants stopped or asked to exit the interview. Most interviewees appeared relaxed or in a good mood, and expanded on the questions, while a small number were tired, reserved, or rushed.

Twenty survey responses were collected from the 11 participating units. Three quarters of respondents were vascular surgeons (n=15, 75%), 2 were Interventional Radiologists, 2 vascular specialist nurses and 1 administrative staff member. There was 1 respondent from 5 vascular units, 2 respondents from three vascular units and 3 respondents from the remaining three units. Regarding the stage of implementation at the time of the survey, twelve participants from 6 units stated that changes were integrated into routines, 6 participants from 6 units that some changes were implemented as a trial, and 2 participants from 2 units that no changes were made yet. Interestingly, participants from three vascular units gave different responses regarding the stage of implementation that their organisation was in.

5.3.2 Main themes

The deductive and inductive codes used in the Framework analysis were summarised into 5 themes: the Programme, the benefit for patients, the role of the team, the resources and organisational processes, and the polarising effect of COVID-19 (Table 29, Figure 21). These five themes captured the main factors that affected the implementation of changes in the CLTI patient pathway and are discussed in detail below with supporting excerpts from the interviewees. The relationship between CFIR domains, codes and final themes is depicted in Figure 22.

Overall, the elements of the Peripheral Arterial Disease Quality Improvement Programme, which formed the implementation strategy, and the view that it was beneficial for patients, were considered helpful by the majority of the interviewees. Similarly, the support of a team of healthcare professionals and organisational support in the form of resources were important requirements for implementation, while the COVID-19 pandemic also played a crucial role as a contextual factor beyond the control of the participants. More nuanced exploration of some aspects of these five themes led to the identification of factors that differed between high and low implementation centres (Figure 23). These were team beliefs, team structure, team compatibility, networks/communication, resources, implementation climate, relative priority, and evidence strength (Table 29).

Table 28 – Interview participant characteristics based on the criteria of the theoretical sampling framework

Axis of diversity	**Operationalised Selection Criteria**	**Participants**
Role in implementation	Team Leader	11
	Team member	5
Occupation	Doctor	15
	Specialist nurse	1
	Administrative staff	0
Specialty of participant	Vascular Surgery	13
	Interventional Radiology	3
Size of organisation	<800 beds	9
	>800 beds	7
Catchment area	< 1 million population	9
	> 1 million population	7
Organisation	A	1
	B	3
	C	2
	D	2
	E	1
	F	2
	G	1
	H	1
	I	1
	J	1
	K	1
Implementation score	High performing	9
	Low performing	7

Table 29 – CFIR domain constructs, corresponding themes, and rating by participating centre, with constructs differing between low and high implementation centres with asterisk

Theme	Institution	Low implementation					High implementation					
		D	F	G	J	K	A	B	C	E	H	I
Programme	Intervention - NVR data collection	+2	M	X	X	-1	0	M	+1	-1	X	-1
	Intervention - Online resources	+1	X	X	X	0	X	+1	0	X	+1	-1
	Intervention - Performance reports	-1	M	X	+2	+2	+2	+2	+1	+2	-1	-1
	Intervention - Webinars/meetings	+1	+2	X	+1	+2	+2	+1	M	+2	+2	-1
	Intervention - PAD QIP overall	+1	+2	+2	+2	+1	M	+2	+2	+1	+1	+1
	Intervention - Adaptability	X	X	X	X	X	+1	+1	+1	X	X	0
	Outer setting - Cosmopolitanism	X	X	X	X	+1	X	+1	+1	X	X	+2
	Outer setting - Peer pressure	X	X	X	+2	+2	X	+2	+2	X	X	X
	Process – Evaluating	M	0	0	+1	-2	+2	+2	-1	+1	0	+2
Patient benefit	Intervention - Evidence Strength*	X	X	X	+1	X	X	-1	X	-1	X	-1
	Intervention - Relative Advantage	M	X	X	M	X	+2	M	M	M	X	M
	Outer setting - Patient needs	M	M	X	X	X	X	+2	+2	+1	+2	-1
	Inner setting - Team beliefs*	+1	M	-2	+1	-1	+2	+2	+1	+2	+1	+2
	Inner setting -Tension for change	+1	+2	+1	+2	X	+2	+2	+1	+2	+2	+2
	Individual - Beliefs/knowledge	+1	+2	+1	0	M	0	+1	+2	+1	+1	+1
Teams	Inner setting - Team structure*	+1	+1	+1	-2	X	M	+2	+1	+1	+2	+1
	Inner setting – Teamwork	+2	+2	0	0	0	+1	+2	M	+1	X	+2
	Inner setting - Team culture	X	+2	X	X	-2	+1	M	0	X	X	-2
	Inner setting - Team compatibility*	+2	-1	-2	+1	X	+2	+1	+1	+2	+1	+1
	Inner setting - Network/ Communication*	-1	+2	-2	+2	-1	-1	+2	+2	+2	X	+2
	Process – Engaging	M	+1	M	+1	M	+2	M	+1	+2	+2	+2
Resources/ organisat. process	Intervention - Intervention source	0	0	0	0	X	0	+2	0	0	0	X
	Intervention – Cost	-1	0	X	0	0	-1	+1	+1	0	X	+1
	Inner setting - Structural characteristics	-1	-2	X	X	0	X	-1	0	+2	0	X
	Inner setting – Resources*	-2	-2	-2	M	-2	M	M	M	M	+1	+2
	Inner setting – Implement. climate*	0	0	X	X	X	+2	+2	X	X	+2	0
	Inner setting - Leadership engagement	0	M	+1	+2	-2	+1	M	-1	+2	+2	+2
	Outer setting - External policy incentives	X	M	X	0	+1	X	M	0	X	X	-1
COVID	COVID-19	M	-1	+1	M	-2	M	M	+1	+2	-1	+1
	Inner setting - Relative priority*	-1	-2	X	-2	-2	-1	M	X	X	X	+2

X : no information; M: mixed effect on implementation; 0: no effect on implementation

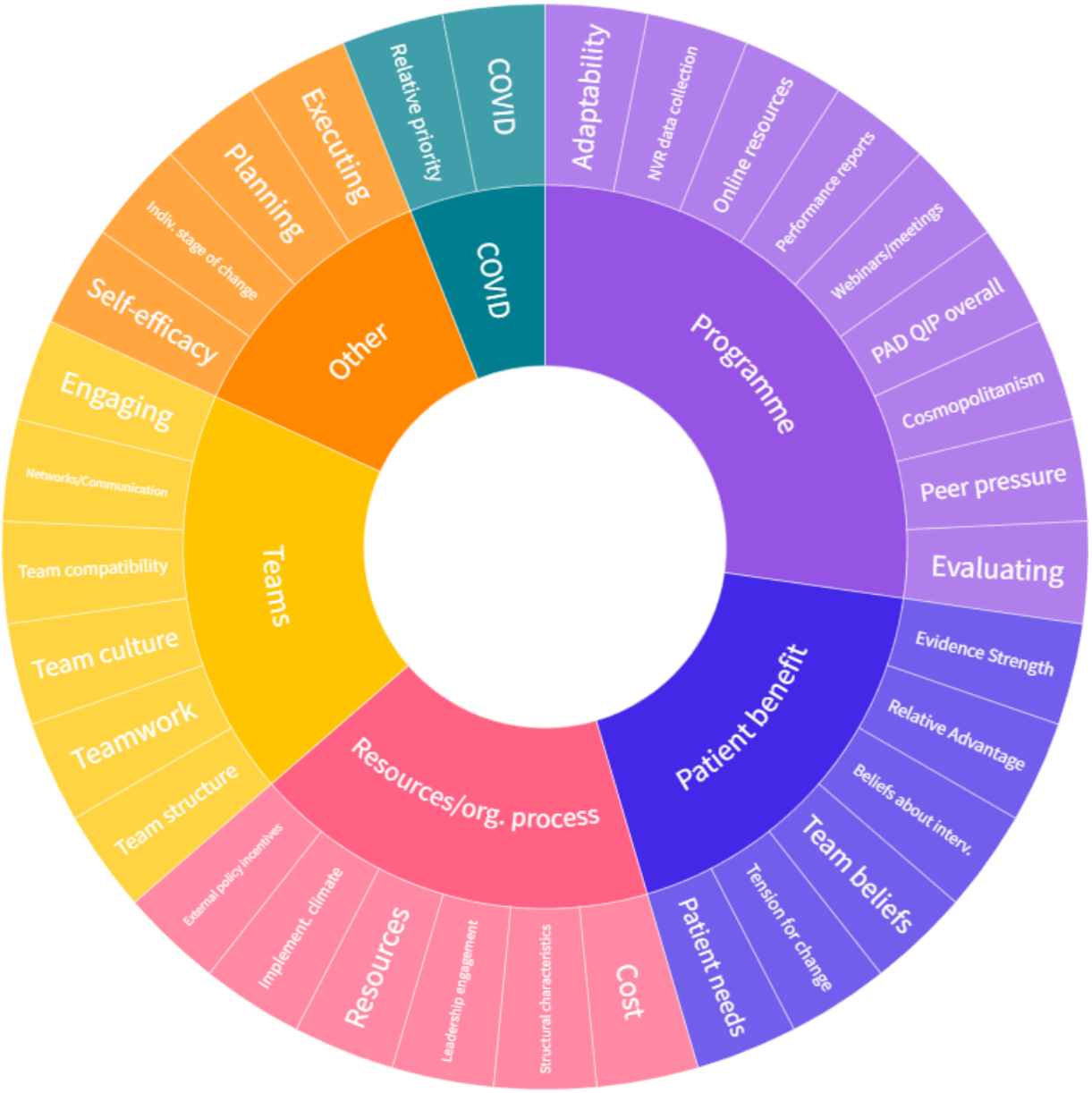

Figure 21 – Final themes and their corresponding CFIR constructs

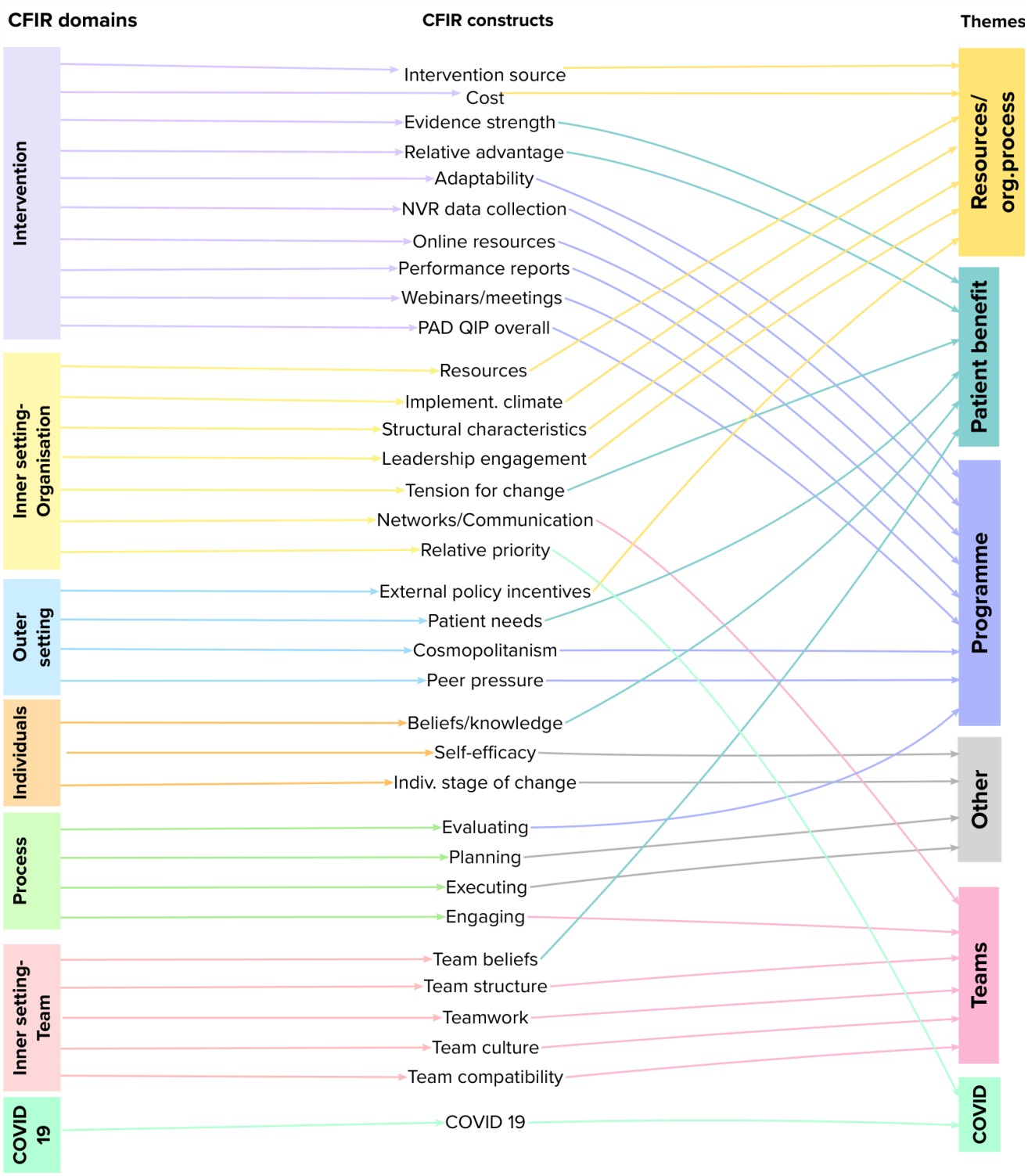

Figure 22 – Relationship between CFIR domains, CFIR constructs and themes

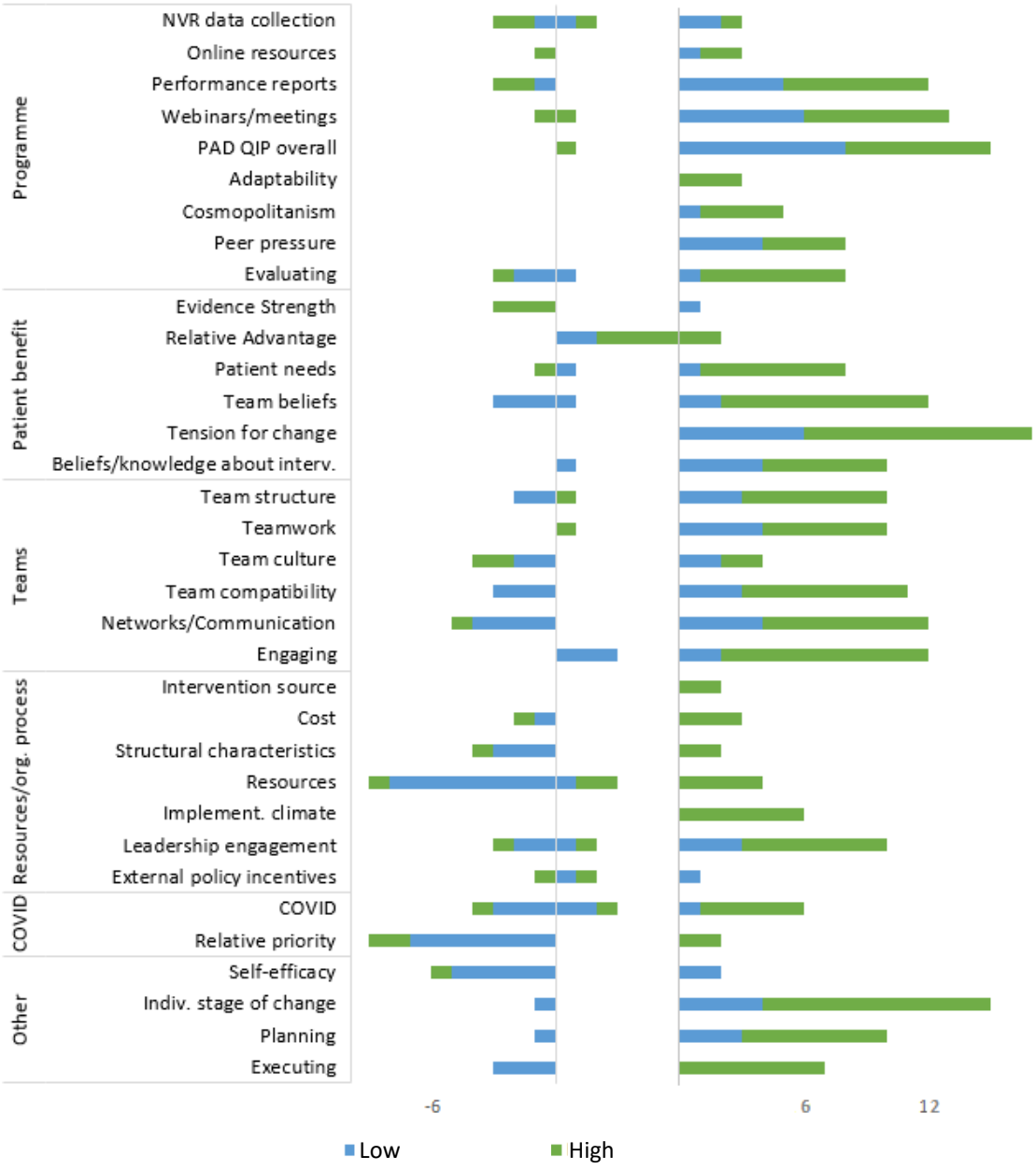

Figure 23 - Rating of CFIR constructs in high (green) and low (blue) implementation facilities

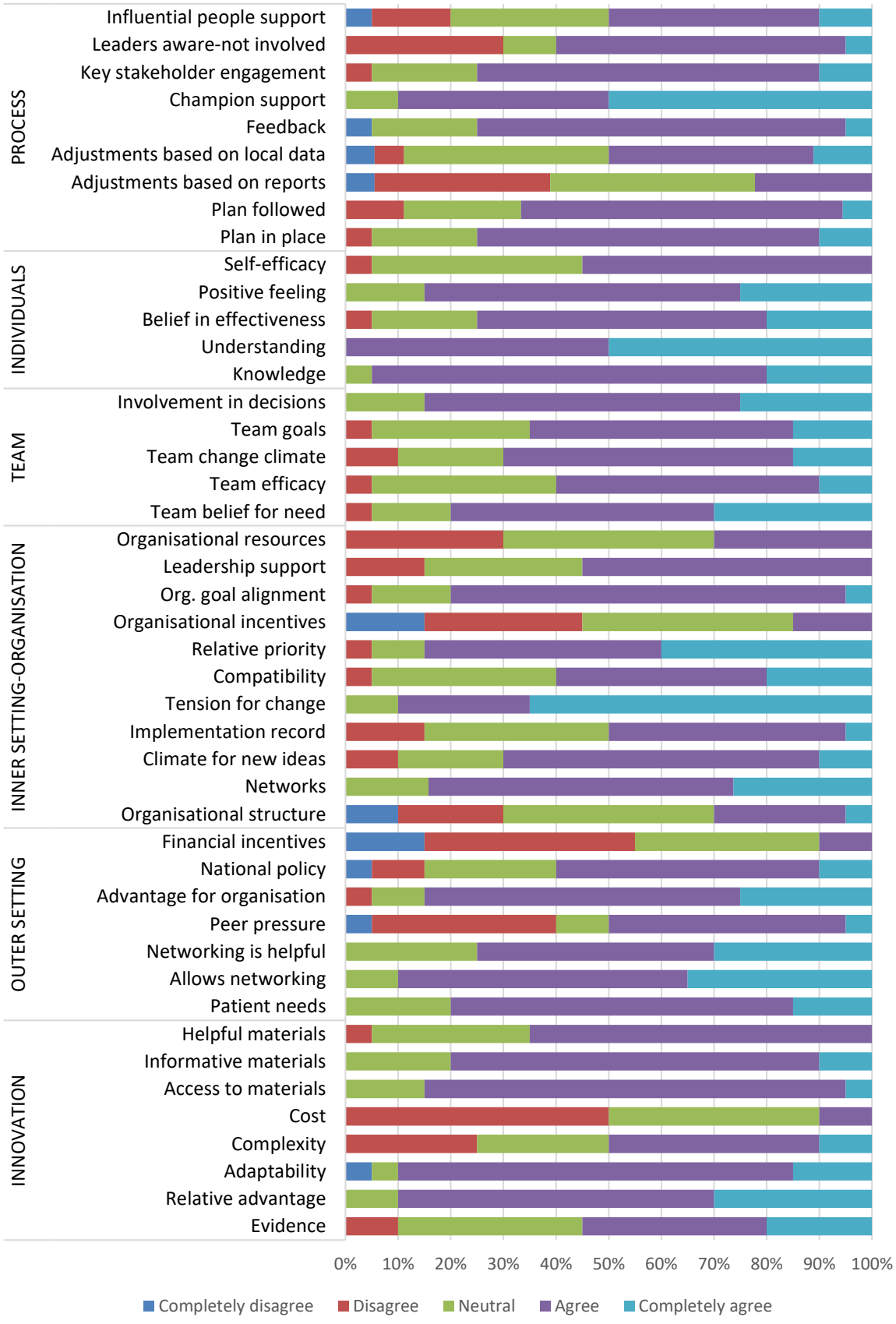

Figure 24 – Illustration of the results from the online survey

Table 30 – Results from the online survey

		Completely disagree	Disagree	Neutral	Agree	Completely agree	Total responses
INNOVATION	Evidence	0	2	7	7	4	20
	Relative advantage	0	0	2	12	6	20
	Adaptability	1	0	1	15	3	20
	Complexity	0	5	5	8	2	20
	High cost of changes	0	10	8	2	0	20
	Access to materials	0	0	3	16	1	20
	Informative materials	0	0	4	14	2	20
	Helpful materials	0	1	6	13	0	20
OUTER SETTING	Meets patient needs	0	0	4	13	3	20
	Programme allows networking	0	0	2	11	7	20
	Networking is helpful	0	0	5	9	6	20
	Other organisations influenced participation	1	7	2	9	1	20
	Advantage for organisation	0	1	2	12	5	20
	National policy	1	2	5	10	2	20
	Financial incentives	3	8	7	2	0	20
INNER SETTING - ORGANISATION	Organisational structure	2	4	8	5	1	20
	Existing networks	0	0	3	11	5	19
	Climate for change	0	2	4	12	2	20
	Implementation record	0	3	7	9	1	20
	Tension for change	0	0	2	5	13	20
	Compatibility	0	1	7	8	4	20
	Relative priority	0	1	2	9	8	20
	Organisational incentives	3	6	8	3	0	20
	Organisational goal alignment	0	1	3	15	1	20
	Leadership support	0	3	6	11	0	20
	Organisational resources	0	6	8	6	0	20
TEAM	Team belief for need	0	1	3	10	6	20
	Team efficacy	0	1	7	10	2	20
	Team change climate	0	2	4	11	3	20
	Team goals	0	1	6	10	3	20
	Involvement in decisions	0	0	3	12	5	20
INDIVIDUALS	Knowledge of programme	0	0	1	15	4	20
	Understanding	0	0	0	13	13	20
	Belief in effectiveness	0	1	4	11	4	20
	Positive feelings about change	0	0	3	12	5	20
	Self-efficacy	0	1	8	11	0	20
PROCESS	Plan in place	0	1	4	13	2	20
	Plan followed	0	2	4	11	1	18
	Adjustments based on reports	1	6	7	4	0	18
	Adjustments based on local data	1	1	7	7	2	18
	Feedback shared with team	1	0	4	14	1	20
	Champion support	0	0	2	8	10	20
	Key stakeholder engagement	0	1	4	13	2	20
	Leaders aware-not involved	0	6	2	11	1	20
	Influential people support	1	3	6	8	2	20

5.3.3 The Programme

The opinion of the interviewees about the programme overall was largely positive. Interviewees commented on several aspects of the programme itself that were beneficial to them. One of the most important aspects was thought to be the ability to compare themselves with peers, and this took the form of benchmarking and external monitoring. These were considered critical facets of the intervention in and of themselves, as external drivers to ensure improvement work was enacted. A surgeon from Centre J commented that the programme added a stimulus *"because you don't want to go to the next meeting with nothing to show for yourself."*

Other surgeons commented that they found it useful to observe the progress of other centres towards the implementation of the intervention. Interestingly, the idea of peer comparison served as a lever for some participants to apply pressure on colleagues and management within their centre to gain resources and drive change forward. A surgeon from centre B mentioned:

> *"I think the peer comparison is a benefit as well because that allows us to go to Trusts and say you know, this is where we need to be heading really."*

Some interviewees used the notion of being part of a large national quality improvement programme – where they were explicitly being compared with others – to draw the attention of management and the wider organisation to the programme:

> *"I think the fact that it's a national quality improvement program means that you will get support within the organization, support within the department because when it's raised at a national level, the degree of managerial support… it provides a drive to the institution to get involved." (surgeon, centre H)*

Whilst external benchmarking and monitoring led to an air of overt comparison and sometimes pressure to perform, the creation of a "Community of Practice" through the collaborative meetings was valued for its collegiality and ability for interviewees to form new connections with others working in the same field. Participants talked during their interviews about the value of knowledge and experience being exchanged and being

able to discuss problems and potential solutions with others who were facing similar issues. Several participants talked about taking interventions that were trialled in other centres and applying them to their own. A specialist nurse from Centre D stated that changes implemented to improve that centre's referral program were inspired from knowledge gained elsewhere. Others talked about feeling reassured that they weren't the only ones struggling. A surgeon from Centre A put forward a positive opinion of the community of practice:

> *"We certainly have very much enjoyed being part of the community who are trying to improve things and coming along and listening in to the way that other people are doing things. You always hear of different ways that may be appropriate for you as a unit to deliver. So I think that's what's been good about it, you know, getting to know other people and how they've been approaching the solution. So if nothing else, it's that joint, sort of, approach and feeling that everybody is pulling towards the same thing and that everybody's units have got similar problems, but people are just trying to find novel ways of getting around those issues."*

The networking opportunities with colleagues from other organisations in the programme, their help with implementation, and the organisational benefits from participation in the programme were also supported by the good agreement with these statements in the online survey (Figure 24, Table 30).

Interview questions also assessed opinion regarding the use and value of the four main elements of the programme: the data collection process, performance reports, quarterly meetings (online or in person) and online resources provided to all centres.

Data collection process

Participants felt that data collection on performance was important to inform and understand baseline activity and to monitor progress. Many participants commented about the fundamental importance of accurate data in order to be able to demonstrate not only the problem but also its potential solution. A surgeon from Centre I said: "Y*ou need the data to be able to demonstrate a problem and demonstrate a solution. The data is vital, so the database is without doubt a vital component to it [the programme]"*.

Despite acknowledgement of the importance of high quality data, some interviewees felt that data collection was time consuming and potentially cumbersome, often requiring administrative staff to perform data entry tasks. When these staff were not available, adherence problems often occurred:

> *"It's become a little bit more cumbersome, the data entry, and I know my outcome, completing the thing now is pretty poor…I do not have a data handling band three (staff) or something to do it for me." (radiologist, centre C)*

Some participants highlighted the potential impact of low case ascertainment and unrepresentative data, and also the lack of clarity associated with some database items, predisposing to the entry of erroneous data:

> *"Some of the things that have recently come on it are unclear. […] I think it's subject to a lot of confounders which might make the data a little patchy and because it's a compulsory field, I have to put something in." (radiologist, centre C)*

Performance reports

The programme performance reports were considered helpful for monitoring and benchmarking, alongside seeking resources from colleagues or funding from management. The concrete nature of the information in the reports was useful, especially as leverage when trying to obtain support to implement changes. A surgeon from Centre K discussed this:

> *"I find the reports are a very useful thing to take to our management when we're trying to get support for implementing changes.[…] Having the data in front of us in black and white, you can't argue with that, can you? It's difficult to ignore it when it's presented to you in a very graphical, easy to understand format, you can't argue, "Oh no, we're doing all right, we just carry on with what we're doing", when you can see quite clearly we're not achieving the targets… It gives us some traction with pushing our cases forward."*

However, some questioned the reliability of the reports due to the data collection and quality issues, and the variability in centre progress along their QI journey.

"It's useful you sending the metrics to us, but I know that relies on how much information you get from us, and I don't know if we're giving you enough information at the moment, to be honest, for that to be accurate assessment of where we stand. So it's been difficult to know how well or how badly we're doing frankly." (radiologist, centre F)

The dichotomy of opinions on the performance reports was also captured in the online survey, where despite most respondents finding the reports and the data collection system very useful (n=12, 60% and n=13, 65% respectively) or moderately useful (n=8, 40% and n=6, 30%) (Figure 25), not many agreed that they made adjustments to their plans based on the reports; more did so based on locally collected data.

Quarterly collaborative meetings

The meetings were viewed as an opportunity to learn from others, share examples of good practice and meet people with a similar mindset to discuss common challenges and solutions. During the meetings, a representative from each centre delivered a presentation on their progress and the changes they had implemented at their centre. Supporting this positive view, the meetings were rated as very useful by 60% of the survey respondents (n=12) and moderately useful by 35% (n=7), while one had not attended. A surgeon from Centre F discussed the benefits of the meetings:

"It's definitely good, because you know, fair enough for me to sit down and think, "oh I'm doing a fantastic job", but I may not be doing a fantastic job, and somebody is obviously already invented that and it would be good to see how different units are addressing the issue, because it's almost as this classical saying that there are different ways of skinning a cat, it can be opposing different ways to achieve the target that you need…If we are trying to do something similar and they actually found it not so helpful then there's no point in repeating the same thing."

There was a general preference for in-person meetings, where participants had the opportunity to talk informally or "*behind the scenes and during lunch, share experiences and share disasters as well*", as a surgeon from centre E stated. However, some

participants preferred online meetings, because they did not have to travel or cancel clinics or other work in order to find the time to attend.

The main criticism about the quarterly meetings pertained to the content becoming repetitive, as some units were making slow progress, and therefore no news to share, whilst others had established progress, which did not vary significantly between meetings.

> *"I think some of the situations maybe don't move on as quickly as we would like and therefore you get quite repetitive feedback from some centres. And I know some centres are very well established and they don't particularly have much to add each four months." (surgeon, centre D)*

Online resources

Few interview participants commented on the online resources and when asked directly about them stated that they had not engaged with them. More information on the usefulness of the online QI resources was provided in the online survey, where this element had the lowest rating, with 4 respondents not having used them, and the rest being equally divided in finding them very useful (n=8) and moderately useful (n=8) (Figure 25).

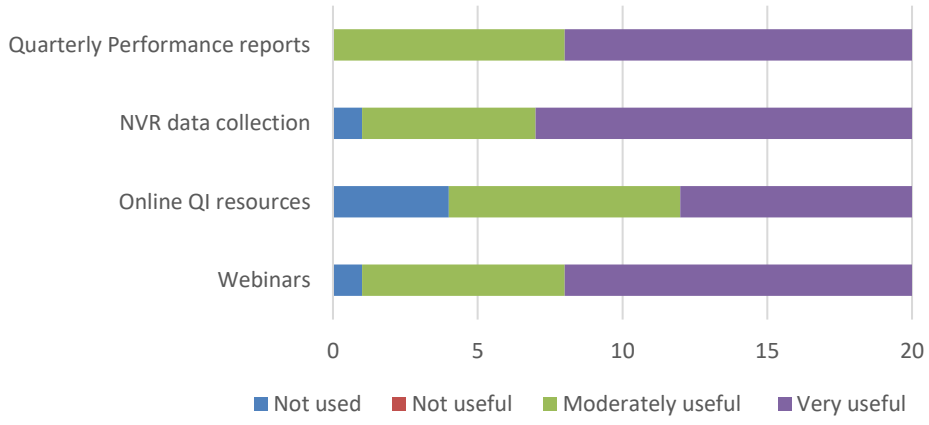

Figure 25 – Usefulness of programme components

5.3.4 The benefit for patients

A prominent theme in interviews with both high and low implementation centre participants was the importance of the problem that the programme addressed for patients, and therefore the existing "tension for change". This is illustrated by the word frequency map created from the interview transcripts (Figure 26). The participants and their clinician colleagues agreed that the delays in treatment of patients with CLTI was a "major problem" and they were committed to participate in this programme to improve understanding and resolve the causes of delays. Participants also reported that CLTI forms a large proportion of the vascular workload, but not enough time is invested on it, so they were eager to change this.

> *"We all agreed that this was a problem that we had that was an important problem. And it was a problem that we could identify some causes of or factors contributing to and for many of those factors there was a fairly straightforward easily implementable solution." (surgeon, centre B)*

> *"The decision to participate really is that we have an enormous workload of PVD (peripheral vascular disease), and I think it's been underrepresented in what we do and what we invest our time in." (surgeon, centre H)*

The focus on patient needs and how the interventions addressed them was central in the argument for their uptake and was perceived as a facilitating factor. Participants felt that "*patients are waiting a very, very long time*" (surgeon, centre E), therefore achieving the target was "*extremely important*" from a patient perspective. They also believed that the programme was beneficial for patients because "*they have the opportunity to be assessed, investigated and treated much more expectantly,* […] *they get a better service*", as a surgeon from centre B mentioned. Other members of the team concurred:

> *"The main thing why we wanted to get involved is to improve the pathway, to get the patients seen, to get them treated, just to be recognized that this is a major problem, that these patients are waiting for months." (specialist nurse, centre D)*

"Yeah, I think from a patient perspective they are extremely important. Ideally every patient in the country should be within that target, but unfortunately, as you're aware, the NHS is where it is and we were never achieving this target, at least pre COVID. […] I think the most important thing that happened was a recognition, which was there already amongst clinicians, that it is a no brainer that these are the patients that require our input first." (radiologist, centre B)

Participants, especially from the high implementation centres, also discussed the relative advantages of the new interventions over previous approaches. The changes were recognised by their colleagues and other stakeholders as *"improvements to the clinical service and the patients" (surgeon, centre A)*. The changes overall provided faster access to assessment, imaging and treatment for patients, who were treated according to their pathology and the evidence-base rather than the availability of resources. Clinicians felt they were managing patients in a more open, efficient and multidisciplinary way, which complied with national guidelines. For example, the urgent one-stop clinic offered patients a complete workup on one visit, the daily MDTs provided a space and time for effective, structured, succinct discussions and new online referral systems allowed better monitoring of referrals.

The overall positive attitude of individuals towards the programme and the changes was also indicated in the survey responses, with most respondents having good knowledge of the programme, understanding why it was adopted in their organisation, being involved in the decision-making process and having positive feelings about the changes (Figure 24).

The beliefs of the team about the intervention and acceptance of the changes was an important differentiating factor between high and low implementation centres, with leads from low implementation centres having more difficulties convincing their colleagues about the benefit of the intervention. A surgeon from low-implementation centre K said: *"Some of my colleagues are like, "I don't know why we're taking part because we're not a leading centre" or whatever".*

Contrarily, in high implementation centres, even when some changes were inconvenient or not compatible with previous ways of working, the team saw their benefit for the

patients, and therefore the changes were easier to establish and sustain. Two surgeons from high implementation centres illustrate this in their comments:

"I guess again, it's the initial thing of "is this more work for me?", the concern about being swamped, and then once you start getting into it, I think as long as you can continue to see benefit for patients, people are prepared to go along with it" (surgeon, centre H)

"it was a major problem, a major headache. So you provide a solution to a headache which makes everybody's life easier and they will embrace it. We got buy-in from all our colleagues, even those who didn't really have much of an interest in lower limb. When people started to realise the benefit, then it's very difficult not to agree to partake." (surgeon, centre I)

The findings from the online survey are concurrent with these views, as most respondents agreed that there was a strong need for service changes to shorten time-to-revascularisation (completely agree n=13, agree n=5), which was also understood by colleagues and stakeholders (completely agree n=6, agree n=10), and that the new practices were better than previous ones (completely agree n=6, agree n=15) (Table 30, Figure 24).

Despite the overall relative advantage of the interventions, some negative aspects were also mentioned by the interviewees, such as the lower number of patients seen in these clinics, the reduction of elective slots (in exchange for the increase in urgent ones), and the inconvenience that patients faced when they had to travel a long distance to the arterial centre for the urgent clinic. It was also recognised that patients referred to peripheral hospitals still waited much longer than the patients referred to the arterial centre, due to the limited resources in terms of staffing and clinics at those hospitals.

"I think there's still mixed feelings across the department. I think there are some Consultants who feel it's not a very good use of consultant time because in a morning in a routine consultant clinic we would see more patients. So some colleagues are more keen on it, other colleagues are less keen on it." (surgeon, centre D)

Finally, despite the positive aspects of the changes for patients and staff, some participants expressed their uncertainty about the evidence supporting the interventions and their effect on long-term patient outcomes, such as amputation rates. Interestingly, the lack of evidence was only highlighted by high implementation centre participants. Even though high quality evidence was lacking, there was clinical consensus among the participants that the recommendations being implemented in practice were reasonable. As a surgeon from centre E mentioned:

"I think that they are made-up timelines and they are very aspirational, but I totally agree with them and we see in our units that patients that don't meet those timelines actually have worse outcomes. I cannot really demonstrate it with numbers, but this is what we're seeing and definitely this is the feel amongst all the colleagues in the unit."

"I think the evidence support for them is not great, but I think the evidence in peripheral arterial disease generally is not great because it's such a heterogeneous group of patients. But I think it accords with what most sensible vascular surgeons would feel. This is a time sensitive disease and the time scales that were suggested in terms of the 5 days and the 14 days I think were sensible. I think that we can't say anything more than that, 'cause we don't have the evidence to support it, but I think most vascular surgeons would agree with that, and certainly I think they're reasonable." (surgeon, centre B)

Figure 26 – Word cloud depicting the 100 most frequent stemmed words present in the interview transcripts. It is a visual representation of word frequency, with more frequently used words having larger font size.

5.3.5 The role of the team

Team structure, team compatibility and networks within the organisation, as part of the "Inner setting" domain of CFIR, were differentiating factors between high and low implementation units, while teamwork and engagement with the process were viewed as facilitating factors by all participants. The presence of a group of "*like-minded individuals working together*" with a common goal was considered by many interviewees as the main facilitating factor of the implementation process. This collective buy-in to achieve common goals and priorities enabled the centre leads to make changes without facing opposition and obstacles.

> *"You've got to believe as a unit that it's good for the patient. And if you accumulate a critical mass, things will happen. If not everybody agrees this is a priority, if seven of us think there are seven different priorities, nothing will get done. When you are trying to bring change, you need all or at least a majority of your colleagues to feel that this is important and this change will help the patient. It's the thing about buying into it. So I think having a core team working towards the same cause is always the best way to get anything done. You cannot win on your own in the NHS." (surgeon, centre F)*

> *"So I think having a team that was invested was the best thing and having a team that's willing to all pool work and just to get it done I think is useful as well. Nobody was saying "oh I have to do this bypass or I have to do that or I'm not doing this or that". Everyone was working together." (surgeon, centre D)*

The programme also aligned with the priorities of some vascular teams and was compatible with work they were keen to do or were doing. According to a surgeon from centre A:

> *"it was something that we were always keen to be involved with as it was rolled out and have been keen to try and improve outcomes with lower limb revascularisation anyway, so it was a natural thing for us to do".*

The teams generally involved consultants, specialist nurses, ultrasound technicians, managers and QI experts and expanded across both vascular and radiology departments. The structure of the team and the level of participation of colleagues in the decision-making and feedback varied between teams and strongly influenced the success of implementation. In some centres, such as centre B, everyone contributed to changes according to a surgeon, *"the interventional radiologists secured same-day CTA and MRA slots, vascular nurses agreed to staff the acute clinics, the ultrasound technicians bought into it"*. They describe the structure of the team and the involvement of team members in more detail:

> *"We have a very good team in that it functions as a team here. So the team is formally led by a clinical lead, but in practice most decisions are made collectively on the basis of discussions, both formal and informal across the unit, and that includes with the vascular nurse specialists and the IR teams. We don't have individual sort of silos. We talk to each other, we bounce ideas off each other and we generally come to collective agreements, and that's a feature of the team here."*

In other centres, two or three people led the change and others followed (top-down approach), as others were enthusiastic but reluctant to take action. A surgeon from centre A describes this approach:

> "*They're enthusiasts and are very good at rallying the troops, they're not so good at the small detail. So they're very happy to be involved and they're very enthusiastic about change and they're on board with the ideas that we've got, but actually delivering it, effectively the group that we have in terms of bringing about most of the change is a slightly top down group."*

Finally in a handful of low implementation centres no other team members were involved in the planning and execution apart from the lead.

> *"I ought to have someone else on board with me, 'cause I'm the only one from [centre name] that has ever attended those meetings." (surgeon, centre J)*

There was also varied involvement of interventional radiology and other specialties, such as diabetes specialists, anaesthetists and care of the elderly physicians. The nature and quality of professional networks and communications between departments within an organisation played an important role in the implementation efforts. Involvement of interventional radiologists was crucial for the programme, because they were responsible for treating patients with endovascular methods. If their support was not gained, patients awaiting endovascular treatment faced longer delays compared to patients awaiting open surgery, who were treated by vascular surgeons. Good communication and collaboration with interventional radiologists was reported in most of the high implementation centres, some of which had established close working relationships prior to the start of the programme and *"regarded the IR Consultants and the nursing and support staff in IR as part of the team",* as a surgeon from centre B stated. Others also supported the importance of this factor in facilitating the implementation of changes.

> *"So the nice thing is that our relationship with IR was sorted and established way before any of this has happened and we work as a team." (surgeon, centre E)*

> *"I think it's a having a core group of endovascularists, and I use that term specifically in terms of endovascular surgeons and endovascular interventional radiologists. Having a core group of collaborative colleagues, who are kind of trying to drive through these changes, that's the biggest positive from this.[…] This is about us collaborating and improving patient care pathways. That's historically where the barriers have been. It's been a collaborative project, about how we can just try and streamline these patients through a service." (radiologist, centre F)*

However, vascular leads in some centres had difficulty engaging IR colleagues in the implementation effort. They attributed this to the different priorities of the radiology department and the lack of time to engage with QI work due to high clinical workload. The lack of support from IR hindered the implementation of changes considerably, with four of the 5 centres that did not involve IR being in the low implementation group.

> *"So we have good colleagues in radiology, but their priorities are not necessarily the same as ours" (surgeon, centre K)*

"I mean we've tried to encourage that here by ensuring the Radiologists understand and are on board with what the ideas of the project are but they give it, shall I say, a limited amount of headspace when they're trying to deal with everything else they've got to deal with. I think that as a unit, if we could have got the radiologists to come along and attend, that would have been better, you know. […] (The Interventional Radiologists) They've been very stretched so that they sort of see attending these kind of things as luxury and that's the problem. And when you need a team approach that's difficult." (surgeon, centre A)

A radiologist from centre B ascribed this attitude to the fact that *"many times there is no sense of ownership on the interventional radiologists in order to deliver this short timeframe*" and that even though they understand its importance, they could not see the benefit of participating in a program like this.

When there were differences of opinion or conflicting priorities within the team, it was difficult to gain consensus and implement any change to the service delivery or ways of working. In these centres, the main barrier to implementation was the lack of buy-in from clinical groups, as every step was met with obstacles. Some centres managed to overcome this, as a surgeon from centre C discussed:

" With the urgent clinic slots, some people were slightly reluctant. Some people have slightly different opinion, but everybody accepted it. […] But getting everybody to agree on a way forward was the most difficult thing. We've done that, but that was the hardest thing probably. "

However, some teams were unable to reach an agreement about changes to implement and a way forward, as the issue of different approaches, personalities and priorities could not be resolved.

"I think the main difficulty is currently gaining a consensus opinion from colleagues that this should be a priority in the changes that we need to make within the unit. We've found that across all other changes we're trying to introduce, everything seems to be discussed, everyone thinks it's a good idea, then someone who thinks it's not a good idea puts in a different… and round you go again. There's all these things on the

agenda and month after month, and there are great ideas for improvement, but none of them ever actually happen." (surgeon, centre K)

This was associated with the culture within the team and individual characteristics of team members. For example, the resistance to change by some team members led to objections to interventions that impacted on people's ways of working.

"There's always, you know, I wouldn't say brick walls, but certainly obstructions put up to any form of change where people feel that their normal way of working is being impacted. […] So every single step was met with barriers in some shape or form, whether or not it was just people being difficult, or whether or not it was significant barriers to the way in which things were planned to be done, and each of those had to be overcome. And people not wanting to participate, because it changes the way in which they practice." (surgeon, centre I)

It was not possible to capture the level of teamwork and the involvement of groups of healthcare professionals in the implementation process in the online survey. In general, there was strong agreement among the respondents that they were involved in the decision-making process about the programme and that they had good working relationships with other departments in their organisation (85% agreed with each statement). However, the responses were more neutral regarding the reception of new ideas by their team (team change climate) and the confidence of team members in their ability to make changes (team efficacy), especially in low implementation centres (Figure 24).

5.3.6 Resources and organisational processes

The scarcity of resources was one of the main barriers to implementation of changes according to participants and a differentiating factor between high and low implementation centres. In addition to material resources, such as bed capacity, they highlighted staffing issues in terms of vascular and interventional radiology Consultants as well as radiographers, vascular specialist nurses and operating theatre nurses. The shortage of imaging slots, operating theatre lists and interventional radiology lists limited the ability of vascular teams to review, investigate and treat patients in a timely

manner. Some centres experienced a further reduction to their usual bed and operating list capacity during the implementation period, due to the allocation of hospital beds to medical specialties during the COVID-19 pandemic and due to relocation of the vascular centre to a different hospital.

> *"With the best will in the world, if there's not the rooms available or if there's not the interventional nurses to run the rooms, it doesn't matter that we know the target is five days, if there's no one to actually do the procedures, we're kind of stuck." (surgeon, centre K)*

The lack of time to engage with quality improvement work, collect data and review the patient pathways was also mentioned as a significant barrier to change.

> *"Time. Aspirationally, we want to be doing things like participating fully in quality improvement both locally and nationally, and it's really important that you've got a clinical lead who's really engaged in it and helps deliver it. So that's the most difficult thing, is the pressure of time juggling those things. I think that's the biggest barrier to a lot of our change."* (surgeon, centre A)

Despite that, most of the high implementation units managed to obtain funding to employ a CLTI pathway coordinator, while others achieved changes by reallocating existing resources, utilising existing staff and clinic space, so the overall cost of the interventions for the organisation was considered minimal. These views on cost were also observed in the survey responses, where most participants disagreed with the statement that the changes were associated with high costs for the organisation, with only 2 participants agreeing.

The ability to find the necessary resources by repurposing existing funds or negotiating with management for additional ones was one of the defining characteristics of the high implementation units compared to the low implementation ones.

> *"We've just shuffled the cards. We haven't asked for any more resources, we're just trying to use the resource that we've already got a bit more efficiently." (surgeon, centre C)*

The resource allocation was more challenging when the structure of the organisation included multiple peripheral network hospitals and covered a large geographical area. In these cases, participants admitted that the quality of care the patients received in network hospitals was not as good as the main arterial centre, because there was not enough clinical staff to cover frequent clinics at those sites and it was difficult to track patients' progress and their investigations remotely. Consequently patients had to wait longer for an appointment in clinic. Most participants felt that they were unable to address the problem of longer waiting times for peripheral sites during the implementation of the programme, but this was included in their plans for the future.

To gain support and resources from management, the local leads stated that they highlighted the national reach of the programme and the source of the intervention being a professional society. However, the lack of financial incentives made it difficult to gain more resources for the vascular services for the implementation of changes and convince all stakeholders to engage.

> *"I think the only way that you can moderate behaviour of senior management is through the financial targets and incentives. And a target such as a two-week wait or four or five-day wait means nothing to them unless it comes with a financial penalty for not meeting that target. […] Yes, they don't want to be last in the whole country but they're very happy to sit comfortably in the bottom third if they're not going to be highlighted and picked out in the national press." (surgeon, centre B)*

The absence of financial incentives, organisational incentives and organisational resources for the implementation of changes was also noted by the survey respondents, as very few reported their presence (n=2, 3, and 6, respectively) (Figure 24).

Even though reducing delays to treatment for patients with CLTI was considered a priority for clinicians, it was not always perceived as such but management teams. The scarcity of available resources was often associated with the lack of organisational leadership engagement and the overall implementation climate in the organisation.

Implementation leads sought support at different levels of the organisation. A small number had discussions with senior management. As a surgeon from centre I suggested,

"Getting money out of the NHS is difficult, there's no point talking to the junior management, you may as well go straight to the senior management, you need to get the Trust Board and the executives on board". However, a low implementation centre approached senior management to seek support and did not receive it. The interviewee explained that the managers were busy with multiple items on the agenda, including clinical issues that required immediate attention such as rota gaps, and there was no progress with the quality improvement projects.

The majority of participants mentioned that they did not approach the senior management and opted to gain approval for the changes at departmental or divisional level. There were various reasons for this approach. Some felt that the Trust leaders were already very busy dealing with requests from multiple departments:

> *"We're amongst a large group of people seeking support from them and you know, it's a constant thing, it hasn't changed because of the PAD QIP. But in terms of the issues that vascular surgery generally has to face, we've been pushing those for years. Unfortunately, so is every other specialty and the management structure within the Trusts are fielding all those issues and generally batting them away to you know, to a… the To Do List basically." (surgeon, centre B)*

Another group felt that they had adequate support at departmental level, and did not engage with senior leadership because they did not need to.

> *"I don't see in my Trust there is managerial barriers to change, and I know which doors to open to unblock things and we've done that, we've escalated where we needed to escalate and we've got an absolutely fantastic divisional director in sort at managerial level." (surgeon, centre A)*

This was often the case when vascular surgeons or vascular interventional radiologists with an interest in the programme occupied leadership positions within the department, division or organisation, and therefore were able to approve the required funds and resources. In these instances there was a favourable implementation climate, which was perceived as helpful and not obstructive, and was a factor only discussed as facilitator by high implementation centre representatives.

"I think our immediate management are supportive. To put it this way, we haven't had any resistance that we had to go to the senior management level at all. We haven't encountered anybody stopping us from doing what we wanted to do and that's when we approach the senior team to say we need some more resources to do it." (surgeon, centre F)

Others did not approach senior managers because they thought that they would be unhelpful, based on their previous experience, as described by a surgeon in centre C:

"Our current senior management is very hands off and doesn't engage much with us, so the senior managers have been pretty hopeless."

5.3.7 The polarising effect of COVID-19

The COVID-19 outbreak occurred a month before the implementation phase started, therefore the programme was carried out during the pandemic period. This had important implications for the centres, regarding the tension for change and organisational priorities. The perception of the COVID-19 pandemic as a facilitator or barrier perhaps depended on the light under which the changes were viewed. Some of the high implementation centres aligned the purpose of the changes, which was to reduce time from admission to procedure, with the overall efforts of the organisation to minimise time patients spent in hospital. Others did not use that argument, and therefore the aims of the programme were perceived as a competing priority, mainly in low implementation centres. The two approaches are described in greater detail below.

Many participants stated that the pandemic was an opportunity to make changes, as it created the need for interventions to minimise the time patients spent in hospital, which aligned with the aims of the programme. Guidance issued during the pandemic recommended that only patients with urgent conditions were admitted and operated on, with elective work being deferred. CLTI is considered an urgent condition, so the focus on acute care and the cancellation of elective work increased the availability of resources, such as access to clinic and operating theatre for patients with CLTI.

"Most of this was driven by COVID. So we were tasked at the start of the COVID outbreak, with streamlining the care of acute patients so that we didn't have patients in hospital for any longer than was necessary, and we concentrated on dealing with patients who had threat to life and limb and put aside all elective surgeries. So we had the opportunity as a result of COVID, to make some significant changes." (surgeon, centre B)

"COVID had mixed efforts. I know a lot of places were saying how little we did. We actually were the biggest users of theatre, because our patients you can't really send homes. So we were being prioritized for emergencies. It's had a massive effect on the waiting list times for the non-acute patients, but we actually were getting a lot of the acute stuff done." (surgeon, centre G)

It also allowed clinicians to make decisions about the prioritisation of patients based on best practice and patient clinical needs, not externally imposed performance targets. For example, some centres introduced an urgent clinic or increased the frequency of existing CLTI clinics. As a radiologist from centre B mentioned, "*COVID gave us the liberty as clinicians to decide what is good for our patients and also advise and take it forward*". Additionally, in some centres the resource allocation from the Trust management for the acute patients increased, in order to reduce the length of stay in hospital.

"Suddenly we had a directive from the Trust to clear the wards, reduce bed days, only admit people who were true emergencies. But we would need more resources in order to facilitate that, and lo and behold, they provided those resources. So COVID did have benefit for us in terms of input, source allocation and expediting that resource allocation. Things that would have taken us a lot longer to get permission or agreement to do, were literally done overnight." (surgeon, centre I)

Not involving middle management in the discussions during the COVID-19 period also expedited the decision-making and implementation process, as *"a lot of the middle management were working from home and this facilitated the direct talk with higher management and got things moving very quickly"* according to a surgeon from centre E. It also affected the attitude of healthcare professionals and other stakeholders towards change, as during the pandemic people were more adaptable.

"the biggest thing is that change happening quickly and sort of without having to negotiate massively with lots of different people about how to do things differently. And people were also prepared to do things differently." (surgeon, centre A)

"We knew what we wanted and then actually it took COVID to drive some of this change. […] It took COVID to break down some of those silos that everyone works in. I mean a lot of it has come back again, but we've got some of the things in place that we wanted." (surgeon, centre J)

However, others felt that the COVID-19 pandemic had an overall negative effect on implementation efforts. This argument was supported by the reduction in bed capacity, operating theatre and interventional radiology availability, and the loss of staff due to sickness/self-isolation, redeployment and burnout.

"We have had to reduce the number of IR lists because of staffing. The number of people self-isolating at various points has been prohibitive on running several lists in parallel. […] And then with the pandemic, people going off, people getting burnt out..." (radiologist, centre C)

This was possibly associated with the varying restrictions to clinical work that NHS organisations put in place during the pandemic. Some participants mentioned that the theatre capacity increased due to cancellation of elective work (centre I), while others that it decreased (centre F).

"Lots of other vascular procedures or other non-urgent procedures, AAA and that sort of things weren't being done, so the actual patients coming through for vascularization were taking priority." (surgeon, centre I)

"The negative is there is too much bed pressures all the time at the moment. The theatres that are available to us are less. So the beds are always full, recovery is always full, we have had to have cancellations a few times and obviously the waiting list has gone up." (surgeon, centre F)

Other reported effects of the pandemic included the lack of time to do QI due to competing priorities and loss of focus on implementation. As a radiologist from centre F

mentioned "*we had grand hopes to be able to focus on this and I suspect everybody is saying the same thing in that obviously since COVID it's fallen by the wayside*." A surgeon from centre K echoed this:

> *"I think it just took the focus off of all of the other pathways and all of the other quality programs and all of the other changes we were trying to implement, and it's been very hard. Because we totally lost focus."*

These competing priorities during the COVID-19 pandemic at organisational level also limited the engagement of the Trust leadership with the programme, as they focused on COVID-related issues and the constantly changing policies during the pandemic.

> *"I think also we need to try and escalate it to a wider audience within the Trust, and that's difficult, because frankly their focus is elsewhere at the moment and we tend to be left very much to our own devices in vascular. […] At the moment their priority is keeping COVID out of ITU and things like that, rather than actually trying to deal with these sort of issues." (surgeon, centre B)*

5.3.8 Other themes

Individual self-efficacy and stage of change

Nine interviewees stated that they volunteered to participate in the programme because they recognised the potential benefit for patients. The other 7 interviewees mentioned that the role was delegated to them due to their prior interest in PAD or their availability based on the distribution of departmental workload.

Some participants also mentioned that they felt they had not devoted enough time to the implementation of changes and others expressed their disappointment about not making changes due to factors beyond their control, such as the lack of resources, and their frustration because their ideas were not materializing.

> *"It's got to a point that you can put a certain amount of effort in, but then it's actually… what you need to happen isn't happening." (surgeon, centre G)*

> *"When I started I was all enthusiastic, and (a colleague) was like, in 18 months' time, you're going to be so fed up, because you're gonna realize all of your ideas aren't*

going to be checked, you're not going to institute anything, and so I've reached that point" (surgeon, centre K)

Process planning and execution

While describing the process of making changes, some participants mentioned that the change happened due to COVID without much planning, "*it almost happened*" (surgeon, centre F), or through informal discussions, "*really ad hoc*" (surgeon, centre C), while others held planning meetings with stakeholders to discuss about the changes. A surgeon from centre A mentioned the importance of the interventions being "sustainable and system-based", while a participant from centre B highlighted the role of the multidisciplinary team discussions:

"We had a multidisciplinary discussion about ways we could address our performance and which of the QIF proposals were the most important, and which of the QIF proposals we were falling down on. We identified the problems that we wish to solve and potential ways to solve that problem. " (surgeon, centre B)

To inform the decision-making process and identify areas that required improvement, some centre leads conducted audits and reviewed their baseline performance prior to making changes, while others did not follow a structured approach. A surgeon from centre I described the process of using data to decide what changes to implement:

"So we looked at a group of CLTI patients coming through, where the delays were, where the lack of what we would consider to be appropriate care, particularly that in terms of investigation, amputation, and so forth, and with that data we effectively figured out where we could have maximum impact with a certain amount of money that we had."

When plans had been put in place, some participants felt that they had addressed most of the problems identified at the planning stage.

"We identified the problems which we thought were important, we put in short term solutions where possible and long term solutions where short term solutions weren't possible, and have addressed the vast majority." (surgeon, centre B)

Others mentioned that their plans had to be adapted to the COVID pandemic. Most commonly a previously established CLTI clinic became a clinic for all urgent vascular

pathology, because all other clinics were cancelled. Some interviewees also expressed the importance of changing one thing at a time through a step-by-step process with "little wins often".

> *"We haven't tried to incorporate too many changes, we just want one thing at a time, so we haven't faced much resistance." (surgeon, centre F)*

5.4 Discussion

This mixed methods study identified barriers and facilitators associated with the implementation of the Peripheral Arterial Disease Quality Improvement Framework in NHS-based vascular services. Facilitating factors associated with the QI collaborative included the concrete timeframes, external performance monitoring, peer comparison and benchmarking, and involvement with a national programme which helped to obtain resources to implement changes. Learning from others, adopting others' ideas for change and sharing experiences was also useful. Accurate data on performance were considered essential for leveraging resources, but data entry was onerous and required dedicated staff.

The main factors that were viewed by participants as facilitating change were: a) the presence of supportive engaged "like-minded" colleagues and good inter-departmental networks that facilitated teamwork, b) a common understanding of the size of the problem (tension for change) and the patient benefit from addressing it, and c) the approval of changes and resource (re-)allocation with managerial support. Conversely, factors that hindered implementation were a) differing opinions about resource allocation within the team due to conflicting organisational and departmental priorities and individuals' resistance to change, b) lack of organisational leadership support and c) lack of resources (staffing, imaging and operating availability, bed capacity, time).

To our knowledge, this was the second quality improvement programme implemented in the vascular surgery setting. The first was the Abdominal Aortic Aneurysm Quality Improvement Programme (AAA QIP), a QI Collaborative of 90 vascular centres in the UK, delivered from 2010 to 2012, which aimed to reduce postoperative mortality following elective AAA repair[453]. The programme achieved its goal and factors that affected its

successful implementation included the active engagement of all key stakeholders and opinion leaders (vascular surgeons, radiologists, vascular nurses, anaesthetists, managers, patients), the organisational leadership support, the use of patient stories, the importance of the problem and existence of agreed national standards, the provision of data to attract additional organisational resources, and the role of collaborative meetings for reporting progress and sharing outcomes. The current study builds on the findings of the AAA QIP, by evaluating the factors that affected implementation using a determinant framework and implementation science theory, and offers suggestions for addressing barriers to improve future vascular QI studies.

The PAD QIP followed the collaborative approach operationalised by the Institute of Healthcare Improvement[301], which includes healthcare teams from multiple sites supported by a group of experts, coming together to address a specific healthcare topic, following a model for improvement that includes measurable aims and data collection on performance, and engaging in structured activities that promote collaboration, learning and sharing ideas and experiences[299]. Participation in the QI Collaborative was perceived as more beneficial than working alone to implement changes. Even though this study did not evaluate the quantitative outcomes of the programme, there is evidence that QI collaboratives are effective in improving the processes they address[299,300], and may be more effective than centres attempting changes individually[454,455].

The theory of change supporting QI collaboratives is that more progress in the implementation of changes is achieved with benchmarking and collaboration, whilst forming a "community of practice" [294]. This term was introduced by Wenger and refers to a group of people with a shared goal or problem, interacting often and learning from each other[456]. Participants in our study found the interaction of professionals from different organisations during collaborative meetings useful, reporting that it promoted sharing of knowledge and experience under the guidance of an expert team, as in other studies[304,382,457,458]. This phenomenon has been explained using transactive memory systems theory, according to which "a group is more knowledgeable than an individual"[459]. In this case, some centre leads had prior experience with implementing

changes to improve the CLTI patient pathway, and the collaborative events offered an opportunity for other participants to benefit from this.

Other elements of QI collaboratives documented as valuable include the measurement of baseline performance and feedback on progress to maintain motivation and seek additional resources[460] and sharing of performance among the teams that allows peer comparison[457]. Additionally, the legitimacy and national reach of the programme, demonstrated by its endorsement by a national professional body (the Vascular Society of Great Britain and Ireland), has also been reported as helpful in another study[382].

This study also provides insight into how the context affected participants' implementation. Context represents key elements of the environment in which an intervention is being implemented, and includes physical, social and cultural attributes of a clinical setting, such as leadership, organisational dynamics, resources, collaboration, as well as attributes of the healthcare system[244,366]. A review of implementation studies in secondary care found that context was the most important factor affecting the success of implementation[286], whilst the need to study how "context-sensitive" an improvement intervention is and understand which contextual factors affect improvement has also been highlighted[365]. A recent systematic review identified that the most important organisational features that influence implementation of evidence-based practices are: organisational culture, leadership, champions, resources, collaborative networks, teamwork, communication, evaluation, and feedback[283]. These factors are interrelated in complex ways, and leadership is a factors that influences the rest[283]. As the programme was implemented in 11 different vascular units, we were able to focus on the effect of contextual factors on the implementation process and its results, and discover how the participants perceived this context through the interviews. The use of the CFIR framework for the design and analysis of the study was beneficial in this respect, as it includes all the important factors highlighted in the systematic review.

Firstly, organisational culture describes the overall attitude of an organisation towards innovations, and can be manifested in various ways. Lengnick-Hall et al describes organisations as "Incorporators", those who make small changes to incorporate the

intervention in existing practices, “Early investors”, those who make substantial changes from the start and then maintain them, and “Learners”, organisations that make gradual changes through a continuous process of evaluation and improvement[461]. In our study, participants from high implementation centres reported a positive implementation climate receptive to changes, that was linked with presence of supportive departmental leadership and availability of resources.

The availability of resources in particular was mentioned by all participants and was mostly described as a barrier, due to lack of materials, personnel and time. In some centres, existing resources were re-allocated to the intervention, in others the teams managed to obtain additional resources, while the remaining teams were unsuccessful in finding the resources necessary to make changes. This is reflected in the literature, where many studies have reported the importance of financial resources and sufficient staffing levels with low turnover for the implementation process[283,458,462]. Staffing was particularly challenging in our study, due to redeployment and staff sickness during the COVID-pandemic. This staffing crisis led one of the centres to revert the changes they had put in place and played a detrimental role in the morale of the implementation team.

One of the resources discussed infrequently was the lead clinician time. Even though dedicated time for the local QI lead was highlighted as an important factor for success in other QI programmes[283,382], this was not brought up extensively in the interviews with leads from our participating centres.

On the other hand, all participants discussed leadership engagement with the programme. Reports on the influence of leadership in the success of QI collaboratives have been mixed. Most studies indicate a positive relationship between implementation of changes and transformational leadership style or leadership support[283,304,463]. The transformational leadership style is characterised by appreciation of other’s efforts, acceptance of different perspectives, inspirational motivation, and positive influence and promotes a supportive learning culture in the organisation, which is conducive for quality improvement and implementation of innovations[464]. Despite this, recent multi-organisation QI collaboratives have highlighted the lack of engagement of senior

organisational leadership as a common problem for local leads to overcome[458,465]. Similarly, hospital executive involvement was limited and with mixed effects in our study. In most centres the programme was discussed with departmental directors and managers but not NHS Trust leaders, as the participants either did not feel they would receive support or they were content with the support they received at departmental level.

Indeed the advantages of involving middle managers, sometimes referred to as first-level leaders, in QI initiatives have recently become apparent[463,466–468]. It has been purported that middle managers can act as "information brokers" between frontline staff and senior leaders, through securing top-level support for grassroots initiatives and encouraging clinicians to add QI projects to their workload[465]. They can also affect the implementation climate within a department and release much needed resources for QI projects[467,469]. Middle managers were supportive of the programme in the majority of high implementation centres and approved the changes proposed by the clinical staff. The centre leads did not expand on how they gained support from middle managers, but research indicates that availability of resources, stakeholder buy-in, organisational fit and patient benefit are elements that affect their decision to support innovations[468].

In surgical QI collaboratives in particular, stakeholder engagement outside the immediate surgical team is essential, as changes may need to be implemented to increase capacity in parts of the patient pathway that are not under the control of the surgical leads, such as access to imaging or theatre sessions[382]. To gain this stakeholder support requires shared understanding of the importance of the problem, and when absent, it is associated with low implementation success, as was shown in our study, and supported by others[286,382].

A major barrier to stakeholder support is the differing roles, priorities and accountabilities of professional groups, which may be related to a lack of understanding of the need for the intervention[286]. For example, a qualitative study exploring the barriers to the implementation of changes related to allied health managers' attitude to change found that they consider local data more influential than external evidence, the quality and applicability of which in their specific context is unclear, and show resistance

to change based on beliefs that change is difficult, avoidance of complaints and wish to maintain the status quo[470]. Similarly in our study, participants mentioned that addressing the delays to treatment for CLTI patients was not considered a priority for some management teams, despite pressure by the clinicians.

Additionally, we identified the important influence of teamwork on implementation efforts, which participants highlighted as a factor that facilitated change when present, and hindered change when absent. In the first systematic review of determinants of success in QI collaboratives, teamwork was found to be one of the few factors that increased short-term success, with teams that worked well together being more successful[304], supporting the findings of our study. Elements that represent good teamwork include clear and effective communication, good working relationships and the ability to solve problems together, and are especially important for projects that require the involvement of multidisciplinary teams[283]. We also found that team size and composition differed between high and low implementation centres, with similar findings reported before. The AAA QIP recommended that teams should consist of at least 3 members[453] while a curvilinear effect of team size on success has been demonstrated, with larger teams having a positive effect up to a point[471].

The beliefs and attitudes of the team members towards the intervention were also important. The perceived effect of the intervention on everyday workload, the additional demands arising from it and the disruption in the usual ways of working have been found to influence implementation success[462]. In this study, implementation leads introduced some changes by showing the patient benefit that derived from them. This justification was sufficient to overcome resistance to change from colleagues.

The social, economic and political environment of implementation, known as the “outer setting”, is also important. This setting includes guidelines and professional standards, inter-organisational networks, funding, external laws and policies, local infrastructure and the target population[282], but is seldom studied in depth in QI studies. However, the PAD QIP was implemented during the COVID-19 pandemic, which was perhaps one of the most influential factors in this study[367]. The pandemic had a widespread effect on the healthcare system, as it shifted the organisational priorities and altered the clinical

work of the participants[114,389]. In our study, the effect of the pandemic on the implementation was mixed. Some centre leads aligned the pathway redesign with the overall efforts of managers to minimise patients' time in hospital, and therefore gained resources and permission to proceed, while others struggled to make changes due to competing organisational priorities and limited engagement of Trust leadership with any issue that was not related to the pandemic. The pandemic-associated demand for service change and absence of "red tape" described by the interviewees has been reported previously by Swaithes et al, who explains the increased flexibility of healthcare organisations to accommodate change and increased capacity to adopt new knowledge observed during the pandemic through the absorptive capacity theory[472]. This critical situation reduced clinicians' resistance to change, increased the public's willingness to accept it, and encouraged decision-makers to make radical decisions due to the need to adapt to new circumstances[473], thus facilitating implementation of novel ideas[472,474]. The rise of digital technologies through investment and allocation of resources is such an example[472] and was also observed in one of our sites, where virtual clinics were set up as a novel way to keep patients under observation out of hospital. It is worth noting that most of the PAD QIP participating centres made changes during and despite the pandemic, whereas in an implementation study in Canada conducted during the same period only one centre continued implementation during that period[475].

The other outer setting factor mentioned by the participants as a barrier to implementation was the lack of financial incentives at national level, which limited the engagement of managers and organisational leaders. This finding is supported by studies that identified a relationship between fiscal investment and policies and the adoption of evidence-based practice in mental health in the US[476]. In April 2022, just before the end of the implementation period, a pay-for-performance scheme was introduced by NHS England with the same target as the programme[477], offering financial incentives to NHS organisations to achieve improvement, and its effect should be explored in further studies.

Finally, other implementation and QI studies suggest that the evidence supporting the proposed intervention is important for the success of the programme. In our field, there was no concrete evidence to support our hypothesis that treating patients within 5 days

from admission would lead to improved patient outcomes. This uncertainty was brought up during the interviews, but there was clinical consensus among participants that the target was reasonable and the rationale for choosing it was clear.

Limitations

This study has several limitations. Firstly, the sample size was relatively small, but there was representation from all centres participating in the programme, and no new inductive codes emerged after the first three transcripts were coded. Secondly, due to the limited time and human resources, the interview transcripts were coded by a single researcher (PB), and 20% were also reviewed by a supervisor with qualitative background (LS), to ensure that important themes were not missed. Additionally, due to the variety of contexts that our programme would be implemented in and lack of knowledge on what barriers we might face, our implementation strategy was not designed to address specific contextual determinants of implementation. Finally, we were unable to explore some factors that have been found to influence implementation in other studies, due to the limited interview time. Longer study interviews would have been difficult due to the busy schedule of the participating healthcare professionals, therefore interview question topics were selective. Future studies are needed to investigate these factors, as well as factors that were absent from the study, such as the facilitation of the implementation by improvement experts. It was not possible to consult with QI experts in this study due to funding constraints, but they have been important for improvement in previous studies[460].

Conclusions

This study explored contextual factors that influenced the implementation of a QI intervention in the UK vascular surgery setting, using qualitative and quantitative methods. The peer comparison and sharing of good practice during the Programme, its focus on patient benefit, the presence of supportive teams and the availability of organisational resources were considered important factors that encouraged the implementation of changes in vascular centres, while the COVID-19 pandemic had a mixed effect. Future studies in this field should retain the elements of benchmarking, peer comparison and networking in their implementation strategy. Additionally, future

QI programmes and implementation studies in vascular surgery should ensure the availability of support from organisational leaders and middle managers, dedicated time of lead clinicians for quality improvement, and participation of a multidisciplinary team of professionals prior to implementation. Finally, more research should be conducted to reveal other contextual factors that may influence implementation in the vascular surgery setting, and how tailored implementation approaches may address them.

Chapter 6. The effect of the COVID-19 pandemic on lower limb vascular procedures for patients with PAD in the UK

6.1 Introduction

In March 2020, the World Health Organisation declared a global pandemic in response to the spread of coronavirus SARS-CoV-2[367]. The pandemic had a significant impact on the delivery of surgical services worldwide, due to the limited access to critical care and operating facilities as well as staff redeployment. In the UK, a national lockdown was implemented from March to June 2020, followed by two additional lockdowns between November 2020 and February 2021[388], in response to the emergence of a new SARS-CoV-2 variant. For vascular surgery, the NHS in England and the VSGBI issued guidance recommending the deferral of elective surgery and consideration of therapeutic options with minimal need for postoperative critical care for emergency procedures, in order to preserve healthcare resources and reduce patient exposure to hospital[389]. The American College of Surgeons published similar recommendations regarding the review and postponement of elective procedures[478].

Changes in the provision of vascular services in response to the pandemic have been documented through surveys of healthcare professionals and institutional reviews[114,390,479]. Outcomes such as postoperative complications and mortality after vascular interventions during the COVID-19 pandemic have also been explored in the COvid-19 Vascular sERvice (COVER) Tier 2 multicentre study[480], the COVID-VAS study[481] as well as other single centre and registry studies[482–485]. However, most studies had a small sample of patients and focused on the first wave of the pandemic that started in March 2020, and did not extend to late 2020 and 2021.

The aim of this study was to examine patterns of care and short-term outcomes of lower limb vascular procedures performed in the UK during the pandemic, compared to the pre-pandemic period.

6.2 Methods

This population-based cohort study used data submitted prospectively in the NVR, a national clinical audit collecting demographic and clinical information on five major vascular procedures (abdominal aortic aneurysms, carotid endarterectomies, lower limb bypasses/endarterectomies, angioplasties and major amputations) undertaken within NHS hospitals in the UK[371]. The NVR captures 81% of open surgical revascularisations, 49% of endovascular revascularisations and 88% of major amputations in the UK[486]. The study involved secondary analysis of existing pseudo-anonymised data and therefore was exempt from NHS Ethics Committee approval. Results are presented in accordance with the RECORD extension of the STROBE statement for observational cohort studies[312].

6.2.1 Study population

The study cohort comprised of adult patients who underwent lower limb open or endovascular revascularisation or major amputation procedures, performed in NHS hospitals between 1 January 2019 and 30 April 2021. Open surgical revascularisation procedures consisted of lower limb bypasses and endarterectomies with or without an endovascular component (hybrid), and endovascular procedures included balloon angioplasties with or without stent. If multiple procedures were performed on different dates during a single hospital admission, the first procedure was analysed as the index procedure, and the subsequent procedures were considered re-interventions. Patient records were excluded if data were missing on key variables (age, comorbidities, smoking status, indication for surgery and procedure details).

6.2.2 Patient characteristics

The NVR dataset contained demographic (patient age at surgery, gender, comorbidities, smoking status) and clinical information (indication for intervention, Fontaine score, date of admission, admission method, date and type of intervention, anaesthetic type), as well as postoperative in-hospital patient outcomes. Information on comorbidities included the presence of diabetes mellitus, chronic obstructive pulmonary disease (COPD), ischemic heart disease (IHD), chronic heart failure (CHF), CKD and stroke. It also

included the patient's SARS-CoV-2 status (positive polymerase chain reaction (PCR) or lateral flow test pre-operatively or post-operatively, COVID-19 symptoms, which were added as data items in April 2020). Patients were considered to have SARS-CoV-2 infection if they had a positive test at any point during the admission or a clinical diagnosis was made based on COVID-19 symptoms.

Indications for intervention included chronic limb ischaemia, acute limb ischaemia, uncontrolled infection, trauma and aneurysm. Chronic limb ischaemia (CLI) was further divided into moderate (Fontaine I and II), if the patient was asymptomatic or had intermittent claudication, and severe (Fontaine III and IV), if the patient had rest pain or tissue loss. The type of anaesthetic was categorised as general or locoregional (including blocks).

6.2.3 Outcomes

The primary outcome was in-hospital mortality after a vascular lower-limb procedure. The secondary outcomes were respiratory, cardiac, renal and cerebrovascular complications, postoperative limb ischaemia and re-interventions (angioplasty, bypass, major amputation, minor amputation).

6.2.4 Statistical analysis

The study was based on a complete case analysis. Revascularisation procedures with open and endovascular elements (hybrid) were analysed as open surgical procedures. Revascularisation procedures were also split into elective and non-elective; major amputations were treated as one group. Changes over time were examined by dividing the time period into pre-pandemic (1 Jan 2019 – 29 Feb 2020) and pandemic sections (1 March 2020 – 30 April 2021) with the pandemic section consisting of three segments: Wave 1 (1 March – 30 June 2020), Respite (1 Jul – 30 Oct 2020), Wave 2/3 (1 Nov 2020 – 30 April 2021). Patterns over time were inspected graphically using smoothing splines.

Continuous variables were summarised using the median and IQR, and categorical variables using frequencies and proportions. To test the significance of changes over time, the Pearson's chi square test was used for categorical variables and the Mann-Whitney U test for continuous variables. Poisson regression and logistic regression were

used to evaluate differences in procedure volume across time periods and differences in the proportion of procedures performed under general anaesthetic, respectively. Logistic regression was also used to evaluate differences in patient characteristics, mortality and complications across time periods.

Four multivariable logistic regression models were developed to estimate the impact of SARS-CoV-2 infection and other demographic and clinical characteristics on in-hospital postoperative mortality. The first model included only the time period when the procedure was performed. The second incorporated the procedure type, anaesthetic type and indication for surgery in addition to the time period. The third model included the previous variables as well as patient age, gender and comorbidities (diabetes mellitus, COPD, IHD, CHF, CKD). The perioperative SARS-CoV-2 status was added as an explanatory variable in the final model, in addition to all the previously included variables. All statistical tests were two-sided and a P-value of <.05 was considered statistically significant. All analyses were performed using STATA 15.1 (StataCorp, College Station, Texas, USA).

6.3 Results

The inclusion criteria were fulfilled by 37,393 procedures performed during the study period and 455 were excluded due to missing data on key variables (age, comorbidities, smoking status, indication for surgery and procedure details). The study analysed information on 36,938 lower limb procedures, comprising of 7,245 (19.6%) major amputations, 16,712 (45.3%) endovascular and 12,981 (35.1%) open surgical revascularisations.

6.3.1 Procedures in each time period

There were 15,501 procedures performed during the 14 months of the pandemic (March 2020-April 2021) compared to 21,437 in the 14 months pre-pandemic (January 2019-February 2020), representing a 27.7% reduction in total procedures. The mix of lower limb vascular procedures performed during the pandemic was significantly different compared to the previous year ($p<0.001$) (Figure 27). There was a decrease in all procedures including major amputations, especially during the peaks of the pandemic

(Wave 1, Wave 2/3) and this reduction was largest for elective revascularisation procedures (Table 31).

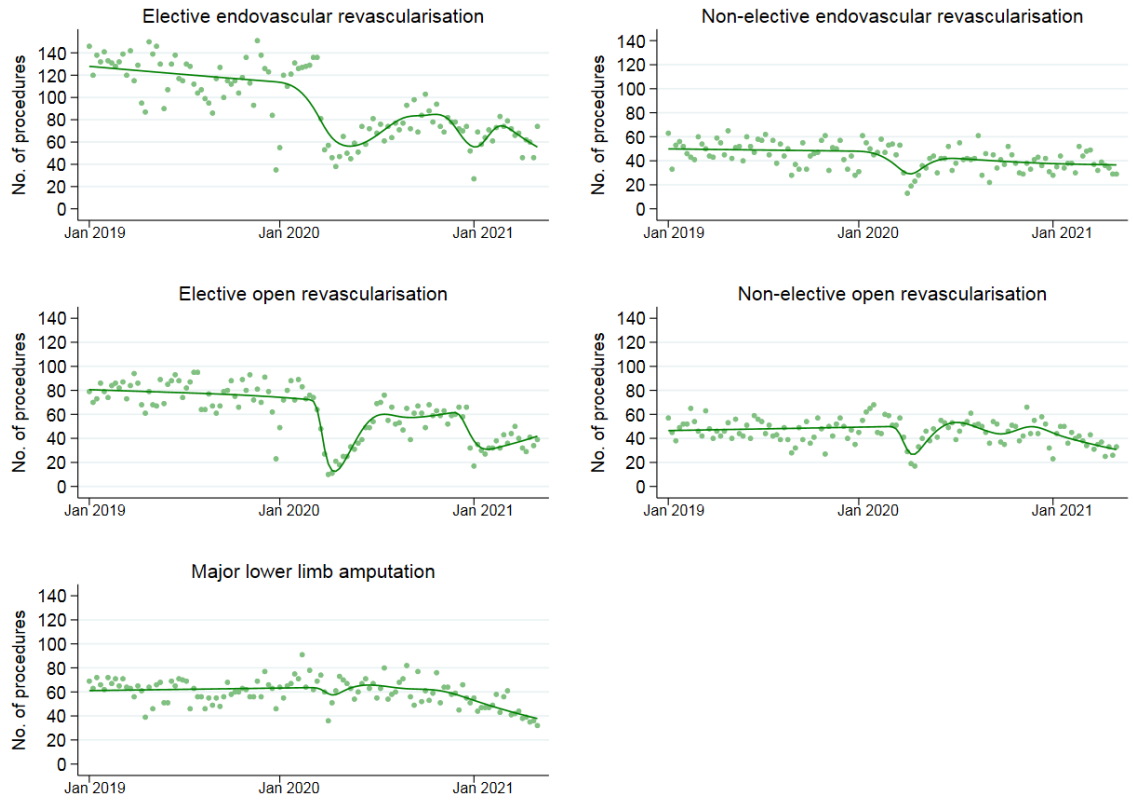

Figure 27 – Weekly volumes of procedures performed from January 2019 to April 2021 by admission method and procedure type (scatterplot) with a smoothed regression line (green line)

Table 31 – Monthly average procedural volume, proportion of procedures performed under general anaesthetic and proportion of patients with suspected or confirmed SARS-CoV-2 infection by type and time period of procedure, as observed and relative (Rel) to 2019 pre-pandemic figures

		Number of procedures (monthly average)				General anaesthetic (%)				SARS-CoV-2 infection (%)		
Procedure		**Pre-pandemic**	**Wave 1**	**Respite**	**Wave 2/3**	**Pre-pandemic**	**Wave 1**	**Respite**	**Wave 2/3**	**Wave 1**	**Respite**	**Wave 2/3**
Major amputation	Observed	270	273	276	213*	71.2	64.3*	67.0*	66.5*	10.5	5.8	14.2
	Rel to 2019		101.1	102.2	78.9		90.3	94.1	93.4			
Elective bypass	Observed	334	160*	264*	181*	86.2	81.1*	81.9*	83.3*	2.3	0.9	1.9
	Rel to 2019		47.9	79.0	54.2		94.1	95.0	96.6			
Non-elective bypass	Observed	207	184	209	176*	88.9	83.8*	85.8*	85.5*	6.2	2.5	8.0
	Rel to 2019		88.9	101.0	85.0		94.3	96.5	96.2			
Elective endovascular	Observed	512	295*	348*	288*	6.0	6.2	6.5	6.7	0.6	0.3	1.0
	Rel to 2019		57.6	68.0	56.3		103.3	108.3	111.7			
Non-elective endovascular	Observed	208	160*	180*	162*	10.3	9.9	10.7	13.1*	5.9	2.2	7.0
	Rel to 2019		76.9	86.5	77.9		96.1	103.9	127.2			

* Statistically significantly different (p-value<0.05) compared to pre-pandemic period.

6.3.2 Did the characteristics of patients having procedures change?

The indication for surgery across the four revascularisation procedures is summarised in Figure 28. Among patients who had a major amputation or non-elective revascularisation, the distribution of the indications did not change during the three pandemic time periods, compared to the distribution observed in 2019. However, there was a distinct change in the pattern among the patients who had elective revascularisation, with a dramatic drop in the number of procedures performed for Fontaine I or II disease (p<0.001). The number of patients treated for trauma, aneurysms and infection remained stable over time.

Patient and procedure characteristics stratified by time period and procedure type are summarised in Table 32. A significantly higher proportion of patients who underwent elective endovascular revascularisation during the pandemic had diabetes (p<0.001), COPD (p=0.024), CHF (p<0.001) and CKD (p<0.001), compared to the pre-pandemic period.

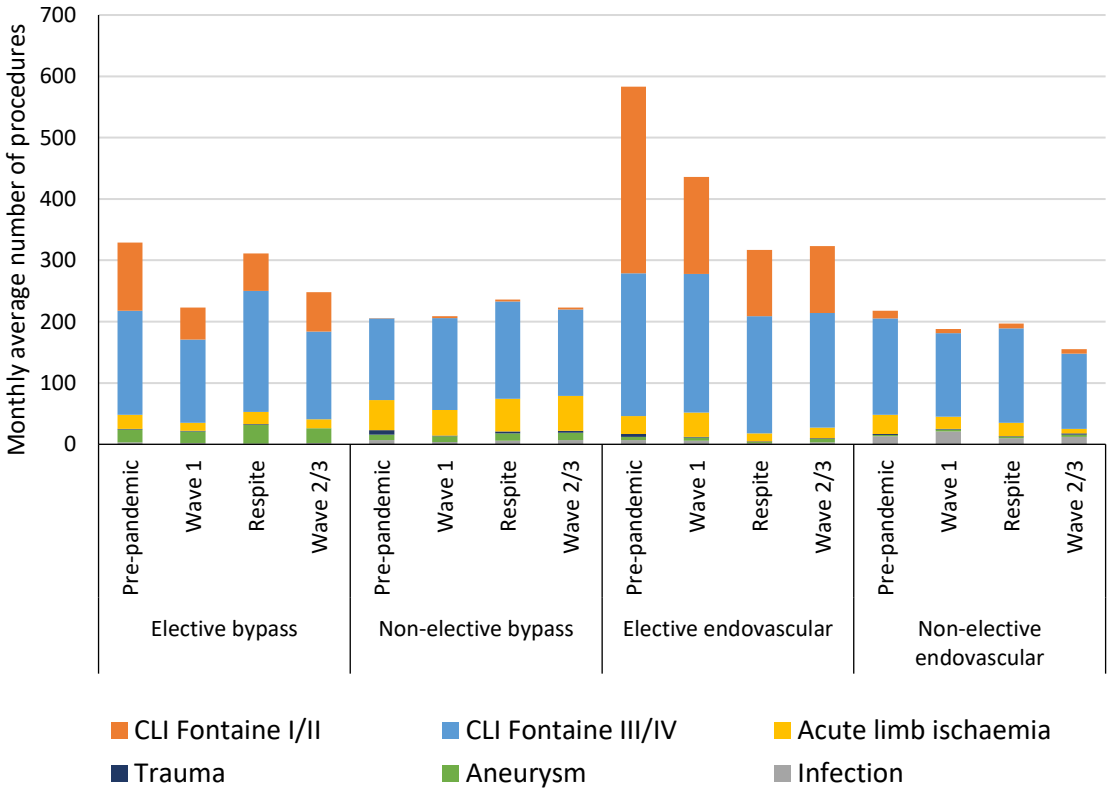

Figure 28 – Monthly average number of procedures by indication for surgery in each time period by procedure type. CLI: Chronic Limb Ischaemia

Table 32 – Patient characteristics by type and time period of procedure

	Major amputation			
	Pre-pandemic	**Wave 1**	**Respite**	**Wave 2/3**
n	3,776	1,091	1,102	1,276
Age – y	69 (60-77)	68 (59-77)	68 (59-76)	69 (60-76)
Men	72.9	72.5	72.7	74.2
Diabetes	56.2	57.2	53.4	54.2
COPD	23.2	22.8	23.5	25.7
IHD	39.8	37.1	37.4	37.3
CHF	12.4	12.4	12.0	11.9
CKD	21.3	20.4	21.1	19.0
Current smoker	31.7	32.7	35.2*	35.9*

	Elective bypass				Non-elective bypass			
	Pre-pandemic	**Wave 1**	**Respite**	**Wave 2/3**	**Pre-pandemic**	**Wave 1**	**Respite**	**Wave 2/3**
n	4,672	639	1,054	1,087	2,901	734	836	1,058
Age – y	69 (62-76)	70 (62-76)	69 (61-75)	70 (62-75)	71 (62-77)	69 (61-77)	69 (60-76)	70 (61-77)
Men	74.5	75.0	77.3	73.1	72.4	73.6	70.5	70.3
Diabetes	33.9	38.0*	36.2	34.2	39.3	40.3	40.7	40.5
COPD	24.3	27.5	25.2	25.4	25.4	28.6	27.0	26.3
IHD	34.9	33.3	34.3	31.9	34.9	37.6	35.4	31.0*
CHF	5.8	5.5	5.7	5.2	8.0	7.8	8.4	7.3
CKD	9.4	11.4	9.4	10.5	12.2	10.5	12.1	11.2
Current smoker	31.4	36.0*	33.3	37.0*	40.4	43.9	44.9*	45.6*

	Elective endovascular				Non-elective endovascular			
	Pre-pandemic	**Wave 1**	**Respite**	**Wave 2/3**	**Pre-pandemic**	**Wave 1**	**Respite**	**Wave 2/3**
n	7,170	1,178	1,392	1,728	2,918	638	719	969
Age - y	71 (63-78)	72 (63-80)	72 (64-79)	72 (64-79)	72 (64-80)	72 (63-80)	72 (63-80)	71 (63-80)
Men	67.4	68.7	66.8	69.2	67.7	69.1	67.5	67.8
Diabetes	44.1	53.4*	48.8*	48.3*	63.6	65.7	65.9	61.3
COPD	16.8	17.7	19.0	19.6*	19.5	18.8	17.5	19.2
IHD	30.3	29.4	33.1*	30.9	34.6	30.7	32.4	31.2
CHF	6.5	8.4*	8.3*	9.8*	12.1	12.4	13.5	11.6
CKD	12.5	16.0*	17.4*	15.6*	23.3	27.0	26.8*	23.0
Current smoker	26.7	25.6	27.4	26.4	24.9	24.8	21.0*	26.0

Data on comorbidities, gender and smoking are presented as percentages, and age as median (IQR).

* Statistically significantly different (p-value<0.05) compared to pre-pandemic period.

There was also a significant increase in the proportion of current smokers undergoing amputation (34.7% during the pandemic vs. 31.7% pre-pandemic, p=0.007), elective (35.4% vs 31.4%, p<0.001) and non-elective (44.9% vs. 40.4%, p=0.001) open surgical revascularisation.

6.3.3 Was there a change in the type of anaesthetic used during the pandemic?

The proportion of amputation procedures performed under general anaesthetic was 66.0% during the pandemic compared with 71.2% in the pre-pandemic period (p<0.001). This reduction was also observed in elective (82.2% vs. 86.2%, p<0.001) and non-elective (85.1% vs. 88.9%, p<0.001) open surgical revascularisation procedures. There was no change in the anaesthetic type for endovascular procedures, which were mostly performed without general anaesthetic (Table 31).

6.3.4 How many patients were reported as having SARS-CoV-2 infection?

Only a small proportion of patients who had vascular procedures had suspected or confirmed SARS-CoV-2 infection during their admission (4.6%, n=708). The rate of SARS-CoV-2 infection for procedures performed during the pandemic was highest for patients having amputation (9.1%, n=361), followed by non-elective bypass (5.1%, n=152) and non-elective endovascular revascularisation (4.7%, n=122), while it was less than 1% for elective revascularisation procedures. The infection rate was higher in the Wave 2/3 period compared to Wave 1 (Table 31).

6.3.5 Did the time that patients spent in hospital change?

The median time from admission to procedure was shorter by 1 day during the pandemic compared to the pre-pandemic period for amputations (3 vs 4 days, p<0.001) and non-elective open surgical (3 vs 4 days, p<0.001) and endovascular (4 vs 5 days, p=0.010) revascularisation procedures.

Median length of stay was also significantly shorter during the pandemic for amputations (18 vs 22 days pre-pandemic, p<0.001), non-elective open surgical revascularisation (12.5 vs 15 days pre-pandemic, p<0.001) and endovascular revascularisation (11 days vs 12 days pre-pandemic, p=0.013).

6.3.6 Complications and re-interventions

There was a statistically significant increase in respiratory complications after amputation and non-elective revascularisation procedures during the periods of Wave 1 and Wave 2/3, while a change was not observed after elective procedures (Table 33). Additionally, rates of cardiac and renal complications, and stroke remained stable during the pandemic for all procedures. However, a significant increase in limb ischaemia complications after elective open and non-elective endovascular revascularisation was found during the 2nd and 3rd Wave of the pandemic (Table 34).

Regarding re-interventions after the primary procedure during an admission, bypass and major amputation rates following elective open revascularisation were significantly increased compared to the pre-pandemic period, but not following other types of revascularisation procedures. There was a significant increase in the proportion of elective and non-elective open surgical procedures that were followed by an unplanned angioplasty during the 2nd and 3rd Wave compared to the pre-pandemic period (Table 34).

6.3.7 In-hospital postoperative mortality

The in-hospital mortality rates after elective open and endovascular revascularisation were 1.6% and 0.9% overall during the pandemic period, and were slightly higher than observed in the pre-pandemic period (1.6% vs 1.1%, p=0.033; and 0.9% vs 0.5%, p=0.005; respectively). Figure 29 illustrates that the increase in mortality was associated with the COVID waves. For elective open revascularisation procedures, the mortality rate doubled during the first months of the pandemic, while for non-elective a significant increase in mortality was observed during the Wave 2/3 period (Table 33). In-hospital mortality after major amputations was also greatest during the Wave 2/3 period, reaching 10.4% (95% CI 8.8-12.2) compared to 7.7% (95% CI 6.9-8.6) in the pre-pandemic period (p=0.022) (Table 33). Postoperative mortality did not change significantly after endovascular non-elective revascularisation procedures, while a significant increase in elective mortality was observed during the peaks of the pandemic.

Table 33 – In-hospital mortality rate and rate of respiratory complications by type and time period of procedure

	In-hospital mortality (%, 95% CI)			
Procedure	**Pre-pandemic**	**Wave 1**	**Respite**	**Wave 2/3**
Amputation	7.7 (6.9-8.6)	7.8 (6.3-9.5)	8.1 (6.5-9.8)	10.4 (8.8-12.2)*
Elective bypass	1.1 (0.8-1.4)	2.0 (1.1-3.5)*	1.9 (1.2-2.9)*	1.1 (0.6-1.9)
Non-elective bypass	4.2 (3.5-5.0)	4.4 (3.0-6.1)	5.1 (3.7-6.9)	6.0 (4.6-7.6)*
Elective endovascular	0.5 (0.3-0.7)	1.1 (0.6-1.9)*	0.6 (0.3-1.2)	1.0 (0.6-1.6)*
Non-elective endovascular	4.2 (3.5-5.0)	5.5 (3.9-7.5)	4.5 (3.1-6.2)	5.7 (4.3-7.3)
	Respiratory complication rate (%, 95% CI)			
	Pre-pandemic	**Wave 1**	**Respite**	**Wave 2/3**
Amputation	8.6 (7.7-9.5)	11.3 (9.5-13.3)*	7.1 (5.6-8.8)	11.9 (10.2-13.8)*
Elective bypass	2.9 (2.4-3.4)	4.1 (2.7-5.9)	2.6 (1.7-3.7)	1.9 (1.2-2.9)
Non-elective bypass	5.1 (4.4-6.0)	8.3 (6.4-10.5)*	5.0 (3.6-6.7)	7.8 (6.2-9.5)*
Elective endovascular	0.2 (0.1-0.3)	0.6 (0.2-1.2)*	0.4 (0.1-0.8)	0.4 (0.2-0.8)
Non-elective endovascular	3.2 (2.5-3.9)	5.8 (4.1-7.9)*	2.1 (1.2-3.4)	5.5 (4.1-7.1)*

* Statistically significantly different (p-value<0.05) compared to pre-pandemic period.

Table 34 – Complications and re-interventions by type and time period of procedure

	Major amputation			
	Pre-pandemic	**Wave 1**	**Respite**	**Wave 2/3**
Complications				
Cardiac	5.6	3.8*	4.2*	4.9
Stroke	0.6	0.5	0.6	0.5
Renal	3.4	2.7	2.5	3.1
Limb ischaemia	3.0	2.0	2.9	3.1
Re-interventions				
Bypass	0.5	0.2	0.4	0.5
Angioplasty	0.7	0.8	1.0	0.5
Major amputation	4.9	2.8*	6.2	4.5
Minor amputation	0.2	0.1	0.3	0.1

	Elective bypass				Non-elective bypass			
	Pre-pandemic	**Wave 1**	**Respite**	**Wave 2/3**	**Pre-pandemic**	**Wave 1**	**Respite**	**Wave 2/3**
Complications								
Cardiac	2.2	2.5	2.3	2.1	4.9	3.1*	4.4	4.5
Stroke	0.3	0.3	0.3	0.5	0.4	1.0	0.7	0.4
Renal	1.2	1.1	0.8	1.0	2.7	2.2	2.2	2.1
Limb ischaemia	2.9	3.8	3.7	4.1*	9.0	8.4	8.4	8.6
Re-interventions								
Bypass	1.3	2.0	2.7*	2.3*	3.4	2.6	3.8	3.0
Angioplasty	1.2	1.1	1.2	2.8*	2.0	1.6	2.2	4.0*
Major amputation	1.0	2.3*	1.3	1.0	7.2	7.5	6.9	5.7
Minor amputation	0.9	1.4	1.6	1.0	4.8	3.8	4.3	4.4

	Elective endovascular				Non-elective endovascular			
	Pre-pandemic	**Wave 1**	**Respite**	**Wave 2/3**	**Pre-pandemic**	**Wave 1**	**Respite**	**Wave 2/3**
Complications								
Cardiac	0.3	0.6	0.3	0.3	1.5	1.4	1.3	1.9
Stroke	0.0	0.1	0.0	0.1	0.2	0.3	0.3	0.2
Renal	0.2	0.3	0.1	0.1	1.2	0.9	1.4	1.0
Limb ischaemia	0.4	0.4	0.9*	0.3	3.3	5.5*	4.5	5.3*
Re-interventions								
Bypass	0.7	0.3	0.6	1.1	3.5	3.0	3.6	4.0
Angioplasty	1.1	1.5	1.9*	1.1	4.3	6.1	4.3	3.6
Major amputation	0.5	0.8	0.9	0.5	6.0	6.9	5.7	6.0
Minor amputation	0.7	1.4*	0.9	0.8	6.8	6.6	5.6	7.1

Data are presented as percentages.

* Statistically significantly different (p-value<0.05) compared to pre-pandemic period.

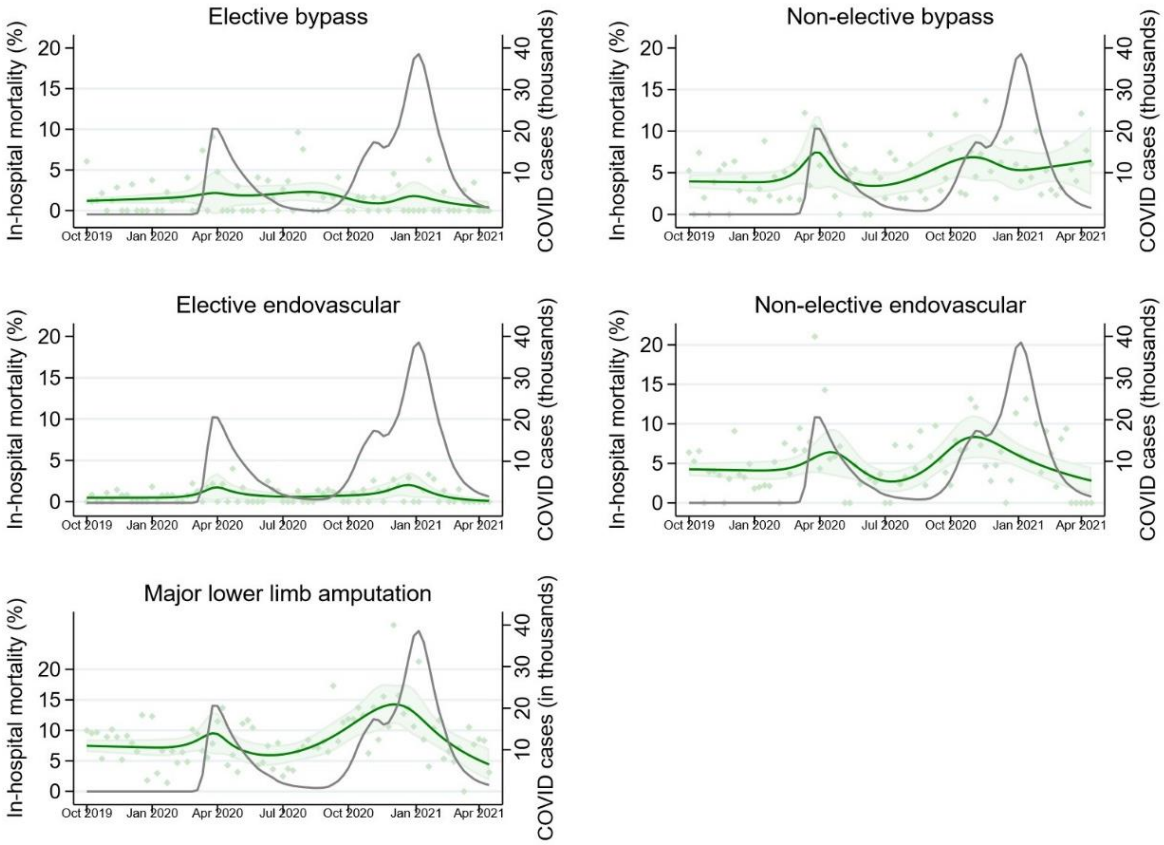

Figure 29 – Weekly average in-hospital mortality over time from October 2019 to April 2021 by procedure type (light green dots), with a smoothed regression line for mortality (green line) and 95% confidence intervals (light green band) (left y-axis). The grey line indicates the number of national cases of SARS-CoV-2 infection in the UK (right y-axis)

The impact of patient and clinical factors on in-hospital mortality from the four regression models are shown in Table 35. As indicated by Model 1, procedures during the COVID-19 pandemic period were associated with excess mortality (adjusted odds ratio (aOR) 1.45, 95% CI 1.23-1.71 for Wave 1, aOR 1.61, 95% CI 1.39-1.86 for Wave 2/3). Adding procedural factors (Model 2) demonstrates that some of the excess mortality was associated with a change in the mix of procedures performed, even though there is still evidence of excess mortality in Wave 2/3 (Model 2 aOR 1.38, 95% CI 1.19-1.59). The increased mortality in Wave 2/3 persisted after further adjustment for patient age, gender and comorbidities, indicating that the excess mortality was not associated with treating patients with worse general health (Model 3, aOR 1.43 [1.23, 1.66]. Finally, after

the inclusion of the SARS-CoV-2 infection variable in the model (Model 4), the time period of procedure was no longer associated with a significant effect on mortality (Figure 30). This suggests the excess mortality in the population of lower limb procedures performed during the pandemic is predominantly attributable to SARS-CoV-2 infections among individuals. Compared to patients without SARS-CoV-2 infection, the SARS-CoV-2-positive patients had 6 times higher in-hospital mortality, after adjusting for age, gender, comorbidities, indication for surgery, type of procedure, type of anaesthetic and time-period of procedure (aOR 5.88 [95% CI 4.80, 7.21], p<0.001). The overall mortality rate among those with SARS-CoV-2 infection was 25.0% (n=177).

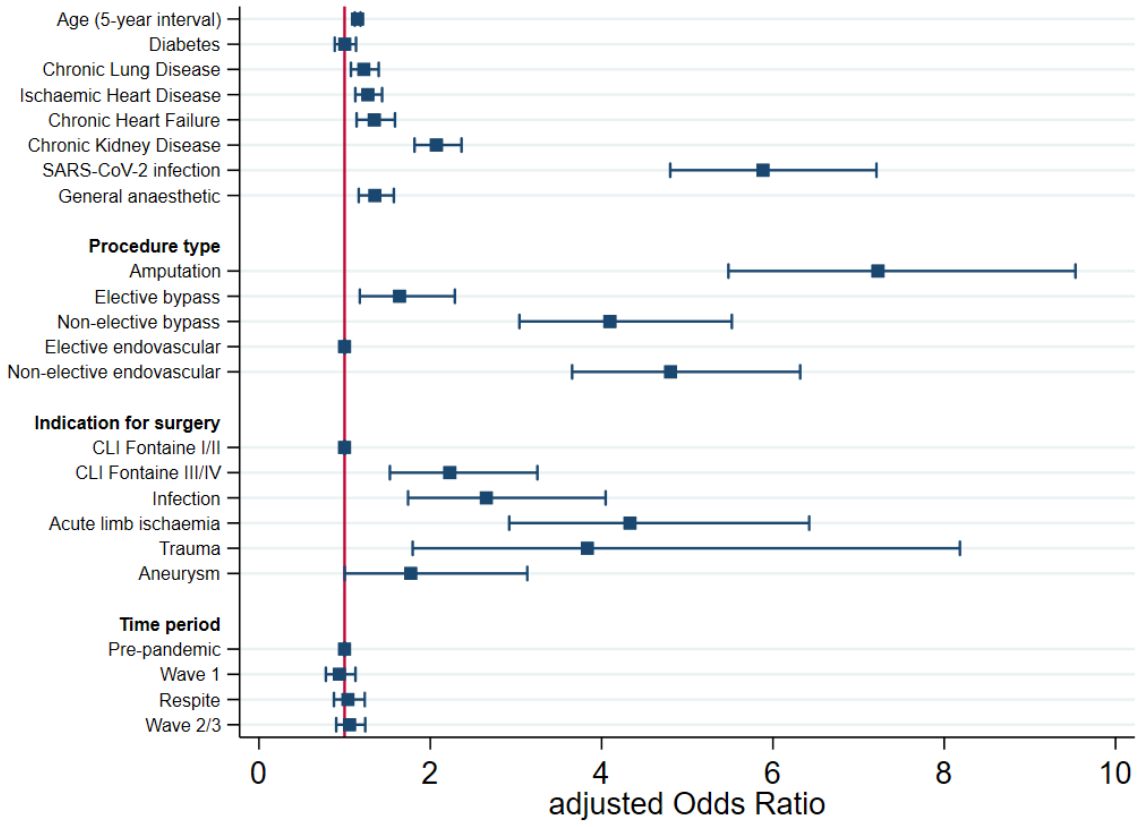

Figure 30 – Coefficients plot of the adjusted odds ratio (aOR) and 95% confidence intervals for in-hospital mortality after lower limb vascular procedures. The red line indicates aOR of 1. CLI = chronic limb ischaemia

Table 35 – Adjusted odds ratio for in-hospital mortality based on multivariable logistic regression models

	Model 1	Model 2	Model 3	Model 4
Time period of procedure				
Pre-pandemic	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Wave 1	1.45 (1.23, 1.72)	1.16 (0.97, 1.38)	1.19 (1.00, 1.41)	0.94 (0.78, 1.13)
Respite	1.32 (1.12, 1.55)	1.15 (0.97, 1.36)	1.18 (0.99, 1.39)	1.04 (0.88, 1.23)
Wave 2/3	1.61 (1.39, 1.86)	1.38 (1.19, 1.59)	1.43 (1.23, 1.66)	1.06 (0.90, 1.24)
SARS-CoV-2 infection				5.88 (4.80, 7.21)
Procedure type				
General anaesthetic		1.13 (0.98, 1.31)	1.32 (1.14, 1.53)	1.35 (1.17, 1.58)
Elective endovascular		1.00 (reference)	1.00 (reference)	1.00 (reference)
Amputation		8.96 (6.82, 11.89)	8.51 (6.47, 11.19)	7.23 (5.48, 9.53)
Elective bypass		1.69 (1.22, 2.36)	1.73 (1.24, 2.40)	1.64 (1.18, 2.29)
Non-elective bypass		4.64 (3.45, 6.23)	4.55 (3.38, 6.11)	4.10 (3.04, 5.52)
Non-elective endovascular		5.59 (4.26, 7.34)	5.21 (3.96, 6.83)	4.81 (3.66, 6.32)
Indication for surgery				
CLI Fontaine I/II		1.00 (reference)	1.00 (reference)	1.00 (reference)
CLI Fontaine III/IV		2.66 (1.83, 3.87)	2.17 (1.49, 3.17)	2.23 (1.53, 3.25)
Infection		2.84 (1.87, 4.31)	2.58 (1.70, 3.93)	2.65 (1.74, 4.05)
ALI		4.81 (3.25, 7.12)	4.41 (2.98, 6.52)	4.33 (2.92, 6.42)
Trauma		2.95 (1.40, 6.21)	3.79 (1.79, 8.01)	3.83 (1.79, 8.18)
Aneurysm		1.99 (1.13, 3.51)	1.73 (0.98, 3.06)	1.77 (1.00, 3.13)
Patient characteristics and comorbidities				
Age (5-year interval)			1.15 (1.12, 1.19)	1.15 (1.12, 1.18)
Female			1.10 (0.97, 1.24)	1.10 (0.97, 1.25)
Diabetes			1.01 (0.89, 1.14)	1.00 (0.88, 1.13)
COPD			1.24 (1.09, 1.41)	1.23 (1.07, 1.40)
IHD			1.22 (1.08, 1.38)	1.27 (1.12, 1.44)
CHF			1.33 (1.13, 1.57)	1.35 (1.14, 1.59)
CKD			2.10 (1.84, 2.39)	2.07 (1.82, 2.36)

Data are presented as adjusted odds ratio (95% confidence interval).

6.4 Discussion

This study found an overall 28% reduction in vascular lower limb surgical activity during the COVID-19 pandemic period compared to the previous months, with greater effects observed in elective revascularisation procedures. Even though the proportion of patients with SARS-CoV-2 infection undergoing vascular procedures was only 4.6%, a COVID-19 diagnosis was associated with 6 times higher mortality, even after adjusting for patient and procedure characteristics. The overall complication and reoperation rates were comparable to the previous year, but there was a significant increase in in-hospital mortality after elective revascularisation and amputation procedures, mainly related to concomitant SARS-CoV-2 infection.

In this study, a 40% decrease in elective revascularisation procedures was noted during the pandemic. This decline in vascular activity has also been reported for carotid endarterectomies, aortic aneurysm repairs and lower limb procedures by another UK study during the first wave of the pandemic[487]. Similar decrease in elective activity has been recorded in other countries, such as Italy[485] and the United States[397]. The postponement of non-urgent surgical procedures and the prioritisation of urgent and emergency work was recommended by surgical professional bodies in order to reduce the exposure of patients to hospitals and preserve critical care resources. This decrease in surgical volume stems mainly from the reduction in procedures performed for mild or moderate chronic limb ischaemia (Fontaine I/II), while the number of procedures for severe limb ischaemia (Fontaine III/IV) remained stable. This is reassuring, as it indicates that urgent limb-saving procedures continued to be performed. The reduction in procedures for claudication was also noted in a report from the Swedish Vascular Registry and Southern Italy[488,489]. Interestingly, the Swedish report did not identify a significant reduction in vascular procedures overall during 2020 compared to previous years, which may be due to the fact that no national lockdown was imposed in the country[488].

Previous studies from the Netherlands and Italy noted an increase in amputation rates, which was attributed to hospital avoidance and subsequent delayed presentation with severe limb ischaemia[490–494]. However, we did not identify a significant increase in

primary major amputations. This finding is supported by previously published studies, which are however limited to patients with diabetes[495,496].

Regarding differences in the patterns of care, patients undergoing elective endovascular revascularisation procedures during the pandemic period had more comorbidities, such as diabetes, COPD, CKD and chronic heart failure. Increase in some of these comorbidities was also noted in a US study[497]. There has also been an increase in the proportion of current smokers that underwent amputation and open surgical revascularisation, which may be an indication of the impact of lockdown on mental health and change in smoking habits[498]. Only a small proportion of patients included in this study had SARS-CoV-2 infection, similar to other studies[489]. The infection rate was higher in Wave 2/3 compared to Wave 1, which may be related to more and better testing at later stages of the pandemic.

Additionally, we did not identify an increase in revascularisation procedures performed endovascularly in this study, even though this has been described by the international COVER study[114], as well as single centre studies from the US and Portugal[499]. These studies may be at risk of selection bias, as they involved units that registered to participate, rather than population-level data. Moreover, we found that more open surgical procedures (revascularisation and amputation) were performed under loco-regional anaesthesia during the pandemic period compared to pre-pandemic, which has also been described in a study from Portugal[499]. This approach may have been chosen where possible in an attempt to preserve critical care resources, avoid the use of anaesthetic equipment and staff and reduce the risk of pulmonary complications associated with the use of general anaesthetic. Additionally, this practice of performing revascularisations under loco-regional anaesthesia is supported by an update of the European Society of Vascular Surgery guidelines for ALI, published in early 2022[500].

Both median time from admission to procedure and length of stay were shorter during the pandemic. Due to the high rates of SARS-CoV-2 transmission in hospital, this finding may indicate a conscious effort by healthcare staff to reduce the length of stay in hospital. It may also be related to the fact that there was less pressure on emergency

theatre capacity by other specialties, since professional bodies recommended non-operative treatment for acute conditions such as appendicitis.

In-hospital mortality after elective revascularisation procedures and major amputations was higher during the pandemic compared to the pre-pandemic period. This increase can be explained by the presence of SARS-CoV-2 infection, which was associated with a 6-times increase in mortality. In our study, patients with SARS-CoV-2 infection had a postoperative mortality rate of 25%, which is comparable to the 30-day mortality of 23.8% reported by the multicentre COVIDSurg study[501] and two studies of vascular procedures from Lombardy (25% in-hospital mortality in patients with COVID-19)[396,482]. It is also lower than the 30-day mortality rate of 37.3% after vascular surgery procedures reported in the COVID-VAS multicentre study from Spain for patients with SARS-CoV-2 infection during the first wave[481]. Notably, there was no change in mortality or postoperative complications after vascular procedures in the Swedish registry[488].

The main strength of this study is the large sample size and the long study period, which included the three waves of the pandemic in the UK. Additionally, historical data allowed the comparison of the pandemic period with pre-pandemic patterns of care and outcomes.

This study has certain limitations. Firstly, due to population-based observational study design, there is a possibility that the rate of SARS-CoV-2 infection was under-reported during data collection. Another factor that may have contributed to under-estimation of the rate of SARS-CoV-2 positive patients is the limited availability of diagnostic tests during the first wave of the pandemic. Secondly, the case ascertainment of endovascular revascularisation procedures in the National Vascular Registry is lower than open surgical revascularisation procedures[164]. Thirdly, procedural volumes may have been impacted by under-reporting during the pandemic period, but this would not have an effect on the patterns of care and outcomes that this study presented.

In conclusion, there was a 28% reduction in vascular lower limb surgical activity during the COVID-19 pandemic, which was more marked for elective procedures. The overall complication and re-operation rates were comparable to the previous year but mortality was increased, mainly due to concomitant SARS-CoV-2 infection, which was associated

with higher mortality in vascular patients admitted with lower limb ischemic conditions. This indicates that strategies should be developed to define criteria for priority access to care for patients who need it most and which would limit the excess mortality due to delays to treatment. Operational plans should also be in place to enable a rapid return to normal operations while ensuring that the risk of infection for PAD patients is minimised.

Chapter 7. Discussion and Conclusions

7.1 Summary of key findings

CLTI represents a severe form of lower limb atherosclerotic disease with risk of adverse outcomes. Two national reports (NCEPOD in 2014 and GIRFT in 2018) highlighted deficiencies in the management of patients with CLTI with negative impact on patient outcomes, and pointed towards areas where the provision of care could potentially be improved[206,236]. Consequently, the VSGBI PAD QIF recommended specific timelines from referral to treatment for patients with CLTI; 5 days for admitted patients with severe disease, and 14 days for non-admitted patients[237]. This guidance was based on expert opinion rather than evidence, due to the scarcity of studies exploring the association between treatment delays and patient outcomes. Additionally, it was acknowledged that the timescales were challenging, due to the limited resources and high service demand in NHS arterial centres, but specific recommendations on how to achieve them were not provided, owing to lack of evidence-based effective interventions[237].

Delays arise at every step of the patient pathway and have been described in a systematic review by Nickinson et al[240]. Currently, it is unclear which factors contribute most to the delays to revascularisation for patients with CLTI and only a limited number of small studies have investigated their effect on outcomes. It is also worth noting that any changes in the vascular service that aim to address delays may have wider consequences for other patients, the workforce or the organisation itself and their effectiveness may depend on the context in which they are implemented. Therefore, any such efforts should adhere to the principles of quality improvement and implementation science, with clear measurement and evaluation processes. Additionally, there has been no coordinated effort to apply best practice guidance in a systematic manner in the management of this patient group.

This thesis contributes new knowledge to the identified gaps in the literature. Factors associated with delays to treatment in patients with CLTI were identified and ways to address them were explored through the implementation and evaluation of a Quality

Improvement Collaborative programme. The findings from the studies in this thesis and the answers to the five research questions are summarised below.

The population-based cohort study in chapter 2 aimed to identify patient and pathway factors that affect the timing of revascularisation for patients presenting as emergencies with CLTI, using NVR data. Between 2016 and 2019, only 50.6% of patients admitted as emergencies with CLTI to NHS arterial centres received revascularisation within the recommended 5 days from admission. Given the VSGBI best practice guidance for these patients was only published in 2019, it might be argued that it is unreasonable to expect many NHS hospitals to be meeting this standard during the period examined in the study. However, the recommendation reflects a consensus about expected standards of care in the UK, against which services can benchmark their performance and will hopefully motivate improvement. Our findings provide a baseline for comparison with future performance. We also found that the timing of revascularisation was associated with a number of patient characteristics, such as age, comorbidity burden, smoking status, Fontaine score and presenting problem, the type of procedure performed, the hospital procedure volume, and the day of admission, with the worst performance observed on Tuesday and Wednesday. The association of the time to revascularisation with the day of admission is concerning and solutions that remove this source of variation should be sought, such as the delivery of a 7-day service for lower-limb revascularisation, as advocated by GIRFT. However, implementing a 7-day service may be hindered by various factors, such as the limited availability of staff, and IR and surgical operating theatre availability, therefore a feasibility study should be undertaken prior to its widespread adoption.

In chapter 3, a population-based cohort study using data from 10,183 patients collected in HES was conducted to evaluate the association of the timing of revascularisation with major amputation and mortality rates at 1-year for patients admitted to hospital as emergencies with CLTI. It demonstrated that patients undergoing infrainguinal revascularisation for CLTI had 1-year mortality rate of 27.3% and 1-year ipsilateral major amputation rate of 15.7%, with most amputations occurring in the first few months after revascularisation. Longer time from admission to revascularisation was independently and significantly associated with higher mortality in patients with tissue loss but not in

those with less severe forms of PAD. We determined that if all patients with tissue loss were revascularised within 5 days, the 1-year mortality rate would be reduced by 2.3%. There was no evidence of an association between delay to revascularisation and major amputation, after adjustment for patient and admission factors. Interestingly, time to revascularisation was longer for patients with tissue loss compared to those without, indicating that patients with more severe presentation waited longer for revascularisation.

Chapter 4 described the implementation and short-term outcomes of the PAD QIP, a QI collaborative between eleven vascular centres in England. The aim was to assess whether the implementation of changes to the vascular services through a QIC reduced delays to revascularisation in patients presenting with CLTI in line with the PAD QIF recommendations. Various interventions were adopted by the participating centres, such as daily triage of referrals, introduction of urgent one-stop CLTI clinics or urgent slots in existing clinics, expedited imaging, frequent MDTs, dedicated IR sessions, and employment of coordinators that tracked patients along the pathway. Based on a controlled interrupted time series analysis undertaken at the end of the programme using NVR data from 9,608 hospital admissions, the PAD QIP centres significantly increased the proportion of patients revascularised within 5-days, and reduced the length of hospital stay and 30-day readmission rate during the implementation period compared to their baseline. The reduction in LOS and readmission rate was significantly higher than that observed in non-participating UK centres, while the increase in 5-day revascularisations was comparable to the temporal trend of improvement observed in the rest of the UK.

In addition to the quantitative analysis of short-term outcomes, a mixed methods study of 16 semi-structured interviews and an online survey with clinicians from the participating centres was also performed during the implementation period and aimed to identify factors that influenced the local uptake of changes and the success of the QIC in a vascular surgery setting (chapter 5). Facilitating factors associated with the QI collaborative included the concrete timeframes, external performance monitoring, peer comparison, learning from others and sharing of experiences. The main factors facilitating change were the presence of supportive teams and good inter-departmental

networks, a common understanding of the problem and the patient benefit from addressing it, and the managerial support of proposed changes. Conversely, factors that hindered implementation were the differing opinions about resource allocation due to conflicting priorities and resistance to change, the lack of organisational leadership support and the lack of resources. Based on these findings, future QICs in vascular surgery may benefit from retaining the elements of benchmarking, peer comparison and networking in their implementation strategy, and should also ensure the availability of support from organisational leaders and middle managers, dedicated time of lead clinicians for quality improvement, and participation of an enthusiastic multidisciplinary team of professionals prior to implementation.

The COVID-19 pandemic was an important contextual factor that affected the implementation of changes, as three national lockdowns were implemented in the UK from March to February 2021, which caused significant disruption in vascular service delivery[388]. These lockdowns had a mixed effect on the PAD QIP participating centres. Some centre leads aligned the pathway redesign with the overall efforts to minimise patients' time in hospital, and therefore gained resources and permission to proceed. Other centres struggled to make changes due to competing organisational priorities and limited engagement of Trust leadership with any issue that was not related to the pandemic.

A population-based cohort study (chapter 6) aimed to provide more information about the context in which the intervention was implemented, by investigating the effect of the COVID-19 pandemic on the procedure volume, patterns of care, and short-term outcomes of lower limb vascular procedures performed in the UK. This study of 36,938 procedures concluded that there was a 28% reduction in vascular lower limb surgical activity during the COVID-19 pandemic, which was more marked for elective revascularisation procedures. Complication and re-operation rates were comparable to the pre-pandemic levels but mortality was increased and related to concomitant SARS-CoV-2 infection, which was associated with six times higher mortality. The reduction in elective activity described in this chapter may explain the national trends noted in chapter 4, as it increased the availability of operating theatre lists to perform non-elective revascularisation procedures, and modified hospital pathways reduced patient

exposure to hospital, perhaps contributing to a shorter length of stay. Based on these findings, we recommended that every effort should be made to deliver COVID-19-free pathways to minimize operative mortality while vascular services were restored, and that operational plans should be in place to enable a rapid return to normal operations while ensuring minimal risk of infection.

7.2 Limitations

This thesis and its findings also have limitations. Firstly, the studies in chapters 2, 4, and 6 were based on NVR data and while the NVR has a high case-ascertainment for lower-limb open surgical revascularisations (86%), it only captures around 48% of all lower limb endovascular procedures. However, there is no evidence to suggest that procedures were preferentially captured in a way that would alter the results, and indeed many of the missing endovascular procedures may represent day-cases that were excluded from the analyses. Additionally, the NVR does not collect data on patients who did not undergo a revascularisation procedure and were treated conservatively or had primary amputation. Even though the outcome of this patient cohort may be affected by delays to presentation or vascular review, this is outside the scope of the studies in this thesis, as the time-to-revascularisation metric would not be applicable. There may also be inconsistencies in the way that some procedures, such as common femoral endarterectomy, hybrid procedures, and multiple procedures in an admission are captured. To mitigate some of that risk, procedures were manually categorised as hybrid during the analysis if both an endovascular and an open procedure were recorded on the same date. The first procedure of an admission was considered the “index” procedure and further procedures as re-interventions, while multiple admissions of a patient were analysed separately. The laterality of the procedure was not explored in these studies.

Secondly, the NVR dataset does not record previous hospital admissions or outpatient reviews, therefore some of the emergency admissions documented as “non-elective” in the NVR system may represent expedited procedures of patients that followed the outpatient pathway instead of emergency presentations. Thirdly, the NVR does not capture the date of symptom onset, which would be a better marker of delays, or the

complexity of disease, that may be associated with delays due to requirement for additional imaging investigations or multidisciplinary input. It is also possible that some of the variables, such as smoking, may not be accurately captured and that self-reporting may lead to omission of negative outcomes. However, healthcare professionals have a duty to audit and accurately report on their practice according to the General Medical Council's Good Medical Practice guide, therefore conscious "gaming" of the NVR is very unlikely.

Regarding the second study (chapter 3), the data source was an administrative database, which is prone to errors, such as omission of clinical information or inaccurate coding, and does not optimally collect the severity of PAD. Therefore, some patients with emergency CLTI admission may have been excluded from the study. Additionally, the results were adjusted for many patient and admission characteristics that have been associated with mortality or major amputation in previous studies, but there may have been residual confounding factors that were unaccounted for and may have influenced the outcome, such as smoking, atherosclerotic burden, physiological measurements and biochemical markers. This study did not include patients that were treated conservatively or had primary amputation, as time-to-revascularisation was the variable of interest.

In chapter 4, changes to the vascular services were introduced throughout the duration of the programme, not all at the start, and it was not possible to identify the exact time specific interventions were adopted in each centre. Due to this limitation, it is not possible to evaluate how each intervention affected the outcomes, and whether some were more effective than others.

Regarding the mixed methods study in chapter 5, the sample size was relatively small, but there was representation from all centres participating in the programme. Additionally, due to the limited time and human resources, the interview transcripts were coded by a single researcher, and 20% were also reviewed by a supervisor with qualitative background, to ensure that important themes were not missed. We were also unable to explore some factors that have been found to influence implementation

in other studies, due to the limited time of the participating healthcare professionals, therefore interview question topics were selective.

Finally in chapter 6, due to population-based observational study design, there is a possibility that the rate of SARS-CoV-2 infection was under-reported during data collection. Another factor that may have contributed to under-estimation of the rate of SARS-CoV-2 positive patients is the limited availability of diagnostic tests during the first wave of the pandemic. Procedural volumes also may have been impacted by under-reporting during the pandemic period, but this would not have an effect on the patterns of care and outcomes presented in this study.

7.3 Implications for future research and service delivery

There is still limited evidence on the effect of the timing of revascularisation on long-term patient outcomes, especially when measuring time from symptom onset, which is harder to capture compared to the time of referral or time of admission. Further studies should focus on this less explored research topic.

Additionally, factors identified as significantly associated with higher risk of 1-year major amputation in chapter 3, such as male gender, high comorbidity burden, severe frailty, living in a high deprivation area, and the presence of gangrene are not modifiable, therefore further research is required to identify modifiable factors associated with risk of major amputation following revascularisation and potential effective interventions.

Building on the short-term outcomes of the PAD QIP presented in chapter 4, further research is required to ascertain its long-term effects on patient outcomes and the sustainability of the local interventions implemented during the programme.

The findings in chapter 4 also have implications for vascular service delivery, as vascular units seeking to expedite the revascularisation of patients with CLTI can implement the interventions introduced in the participating centres, which appear to be adaptable and generalizable to different contexts.

Further research is also required to evaluate how tailored implementation approaches may address contextual factors that have been identified in this study as barriers to implementation in the vascular surgery setting.

Finally, greater use of the NVR data could be made for research studies, as it is the only database that covers all NHS vascular units and that provides granular clinical data for vascular arterial procedures. The data controllers for the NVR (NHS England, the Welsh government and the Healthcare Quality Improvement Partnership) have established a data access process for researchers, and a steady stream of research groups have made use of this facility[502-504]. However, more could be made of the resource. One option is for the NVR to be used for platform studies, where RCTs are embedded within cohort studies. An advantage of this approach is that it provides high quality data on the number of patients not participating in the RCT and outcomes outside the trial. An example of this approach has already proven successful in Orthopaedics[505,506]. However, this would require significant financial investment in the NVR to change the IT data collection system and cover the additional administrative activities. Moreover, the issues around data access and retention that affect this type of initiatives[507] would need to be addressed for the NVR and the national clinical audit programme as a whole. Finally, if entering data becomes too complex and time-consuming due to the addition of new data items for research (such as Patient Related Outcome Measures), some clinicians may become disengaged. The challenges of this approach are beginning to be addressed though. Research groups with National Institute for Health and Care Research (NIHR) funding for trials of interventions for vascular diseases are planning to use NVR data to augment the data collected from trial participants.

References

1. Aboyans V, Ricco J-B, Bartelink M-LEL, Björck M, Brodmann M, Cohnert T, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS). Eur Heart J. 2018;39(9):763–816.

2. Björck M, Earnshaw JJ, Acosta S, Bastos Gonçalves F, Cochennec F, Debus ES, et al. Editor's Choice - European Society for Vascular Surgery (ESVS) 2020 Clinical Practice Guidelines on the Management of Acute Limb Ischaemia. Eur J Vasc Endovasc Surg. 2020;59(2):173–218.

3. Conte MS, Bradbury AW, Kolh P, White JV, Dick F, Fitridge R, et al. Global Vascular Guidelines on the Management of Chronic Limb-Threatening Ischemia. Eur J Vasc Endovasc Surg. 2019;58(1S):S1-S109.

4. Bell P, Charlesworth D, DePalma R. The defintion of critical ischaemia of a limb. Br J Surg. 1982;69(Supp 6):S2.

5. Dormandy JA, Rutherford RB. Management of peripheral arterial disease (PAD). TransAtlantic Inter-Society Consensus (TASC). Section D: chronic critical limb ischaemia. Eur J Vasc Endovasc Surg. 2000;19(Supp A):S144-243.

6. Song P, Rudan D, Zhu Y, Fowkes FJI, Rahimi K, Fowkes FGR, et al. Global, regional, and national prevalence and risk factors for peripheral artery disease in 2015: an updated systematic review and analysis. Lancet Glob Health [Internet]. 2019 Aug 1 [cited 2022 Dec 13];7(8). doi:10.1016/S2214-109X(19)30255-4

7. Nehler MR, Duval S, Diao L, Annex BH, Hiatt WR, Rogers K, et al. Epidemiology of peripheral arterial disease and critical limb ischemia in an insured national population. J Vasc Surg. 2014;60(3):686-95.

8. Peach G, Griffin M, Jones KG, Thompson MM, Hinchliffe RJ. Diagnosis and management of peripheral arterial disease. BMJ [Internet]. 2012 Aug 14 [cited 2022 Dec 13];345. doi:10.1136/bmj.e5208

9. Wang W, Zhao T, Geng K, Yuan G, Chen Y, Xu Y. Smoking and the Pathophysiology of Peripheral Artery Disease. Front Cardiovasc Med [Internet]. 2021 Aug 27 [cited 2022 Dec 13];8. doi:10.3389/fcvm.2021.704106

10. Ding N, Sang Y, Chen J, Ballew SH, Kalbaugh CA, Salameh MJ, et al. Cigarette Smoking, Smoking Cessation, and Long-Term Risk of 3 Major Atherosclerotic Diseases. J Am Coll Cardiol. 2019;74(4):498–507.

11. Lu L, Mackay DF, Pell JP. Meta-analysis of the association between cigarette smoking and peripheral arterial disease. Heart. 2014;100(5):414–23.

12. Ngu NL, McEvoy M. Environmental tobacco smoke and peripheral arterial disease: A review. Atherosclerosis. 2017;266:113–20.

13. Blomster JI, Woodward M, Zoungas S, Hillis GS, Harrap S, Neal B, et al. The harms of smoking and benefits of smoking cessation in women compared with men with type 2 diabetes: an observational analysis of the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron modified release Controlled Evaluation) trial. BMJ Open [Internet]. 2016 Jan 8 [cited 2022 Dec 14];6(1). doi:10.1136/bmjopen-2015-009668

14. Kokkinidis DG, Giannopoulos S, Haider M, Jordan T, Sarkar A, Singh GD, et al. Active smoking is associated with higher rates of incomplete wound healing after endovascular treatment of critical limb ischemia. Vasc Med. 2020;25(5):427–35.

15. Reitz KM, Althouse AD, Meyer J, Arya S, Goodney PP, Shireman PK, et al. Association of Smoking With Postprocedural Complications Following Open and Endovascular Interventions for Intermittent Claudication. JAMA Cardiol. 2022;7(1):45–54.

16. Willigendael EM, Teijink JAW, Bartelink M-L, Peters RJG, Büller HR, Prins MH. Smoking and the patency of lower extremity bypass grafts: a meta-analysis. J Vasc Surg. 2005;42(1):67–74.

17. GBD 2017 Risk Factor Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet. 2018;392(10159):1923–94.

18. Peruzzi M, Biondi-Zoccai G, Carnevale R, Cavarretta E, Frati G, Versaci F. Vaping Cardiovascular Health Risks: an Updated Umbrella Review. Curr Emerg Hosp Med Rep. 2020;8(3):103–9.

19. Biondi-Zoccai G, Sciarretta S, Bullen C, Nocella C, Violi F, Loffredo L, et al. Acute Effects of Heat-Not-Burn, Electronic Vaping, and Traditional Tobacco Combustion Cigarettes: The Sapienza University of Rome-Vascular Assessment of Proatherosclerotic Effects of Smoking (SUR - VAPES) 2 Randomized Trial. J Am Heart Assoc [Internet]. 2019 Mar 19 [cited 2023 Feb 18];8(6). doi:10.1161/JAHA.118.010455.

20. Hartmann-Boyce J, Lindson N, Butler AR, McRobbie H, Bullen C, Begh R, et al. Electronic cigarettes for smoking cessation. Cochrane Database Syst Rev [Internet]. 2022 Nov 17 [cited 2023 Feb 18];11. doi:10.1002/14651858.CD010216.pub7

21. Neczypor EW, Mears MJ, Ghosh A, Sassano MF, Gumina RJ, Wold LE, et al. E-Cigarettes and Cardiopulmonary Health: Review for Clinicians. Circulation. 2022;145(3):219–32.

22. Adegbola A, Behrendt C-A, Zyriax B-C, Windler E, Kreutzburg T. The impact of nutrition on the development and progression of peripheral artery disease: A systematic review. Clin Nutr. 2022;41(1):49–70.

23. Nosova EV, Conte MS, Grenon SM. Advancing beyond the 'heart-healthy diet' for peripheral arterial disease. J Vasc Surg. 2015;61(1):265–74.

24. Chen G-C, Arthur R, Mossavar-Rahmani Y, Xue X, Haring B, Shadyab AH, et al. Adherence to Recommended Eating Patterns Is Associated With Lower Risk of

Peripheral Arterial Disease: Results From the Women's Health Initiative. Hypertension. 2021;78(2):447–55.

25. Cecchini AL, Biscetti F, Rando MM, Nardella E, Pecorini G, Eraso LH, et al. Dietary Risk Factors and Eating Behaviors in Peripheral Arterial Disease. Int J Mol Sci [Internet]. 2022 Sept 16 [cited 2022 Dec 14];23(18). doi:10.3390/ijms231810814

26. Selçuk N, Albeyoğlu Ş, Bastopcu M, Selçuk İ, Barutca H, Şahan H. Sarcopenia is a risk factor for major adverse cardiac events after surgical revascularization for critical limb ischemia. Vascular. 2023;31(1):64-71

27. Matsubara Y, Matsumoto T, Aoyagi Y, Tanaka S, Okadome J, Morisaki K, et al. Sarcopenia is a prognostic factor for overall survival in patients with critical limb ischemia. J Vasc Surg. 2015;61(4):945–50.

28. Sivaharan A, Boylan L, Witham MD, Nandhra S, Northern Vascular Centre. Sarcopenia in Patients Undergoing Lower Limb Bypass Surgery is Associated with Higher Mortality and Major Amputation Rates. Ann Vasc Surg. 2021;75:227–36.

29. Hicks CW, Yang C, Ndumele CE, Folsom AR, Heiss G, Black JH, et al. Associations of Obesity With Incident Hospitalization Related to Peripheral Artery Disease and Critical Limb Ischemia in the ARIC Study. J Am Heart Assoc [Internet]. 2018 Aug 21 [cited 2022 Dec 14];7(16). doi:10.1161/JAHA.118.008644.

30. Arinze N, Farber A, Levin SR, Cheng TW, Jones DW, Patel VI, et al. Perioperative outcomes after lower extremity bypass and peripheral vascular interventions in patients with morbid obesity and superobesity. J Vasc Surg. 2020;71(2):567-74

31. Murata N, Soga Y, Iida O, Yamauchi Y, Hirano K, Kawasaki D, et al. Complex relationship of body mass index with mortality in patients with critical limb ischemia undergoing endovascular treatment. Eur J Vasc Endovasc Surg. 2015;49(3):297–305.

32. Keller K, Hobohm L, Geyer M, Münzel T, Lavie CJ, Ostad MA, et al. Obesity paradox in peripheral artery disease. Clin Nutr. 2019;38(5):2269–76.

33. Sabbagh C, Nickinson A, Cullen S, Patel B, Dubkova S, Gray L, et al. The Relationship Between Obesity and Amputation-free Survival in Patients Undergoing Lower-limb Revascularisation for Chronic Limb-threatening Ischaemia: A Retrospective Cohort Study. Ann Vasc Surg. 2022;78:288–94.

34. Lin DS-H, Lo H-Y, Yu A-L, Lee J-K, Chien K-L. Mortality risk in patients with underweight or obesity with peripheral artery disease: a meta-analysis including 5,735,578 individuals. Int J Obes. 2022;46(8):1425–34.

35. Lu Y, Ballew SH, Kwak L, Selvin E, Kalbaugh CA, Schrack JA, et al. Physical Activity and Subsequent Risk of Hospitalization With Peripheral Artery Disease and Critical Limb Ischemia in the ARIC Study. J Am Heart Assoc [Internet]. 2019 Nov 5 [cited 2022 Dec 15]; 8(21). doi:10.1161/JAHA.119.013534

36. Lane R, Harwood A, Watson L, Leng GC. Exercise for intermittent claudication. Cochrane Database Syst Rev [Internet]. 2017 Dec 26 [cited 2022 Dec 15]; 12. doi:10.1002/14651858.CD000990.pub4

37. Joosten MM, Pai JK, Bertoia ML, Rimm EB, Spiegelman D, Mittleman MA, et al. Associations between conventional cardiovascular risk factors and risk of peripheral artery disease in men. JAMA. 2012;308(16):1660–7.

38. American Diabetes Association. Peripheral Arterial Disease in People With Diabetes. Diabetes Care. 2003;26(12):3333–41.

39. Zhang Y, Lazzarini PA, McPhail SM, van Netten JJ, Armstrong DG, Pacella RE. Global Disability Burdens of Diabetes-Related Lower-Extremity Complications in 1990 and 2016. Diabetes Care. 2020;43(5):964–74.

40. Lin X, Xu Y, Pan X, Xu J, Ding Y, Sun X, et al. Global, regional, and national burden and trend of diabetes in 195 countries and territories: an analysis from 1990 to 2025. Sci Rep [Internet]. 2020 Sept 8 [cited 2022 Dec 15]; 10(1). doi:10.1038/s41598-020-71908-9

41. Jude EB, Oyibo SO, Chalmers N, Boulton AJ. Peripheral arterial disease in diabetic and nondiabetic patients: a comparison of severity and outcome. Diabetes Care. 2001;24(8):1433–7.

42. Low Wang CC, Blomster JI, Heizer G, Berger JS, Baumgartner I, Fowkes FGR, et al. Cardiovascular and Limb Outcomes in Patients With Diabetes and Peripheral Artery Disease: The EUCLID Trial. J Am Coll Cardiol. 2018;72(25):3274–84.

43. Hicks CW, Najafian A, Farber A, Menard MT, Malas MB, Black JH, et al. Diabetes does not worsen outcomes following infrageniculate bypass or endovascular intervention for patients with critical limb ischemia. J Vasc Surg. 2016;64(6):1667-74

44. Baubeta Fridh E, Andersson M, Thuresson M, Sigvant B, Kragsterman B, Johansson S, et al. Editor's Choice – Impact of Comorbidity, Medication, and Gender on Amputation Rate Following Revascularisation for Chronic Limb Threatening Ischaemia. Eur J Vasc Endovasc Surg. 2018;56(5):681–8.

45. Yap T, Silickas J, Weerakkody R, Lea T, Santhirakumaran G, Bremner L, et al. Predictors of outcome in diabetic patients undergoing infrapopliteal endovascular revascularization for chronic limb-threatening ischemia. J Vasc Surg. 2022;75(2):618–24.

46. Lu Y, Ballew SH, Tanaka H, Szklo M, Heiss G, Coresh J, et al. 2017 ACC/AHA blood pressure classification and incident peripheral artery disease: The Atherosclerosis Risk in Communities (ARIC) Study. Eur J Prev Cardiol. 2020;27(1):51–9.

47. Bhatt DL, Steg PG, Ohman EM, Hirsch AT, Ikeda Y, Mas J-L, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. JAMA. 2006;295(2):180–9.

48. Ya'qoub L, Peri-Okonny P, Wang J, Patel KK, Stone N, Smolderen K. Blood pressure management in patients with symptomatic peripheral artery disease:

insights from the PORTRAIT registry. Eur Heart J Qual Care Clin Outcomes. 2019;5(1):79–81.

49. Aday AW, Lawler PR, Cook NR, Ridker PM, Mora S, Pradhan AD. Lipoprotein Particle Profiles, Standard Lipids, and Peripheral Artery Disease Incidence. Circulation. 2018;138(21):2330–41.

50. Aday AW, Everett BM. Dyslipidemia Profiles in Patients with Peripheral Artery Disease. Curr Cardiol Rep [Internet]. 2019 Apr 2022 [cited 2022 Dec 15]; 21(6). doi:10.1007/s11886-019-1129-5

51. Kou M, Ding N, Ballew SH, Salameh MJ, Martin SS, Selvin E, et al. Conventional and Novel Lipid Measures and Risk of Peripheral Artery Disease. Arterioscler Thromb Vasc Biol. 2021;41(3):1229–38.

52. Matsushita K, Ballew SH, Wang AY-M, Kalyesubula R, Schaeffner E, Agarwal R. Epidemiology and risk of cardiovascular disease in populations with chronic kidney disease. Nat Rev Nephrol. 2022;18(11):696–707.

53. Arinze NV, Gregory A, Francis JM, Farber A, Chitalia VC. Unique aspects of peripheral artery disease in patients with chronic kidney disease. Vasc Med. 2019;24(3):251–60.

54. Matsushita K, Ballew SH, Coresh J, Arima H, Ärnlöv J, Cirillo M, et al. Measures of chronic kidney disease and risk of incident peripheral artery disease: a collaborative meta-analysis of individual participant data. Lancet Diabetes Endocrinol. 2017;5(9):718–28.

55. Bourrier M, Ferguson TW, Embil JM, Rigatto C, Komenda P, Tangri N. Peripheral Artery Disease: Its Adverse Consequences With and Without CKD. Am J Kidney Dis. 2020;75(5):705–12.

56. Elbadawi A, Elgendy IY, Megaly M, Elzeneini M, Mentias A, Omer M, et al. Temporal trends and outcomes of critical limb ischemia among patients with chronic kidney disease. Vasc Med. 2021;26(2):155–63.

57. Smilowitz NR, Bhandari N, Berger JS. Chronic kidney disease and outcomes of lower extremity revascularization for peripheral artery disease. Atherosclerosis. 2020;297:149–56.

58. Fallon JM, Goodney PP, Stone DH, Patel VI, Nolan BW, Kalish JA, et al. Outcomes of lower extremity revascularization among the hemodialysis-dependent. J Vasc Surg. 2015;62(5):1183-91.

59. Srivaratharajah K, Abramson BL. Women and Peripheral Arterial Disease: A Review of Sex Differences in Epidemiology, Clinical Manifestations, and Outcomes. Can J Cardiol. 2018;34(4):356–61.

60. Hirsch AT, Allison MA, Gomes AS, Corriere MA, Duval S, Ershow AG, et al. A call to action: women and peripheral artery disease: a scientific statement from the American Heart Association. Circulation. 2012;125(11):1449–72.

61. Lo RC, Bensley RP, Dahlberg SE, Matyal R, Hamdan AD, Wyers M, et al. Presentation, treatment, and outcome differences between men and women undergoing revascularization or amputation for lower extremity peripheral arterial disease. J Vasc Surg. 2014;59(2):409-18.

62. Makowski L, Köppe J, Engelbertz C, Kühnemund L, Fischer AJ, Lange SA, et al. Sex-related differences in treatment and outcome of chronic limb-threatening ischaemia: a real-world cohort. Eur Heart J. 2022;43(18):1759–70.

63. Parvar SL, Thiyagarajah A, Nerlekar N, King P, Nicholls SJ. A systematic review and meta-analysis of gender differences in long-term mortality and cardiovascular events in peripheral artery disease. J Vasc Surg. 2021;73(4):1456-65.

64. Conde ID, Erwin PA. Evaluation of the Patient Who Presents With Critical Limb Ischemia: Diagnosis, Prognosis, and Medical Management. Tech Vasc Interv Radiol. 2014;17(3):140–6.

65. Khan T, Plotkin A, Magee GA, Shin L, Woelfel SL, Ziegler KR, et al. Functional ambulatory status as a potential adjunctive decision-making tool following wound, level of ischemia, and severity of foot infection assessment. J Vasc Surg. 2020;72(2):738–46.

66. Flu HC, Lardenoye JHP, Veen EJ, Van Berge Henegouwen DP, Hamming JF. Functional status as a prognostic factor for primary revascularization for critical limb ischemia. J Vasc Surg. 2010;51(2):360-71.

67. Insall RL, Davies RJ, Prout WG. Significance of Buerger's test in the assessment of lower limb ischaemia. J R Soc Med. 1989;82(12):729–31.

68. Armstrong DWJ, Tobin C, Matangi MF. The accuracy of the physical examination for the detection of lower extremity peripheral arterial disease. Can J Cardiol. 2010;26(10):e346-50.

69. Londero LS, Lindholt JS, Thomsen MD, Hoegh A. Pulse palpation is an effective method for population-based screening to exclude peripheral arterial disease. J Vasc Surg. 2016;63(5):1305–10.

70. Lam K, van Asten SAV, Nguyen T, La Fontaine J, Lavery LA. Diagnostic Accuracy of Probe to Bone to Detect Osteomyelitis in the Diabetic Foot: A Systematic Review. Clin Infect Dis. 2016;63(7):944–8.

71. Forsythe RO, Apelqvist J, Boyko EJ, Fitridge R, Hong JP, Katsanos K, et al. Effectiveness of bedside investigations to diagnose peripheral artery disease among people with diabetes mellitus: A systematic review. Diabetes Metab Res Rev [Internet]. 2020 Mar 16 [cited 2022 Dec 16];36(S1). doi:10.1002/dmrr.3277.

72. Aboyans V, Criqui MH, Abraham P, Allison MA, Creager MA, Diehm C, et al. Measurement and Interpretation of the Ankle-Brachial Index: a scientific statement from the American Heart Association. Circulation. 2012;126(24):2890–909.

73. Aday AW, Kinlay S, Gerhard-Herman MD. Comparison of different exercise ankle pressure indices in the diagnosis of peripheral artery disease. Vasc Med. 2018;23(6):541–8.

74. Brouwers JJWM, Willems SA, Goncalves LN, Hamming JF, Schepers A. Reliability of bedside tests for diagnosing peripheral arterial disease in patients prone to medial arterial calcification: A systematic review. EClinicalMedicine [Internet]. 2022 Aug 1 [cited 2022 Dec 16]; 50. doi:10.1016/j.eclinm.2022.101532

75. Normahani P, Poushpas S, Alaa M, Bravis V, Sounderajah V, Aslam M, et al. Diagnostic Accuracy of Point-of-care Tests Used to Detect Arterial Disease in Diabetes: TEsting for Arterial Disease in Diabetes (TrEAD) Study. Ann Surg. 2022;276(5):e605–12.

76. Herraiz-Adillo Á, Cavero-Redondo I, Álvarez-Bueno C, Pozuelo-Carrascosa DP, Solera-Martínez M. The accuracy of toe brachial index and ankle brachial index in the diagnosis of lower limb peripheral arterial disease: A systematic review and meta-analysis. Atherosclerosis. 2020;315:81–92.

77. Wang Z, Hasan R, Firwana B, Elraiyah T, Tsapas A, Prokop L, et al. A systematic review and meta-analysis of tests to predict wound healing in diabetic foot. J Vasc Surg. 2016;63(Supp 2):29S-36S

78. Salaun P, Desormais I, Lapébie F-X, Rivière AB, Aboyans V, Lacroix P, et al. Comparison of Ankle Pressure, Systolic Toe Pressure, and Transcutaneous Oxygen Pressure to Predict Major Amputation After 1 Year in the COPART Cohort. Angiology. 2019;70(3):229–36.

79. Forsythe RO, Apelqvist J, Boyko EJ, Fitridge R, Hong JP, Katsanos K, et al. Performance of prognostic markers in the prediction of wound healing or amputation among patients with foot ulcers in diabetes: A systematic review. Diabetes Metab Res Rev [Internet]. 2020 Mar 16 [cited 2022 Dec 16]; 36(S1). doi:10.1002/dmrr.3278

80. National Institute for Health and Care Excellence (UK). Peripheral arterial disease: diagnosis and management Clinical guideline [CG147] [Internet]. London: National Institute for Health and Care Excellence (UK); 2020 [cited 2022 May 31]. Available from: https://www.nice.org.uk/guidance/cg147

81. Martinelli O, Alunno A, Jabbour J, Cuozzo S, Gattuso R. Duplex ultrasound as a reliable alternative to CT angiography for treatment planning of peripheral artery disease. Int Angiol. 2021;40(4):306–14.

82. Saarinen E, Laukontaus SJ, Albäck A, Venermo M. Duplex surveillance after endovascular revascularisation for critical limb ischaemia. Eur J Vasc Endovasc Surg. 2014;47(4):418–21.

83. Abu Dabrh AM, Mohammed K, Farah W, Haydour Q, Zierler RE, Wang Z, et al. Systematic review and meta-analysis of duplex ultrasound surveillance for infrainguinal vein bypass grafts. J Vasc Surg. 2017;66(6):1885-91.

84. Shwaiki O, Rashwan B, Fink MA, Kirksey L, Gadani S, Karuppasamy K, et al. Lower extremity CT angiography in peripheral arterial disease: from the established approach to evolving technical developments. Int J Cardiovasc Imaging. 2021;37(10):3101–14.

85. Met R, Bipat S, Legemate DA, Reekers JA, Koelemay MJW. Diagnostic Performance of Computed Tomography Angiography in Peripheral Arterial Disease: A Systematic Review and Meta-analysis. JAMA. 2009;301(4):415–24.

86. Moos SI, van Vemde DNH, Stoker J, Bipat S. Contrast induced nephropathy in patients undergoing intravenous (IV) contrast enhanced computed tomography (CECT) and the relationship with risk factors: A meta-analysis. Eur J Radiol. 2013;82(9):e387–99.

87. Menke J, Larsen J. Meta-analysis: Accuracy of contrast-enhanced magnetic resonance angiography for assessing steno-occlusions in peripheral arterial disease. Ann Intern Med. 2010;153(5):325–34.

88. Kribben A, Witzke O, Hillen U, Barkhausen J, Daul AE, Erbel R. Nephrogenic Systemic Fibrosis: Pathogenesis, Diagnosis, and Therapy. J Am Coll Cardiol. 2009;53(18):1621–8.

89. Verma M, Pandey NN, Singh V, Jagia P. A meta-analysis of the diagnostic performance of quiescent-interval-single-shot magnetic resonance angiography in peripheral arterial disease. Eur Radiol. 2022;32(4):2393–403.

90. Cury MVM, Matielo MF, Brochado Neto FC, Soares R de A, Adami VL, Morais JDF, et al. The Incidence, Risk Factors, and Outcomes of Contrast-Induced Nephropathy In Patients With Critical Limb Ischemia Following Lower Limb Angiography. Angiology. 2018;69(8):700–8.

91. Palena LM, Diaz-Sandoval LJ, Candeo A, Brigato C, Sultato E, Manzi M. Automated Carbon Dioxide Angiography for the Evaluation and Endovascular Treatment of Diabetic Patients With Critical Limb Ischemia. J Endovasc Ther. 2016;23(1):40–8.

92. Fontaine R, Kim M, Kieny R. [Surgical treatment of peripheral circulation disorders]. Helv Chir Acta. 1954;21(5–6):499–533.

93. Rutherford RB, Baker JD, Ernst C, Johnston KW, Porter JM, Ahn S, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. J Vasc Surg. 1997;26(3):517–38.

94. Azuma N. The Diagnostic Classification of Critical Limb Ischemia. Ann Vasc Dis. 2018;11(4):449–57.

95. Mills JL, Conte MS, Armstrong DG, Pomposelli FB, Schanzer A, Sidawy AN, et al. The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: risk stratification based on wound, ischemia, and foot infection (WIfI). J Vasc Surg. 2014;59(1):220-34.

96. van Reijen NS, Ponchant K, Ubbink DT, Koelemay MJW. Editor’s Choice - The Prognostic Value of the WIfI Classification in Patients with Chronic Limb

Threatening Ischaemia: A Systematic Review and Meta-Analysis. Eur J Vasc Endovasc Surg. 2019;58(3):362–71.

97. Hicks CW, Canner JK, Mathioudakis N, Sherman R, Malas MB, Black JH, et al. The Society for Vascular Surgery Wound, Ischemia, and foot Infection (WIfI) classification independently predicts wound healing in diabetic foot ulcers. J Vasc Surg. 2018;68(4):1096–103.

98. Weaver ML, Hicks CW, Canner JK, Sherman RL, Hines KF, Mathioudakis N, et al. The Society for Vascular Surgery Wound, Ischemia, and foot Infection (WIfI) classification system predicts wound healing better than direct angiosome perfusion in diabetic foot wounds. J Vasc Surg. 2018;68(5):1473–81.

99. Hata Y, Iida O, Asai M, Masuda M, Okamoto S, Ishihara T, et al. Risk Stratification for 2-Year Mortality in Patients with Chronic Limb-Threatening Ischemia Undergoing Endovascular Therapy. J Atheroscler Thromb. 2021;28(5):477–82.

100. Mayor J, Chung J, Zhang Q, Montero-Baker M, Schanzer A, Conte MS, et al. Using the Society for Vascular Surgery Wound, Ischemia, and foot Infection classification to identify patients most likely to benefit from revascularization. J Vasc Surg. 2019;70(3):776-85.

101. Hicks CW, Canner JK, Sherman RL, Black JH, Lum YW, Abularrage CJ. Evaluation of revascularization benefit quartiles using the Wound, Ischemia, and foot Infection classification system for diabetic patients with chronic limb-threatening ischemia. J Vasc Surg. 2021;74(4):1232-9.

102. Leithead C, Novak Z, Spangler E, Passman MA, Witcher A, Patterson MA, et al. Importance of postprocedural Wound, Ischemia, and foot Infection (WIfI) restaging in predicting limb salvage. J Vasc Surg. 2018;67(2):498–505.

103. Monteiro-Soares M, Boyko EJ, Jeffcoate W, Mills JL, Russell D, Morbach S, et al. Diabetic foot ulcer classifications: A critical review. Diabetes Metab Res Rev [Internet]. 2020 Mar 16 [cited 2022 Dec 17]; 36(S1). doi:10.1002/dmrr.3272.

104. Wagner FW. The Dysvascular Foot: A System for Diagnosis and Treatment. Foot Ankle. 1981;2(2):64–122.

105. Armstrong DG, Lavery LA, Harkless LB. Validation of a diabetic wound classification system. The contribution of depth, infection, and ischemia to risk of amputation. Diabetes Care. 1998;21(5):855–9.

106. Lavery LA, Armstrong DG, Murdoch DP, Peters EJG, Lipsky BA. Validation of the Infectious Diseases Society of America's diabetic foot infection classification system. Clin Infect Dis. 2007;44(4):562–5.

107. Monteiro-Soares M, Russell D, Boyko EJ, Jeffcoate W, Mills JL, Morbach S, et al. Guidelines on the classification of diabetic foot ulcers (IWGDF 2019). Diabetes Metab Res Rev [Internet]. 2020 Mar 16 [cited 2022 Dec 17]; 36 (Supp 1). doi:10.1002/dmrr.3273

108. Ince P, Abbas ZG, Lutale JK, Basit A, Ali SM, Chohan F, et al. Use of the SINBAD classification system and score in comparing outcome of foot ulcer management on three continents. Diabetes Care. 2008;31(5):964–7.

109. Jaff MR, White CJ, Hiatt WR, Fowkes GR, Dormandy J, Razavi M, et al. An Update on Methods for Revascularization and Expansion of the TASC Lesion Classification to Include Below-the-Knee Arteries: A Supplement to the Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). Vasc Med. 2015;20(5):465–78.

110. Kodama A, Meecham L, Popplewell M, Bate G, Conte MS, Bradbury AW. Editor's Choice - Relationship Between Global Limb Anatomic Staging System (GLASS) and Clinical Outcomes Following Revascularisation for Chronic Limb Threatening Ischaemia in the Bypass Versus Angioplasty in Severe Ischaemia of the Leg (BASIL)-1 Trial. Eur J Vasc Endovasc Surg. 2020;60(5):687–95.

111. El Khoury R, Wu B, Edwards CT, Lancaster EM, Hiramoto JS, Vartanian SM, et al. The Global Limb Anatomic Staging System is associated with outcomes of

infrainguinal revascularization in chronic limb threatening ischemia. J Vasc Surg. 2021;73(6):2009-20.

112. Morisaki K, Matsubara Y, Yoshino S, Kurose S, Yamashita S, Furuyama T, et al. Validation of the GLASS Staging Systems in Patients With Chronic Limb-Threatening Ischemia Undergoing De Novo Infrainguinal Revascularization. Ann Vasc Surg. 2022;81:378–86.

113. Nice Guideline Updates Team. Peripheral Arterial Disease: Diagnosis and Management: [A] Evidence review for determining diagnosis and severity of PAD in people with diabetes. diabetes [Internet]. London: National Institute for Health and Care Excellence (UK); 2018. [cited 2022 Dec 17]. Available from: https://www.nice.org.uk/guidance/cg147/evidence

114. The Vascular and Endovascular Research Network (VERN) COVER study collaborative. Global impact of the first coronavirus disease 2019 (COVID-19) pandemic wave on vascular services. Br J Surg. 2020;107(11):1396–400.

115. Saxon JT, Safley DM, Mena-Hurtado C, Heyligers J, Fitridge R, Shishehbor M, et al. Adherence to Guideline-Recommended Therapy-Including Supervised Exercise Therapy Referral-Across Peripheral Artery Disease Specialty Clinics: Insights From the International PORTRAIT Registry. J Am Heart Assoc [Internet]. 2020 Jan 24 [cited 2022 Dec 18]; 9(3). doi:10.1161/JAHA.119.012541

116. van Haelst STW, Koopman C, den Ruijter HM, Moll FL, Visseren FL, Vaartjes I, et al. Cardiovascular and all-cause mortality in patients with intermittent claudication and critical limb ischaemia. Br J Surg. 2018;105(3):252–61.

117. Armstrong EJ, Chen DC, Westin GG, Singh S, McCoach CE, Bang H, et al. Adherence to Guideline-Recommended Therapy Is Associated With Decreased Major Adverse Cardiovascular Events and Major Adverse Limb Events Among Patients With Peripheral Arterial Disease. J Am Heart Assoc [Internet]. 2014 Apr 10 [cited 2022 Dec 18]; 3(2). doi:10.1161/JAHA.113.000697.

118. Armstrong EJ, Wu J, Singh GD, Dawson DL, Pevec WC, Amsterdam EA, et al. Smoking cessation is associated with decreased mortality and improved amputation-free survival among patients with symptomatic peripheral artery disease. J Vasc Surg. 2014;60(6):1565–71.

119. Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. Cochrane Database Syst Rev [Internet]. 2013 May 31 [cited 2022 Dec 18];2013(5). doi:10.1002/14651858.CD009329.pub2/full

120. Thanigaimani S, Drovandi A, Golledge J. A meta-analysis of randomized controlled trials evaluating the efficacy of smoking cessation interventions in people with peripheral artery disease. J Vasc Surg. 2022;75(2):721-9.

121. Abola MTB, Golledge J, Miyata T, Rha S-W, Yan BP, Dy TC, et al. Asia-Pacific Consensus Statement on the Management of Peripheral Artery Disease: A Report from the Asian Pacific Society of Atherosclerosis and Vascular Disease Asia-Pacific Peripheral Artery Disease Consensus Statement Project Committee. J Atheroscler Thromb. 2020;27(8):809–907.

122. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ. 2002;324(7329):71–86.

123. Critical Leg Ischaemia Prevention Study (CLIPS) Group, Catalano M, Born G, Peto R. Prevention of serious vascular events by aspirin amongst patients with peripheral arterial disease: randomized, double-blind trial. J Intern Med. 2007;261(3):276–84.

124. Antithrombotic Trialists' (ATT) Collaboration, Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. The Lancet. 2009;373(9678):1849–60.

125. Berger JS, Krantz MJ, Kittelson JM, Hiatt WR. Aspirin for the prevention of cardiovascular events in patients with peripheral artery disease: a meta-analysis of randomized trials. JAMA. 2009;301(18):1909–19.

126. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). The Lancet. 1996;348(9038):1329–39.

127. Hiatt WR, Fowkes FGR, Heizer G, Berger JS, Baumgartner I, Held P, et al. Ticagrelor versus Clopidogrel in Symptomatic Peripheral Artery Disease. N Engl J Med. 2017;376(1):32–40.

128. Katsanos K, Spiliopoulos S, Saha P, Diamantopoulos A, Karunanithy N, Krokidis M, et al. Comparative Efficacy and Safety of Different Antiplatelet Agents for Prevention of Major Cardiovascular Events and Leg Amputations in Patients with Peripheral Arterial Disease: A Systematic Review and Network Meta-Analysis. PloS One [Internet]. 2015 Aug 14 [cited 2022 Dec 19]; 10(8). doi:10.1371/journal.pone.0135692

129. Ambler GK, Waldron C-A, Contractor UB, Hinchliffe RJ, Twine CP. Umbrella review and meta-analysis of antiplatelet therapy for peripheral artery disease. Br J Surg. 2020;107(1):20–32.

130. Anand SS, Bosch J, Eikelboom JW, Connolly SJ, Diaz R, Widimsky P, et al. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. The Lancet. 2018;391(10117):219–29.

131. Bonaca MP, Bauersachs RM, Anand SS, Debus ES, Nehler MR, Patel MR, et al. Rivaroxaban in Peripheral Artery Disease after Revascularization. N Engl J Med. 2020;382(21):1994–2004.

132. Kaplovitch E, Eikelboom JW, Dyal L, Aboyans V, Abola MT, Verhamme P, et al. Rivaroxaban and Aspirin in Patients With Symptomatic Lower Extremity

Peripheral Artery Disease: A Subanalysis of the COMPASS Randomized Clinical Trial. JAMA Cardiol. 2021;6(1):21–9.

133. Heart Protection Study Collaborative Group. Randomized trial of the effects of cholesterol-lowering with simvastatin on peripheral vascular and other major vascular outcomes in 20,536 people with peripheral arterial disease and other high-risk conditions. J Vasc Surg. 2007;45(4):645–54.

134. Sofat S, Chen X, Chowdhury MM, Coughlin PA. Effects of Statin Therapy and Dose on Cardiovascular and Limb Outcomes in Peripheral Arterial Disease: A Systematic Review and Meta-analysis. Eur J Vasc Endovasc Surg. 2021;62(3):450–61.

135. Kokkinidis DG, Arfaras-Melainis A, Giannopoulos S, Katsaros I, Jawaid O, Jonnalagadda AK, et al. Statin therapy for reduction of cardiovascular and limb-related events in critical limb ischemia: A systematic review and meta-analysis. Vasc Med. 2020;25(2):106–17.

136. Peters F, Kuchenbecker J, Kreutzburg T, Marschall U, Debus ES, Behrendt C-A. Long-Term Effectiveness and Safety of Initiating Statin Therapy After Index Revascularization In Patients With Peripheral Arterial Occlusive Disease. J Am Heart Assoc. [Internet]. 2020 Nov 17 [cited 2022 Dec 19]; 9(22). doi:10.1161/JAHA.120.018338

137. Arya S, Khakharia A, Binney ZO, DeMartino RR, Brewster LP, Goodney PP, et al. Association of Statin Dose With Amputation and Survival in Patients With Peripheral Artery Disease. Circulation. 2018;137(14):1435–46.

138. O'Donnell TFX, Deery SE, Darling JD, Shean KE, Mittleman MA, Yee GN, et al. Adherence to lipid management guidelines is associated with lower mortality and major adverse limb events in patients undergoing revascularization for chronic limb-threatening ischemia. J Vasc Surg. 2017;66(2):572–8.

139. Belur AD, Shah AJ, Virani SS, Vorla M, Kalra DK. Role of Lipid-Lowering Therapy in Peripheral Artery Disease. J Clin Med [Internet]. 2022 Aug 19 [cited 2023 Dec 19]; 11(16). doi:10.3390/jcm11164872.

140. Skeik N, Nowariak ME, Smith JE, Alexander JQ, Manunga JM, Mirza AK, et al. Lipid-lowering therapies in peripheral artery disease: A review. Vasc Med. 2021;26(1):71–80.

141. Bonaca MP, Nault P, Giugliano RP, Keech AC, Pineda AL, Kanevsky E, et al. Low-Density Lipoprotein Cholesterol Lowering With Evolocumab and Outcomes in Patients With Peripheral Artery Disease: Insights From the FOURIER Trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk). Circulation. 2018;137(4):338–50.

142. Nastasi DR, Moxon JV, Norman R, Trollope AF, Rowbotham S, Quigley F, et al. The cost-effectiveness of intensive low-density lipoprotein cholesterol lowering in people with peripheral artery disease. J Vasc Surg. 2021;73(4):1396-403.

143. SPRINT Research Group, Lewis CE, Fine LJ, Beddhu S, Cheung AK, Cushman WC, et al. Final Report of a Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med. 2021;384(20):1921–30.

144. ACCORD Study Group, Cushman WC, Evans GW, Byington RP, Goff DC, Grimm RH, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med. 2010;362(17):1575–85.

145. Saiz LC, Gorricho J, Garjón J, Celaya MC, Erviti J, Leache L. Blood pressure targets for the treatment of people with hypertension and cardiovascular disease. Cochrane Database Syst Rev. [Internet]. 2022 Nov 18 [cited 2022 Dec 20]; 11. doi:10.1002/14651858.CD010315.pub5

146. Thomas Manapurathe D, Moxon JV, Krishna SM, Rowbotham S, Quigley F, Jenkins J, et al. Cohort Study Examining the Association Between Blood Pressure and Cardiovascular Events in Patients With Peripheral Artery Disease. J Am Heart

Assoc. [Internet]. 2019 Mar 19 [cited 2022 Dec 20]; 8(6). doi:10.1161/JAHA.118.010748

147. Bavry AA, Anderson RD, Gong Y, Denardo SJ, Cooper-Dehoff RM, Handberg EM, et al. Outcomes Among hypertensive patients with concomitant peripheral and coronary artery disease: findings from the INternational VErapamil-SR/Trandolapril STudy. Hypertension. 2010;55(1):48–53.

148. Ostergren J, Sleight P, Dagenais G, Danisa K, Bosch J, Qilong Y, et al. Impact of ramipril in patients with evidence of clinical or subclinical peripheral arterial disease. Eur Heart J. 2004;25(1):17–24.

149. Kray JE, Dombrovskiy VY, Vogel TR. Use of angiotensin-converting enzyme inhibitors and freedom from amputation after lower extremity revascularization. Vasc Health Risk Manag. 2017;13:269–74.

150. Høgh A, Lindholt JS, Nielsen H, Jensen LP, Johnsen SP. Use of angiotensin-converting enzyme inhibitors and cardiovascular outcomes following primary vascular surgery: a nationwide propensity score matched follow-up study. Vasc Endovascular Surg. 2012;46(7):515–23.

151. Bodewes TCF, Darling JD, O'Donnell TFX, Deery SE, Shean KE, Mittleman MA, et al. Long-term mortality benefit of renin-angiotensin system inhibitors in patients with chronic limb-threatening ischemia undergoing vascular intervention. J Vasc Surg. 2018;67(3):800-8.

152. Khan SZ, O'Brien-Irr MS, Rivero M, Blochle R, Cherr GS, Dryjski ML, et al. Improved survival with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in chronic limb-threatening ischemia. J Vasc Surg. 2020;72(6):2130–8.

153. Paravastu SCV, Mendonca DA, Da Silva A. Beta blockers for peripheral arterial disease. Cochrane Database Syst Rev. [Internet]. 2013 Sep 11 [cited 2022 Dec 21]; 9. doi:10.1002/14651858.CD005508.pub3.

154. Thomas Manapurathe D, Krishna SM, Dewdney B, Moxon JV, Biros E, Golledge J. Effect of blood pressure lowering medications on leg ischemia in peripheral artery disease patients: A meta-analysis of randomised controlled trials. PloS One [Internet]. 2017 Jun 2 [cited 2022 Dec 21]; 12(6). doi:10.1371/journal.pone.0178713

155. Arya S, Binney ZO, Khakharia A, Long CA, Brewster LP, Wilson PW, et al. High hemoglobin A1c associated with increased adverse limb events in peripheral arterial disease patients undergoing revascularization. J Vasc Surg. 2018;67(1):217-28.

156. Goldman MP, Clark CJ, Craven TE, Davis RP, Williams TK, Velazquez-Ramirez G, et al. Effect of Intensive Glycemic Control on Risk of Lower Extremity Amputation. J Am Coll Surg. 2018;227(6):596–604.

157. Singh N, Zeng C, Lewinger JP, Wolfson AM, Shavelle D, Weaver F, et al. Preoperative hemoglobin A1c levels and increased risk of adverse limb events in diabetic patients undergoing infrainguinal lower extremity bypass surgery in the Vascular Quality Initiative. J Vasc Surg. 2019;70(4):1225-34.

158. McGinigle KL, Kindell DG, Strassle PD, Crowner JR, Pascarella L, Farber MA, et al. Poor glycemic control is associated with significant increase in major limb amputation and adverse events in the 30-day postoperative period after infrainguinal bypass. J Vasc Surg. 2020;72(3):987–94.

159. Lee A, Haddad D, Rybin D, Howell C, Ghaderi I, Berman S, et al. The impact of hemoglobin A1c on outcomes after lower extremity bypass. J Vasc Surg. 2021;73(4):1332-39.

160. Cha J-J, Kim H, Ko Y-G, Choi D, Lee J-H, Yoon C-H, et al. Influence of preprocedural glycemic control on clinical outcomes of endovascular therapy in diabetic patients with lower extremity artery disease: an analysis from a Korean multicenter retrospective registry cohort. Cardiovasc Diabetol [Internet]. 2020 Jun 22 [cited 2022 Dec 22]; 19. doi:10.1186/s12933-020-01072-x.

161. Verma S, Mazer CD, Al-Omran M, Inzucchi SE, Fitchett D, Hehnke U, et al. Cardiovascular Outcomes and Safety of Empagliflozin in Patients With Type 2 Diabetes Mellitus and Peripheral Artery Disease: A Subanalysis of EMPA-REG OUTCOME. Circulation. 2018;137(4):405–7.

162. Li D, Yang JY, Wang T, Shen S, Tang H. Risks of diabetic foot syndrome and amputation associated with sodium glucose co-transporter 2 inhibitors: A Meta-analysis of Randomized Controlled Trials. Diabetes Metab. 2018;44(5):410–4.

163. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med. 2017;377(7):644–57.

164. Waton S, Johal A, Birmpili P, Li Q, Atkins E, Cromwell DA, et al. National Vascular Registry: 2022 Annual Report [Internet]. London: The Royal College of Surgeons of England; 2022 Nov [cited 2022 Dec 22]. Available from: https://www.vsqip.org.uk/reports/2022-annual-report/

165. Mills JL. 18. Lower Extremity Arterial Disease. In: Cronenwett JL, Johnston KW, editors. Rutherford's Vascular Surgery. 8th ed. Philadelphia, PA: Elsevier; 2014. p. 1660–860.

166. Rychlik IJ, Davey P, Murphy J, O'Donnell ME. A meta-analysis to compare Dacron versus polytetrafluroethylene grafts for above-knee femoropopliteal artery bypass. J Vasc Surg. 2014;60(2):506–15.

167. Ambler GK, Twine CP. Graft type for femoro-popliteal bypass surgery. Cochrane Database Syst Rev. [Internet]. 2018 Feb 11 [cited 2022 Dec 22]; 2. doi:10.1002/14651858.CD001487.pub3.

168. Almasri J, Adusumalli J, Asi N, Lakis S, Alsawas M, Prokop LJ, et al. A systematic review and meta-analysis of revascularization outcomes of infrainguinal chronic limb-threatening ischemia. Eur J Vasc Endovasc Surg. 2019;58(1):S110–9.

169. Veith FJ, Gupta SK, Ascer E, White-Flores S, Samson RH, Scher LA, et al. Six-year prospective multicenter randomized comparison of autologous saphenous vein and expanded polytetrafluoroethylene grafts in infrainguinal arterial reconstructions. J Vasc Surg. 1986;3(1):104–14.

170. Dorigo W, Pulli R, Castelli P, Dorrucci V, Ferilli F, De Blasis G, et al. A multicenter comparison between autologous saphenous vein and heparin-bonded expanded polytetrafluoroethylene (ePTFE) graft in the treatment of critical limb ischemia in diabetics. J Vasc Surg. 2011;54(5):1332–8.

171. Sharrock M, Antoniou SA, Antoniou GA. Vein Versus Prosthetic Graft for Femoropopliteal Bypass Above the Knee: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Angiology. 2019;70(7):649–61.

172. Uhl C, Grosch C, Hock C, Töpel I, Steinbauer M. Comparison of Long-term Outcomes of Heparin Bonded Polytetrafluoroethylene and Autologous Vein Below Knee Femoropopliteal Bypasses in Patients with Critical Limb Ischaemia. Eur J Vasc Endovasc Surg. 2017;54(2):203–11.

173. McAnelly S-L, Hajibandeh S, Hajibandeh S, Georgiadis GS, Antoniou SA, Madan M, et al. Bypass Surgery With Heparin-Bonded Grafts for Chronic Lower Limb Ischemia. Ann Vasc Surg. 2017;43:328–46.

174. Suckow BD, Kraiss LW, Stone DH, Schanzer A, Bertges DJ, Baril DT, et al. Comparison of graft patency, limb salvage, and antithrombotic therapy between prosthetic and autogenous below-knee bypass for critical limb ischemia. Ann Vasc Surg. 2013;27(8):1134–45.

175. Hsu CC-T, Kwan GN, Singh D, Rophael JA, Anthony C, van Driel ML. Angioplasty versus stenting for infrapopliteal arterial lesions in chronic limb-threatening ischaemia. Cochrane Database Syst Rev [Internet]. 2018 Dec 8 [cited 2022 Dec 23]; 12. doi:10.1002/14651858.CD009195.pub2.

176. Jongsma H, Bekken J, Ayez N, Hoogewerf CJ, Weel VV, Fioole B. Angioplasty versus stenting for iliac artery lesions. Cochrane Database Syst Rev [Internet]. 2020 Dec 1 [cited 2022 Dec 23];12. doi:10.1002/14651858.CD007561.pub3/full

177. Weissler EH, Wang Y, Gales JM, Feldman DN, Arya S, Secemsky EA, et al. Cardiovascular and Limb Events Following Endovascular Revascularization Among Patients ≥65 Years Old: An American College of Cardiology PVI Registry Analysis. J Am Heart Assoc [Internet]. 2022 Jun 20 [cited 2022 Dec 23]; 11(12). doi:10.1161/JAHA.121.024279.

178. Wong CP, Chan LP, Au DM, Chan HWC, Chan YC. Efficacy and Safety of Intravascular Lithotripsy in Lower Extremity Peripheral Artery Disease: A Systematic Review and Meta-Analysis. Eur J Vasc Endovasc Surg. 2022;63(3):446–56.

179. Clair DG, Mustapha JA, Shishehbor MH, Schneider PA, Henao S, Bernardo NN, et al. PROMISE I: Early feasibility study of the LimFlow System for percutaneous deep vein arterialization in no-option chronic limb-threatening ischemia: 12-month results. J Vasc Surg. 2021;74(5):1626–35.

180. Soares TR, Manuel V, Amorim P, Martins C, Gouveia E Melo R, Ministro A, et al. Hybrid Surgery in Lower Limb Revascularization: A Real-World Experience from a Single Center. Ann Vasc Surg. 2019;60:355–63.

181. Serna Santos J, Söderström M, Helminen R, Aho P, Halmesmäki K, Venermo M. Outcome after Hybrid Outflow Interventions for Chronic Limb-threatening Ischemia. Scand J Surg. 2021;110(2):241–7.

182. Popplewell MA, Davies H, Jarrett H, Bate G, Grant M, Patel S, et al. Bypass versus angio plasty in severe ischaemia of the leg - 2 (BASIL-2) trial: study protocol for a randomised controlled trial. Trials [Internet]. 2016 Jan 6 [cited 2022 Dec 27]; 17. doi:10.1186/s13063-015-1114-2.

183. Hunt BD, Popplewell MA, Davies H, Meecham L, Jarrett H, Bate G, et al. BAlloon versus Stenting in severe Ischaemia of the Leg-3 (BASIL-3): study protocol for a

randomised controlled trial. Trials [Internet]. 2017 May 19 [cited 2022 Dec 27]; 18. doi:10.1186/s13063-017-1968-6.

184. Adam DJ, Beard JD, Cleveland T, Bell J, Bradbury AW, Forbes JF, et al. Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial. The Lancet. 2005;366(9501):1925–34.

185. Bradbury AW, Adam DJ, Bell J, Forbes JF, Fowkes FGR, Gillespie I, et al. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: An intention-to-treat analysis of amputation-free and overall survival in patients randomized to a bypass surgery-first or a balloon angioplasty-first revascularization strategy. J Vasc Surg. 2010;51(Supp 5):5S-17S.

186. Popplewell MA, Davies HOB, Narayanswami J, Renton M, Sharp A, Bate G, et al. A Comparison of Outcomes in Patients with Infrapopliteal Disease Randomised to Vein Bypass or Plain Balloon Angioplasty in the Bypass vs. Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial. Eur J Vasc Endovasc Surg. 2017;54(2):195–201.

187. Bradbury AW, Adam DJ, Bell J, Forbes JF, Fowkes FGR, Gillespie I, et al. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: Analysis of amputation free and overall survival by treatment received. J Vasc Surg. 2010;51(Supp 5):18S-31S.

188. Meecham L, Patel S, Bate GR, Bradbury AW. Editor's Choice - A Comparison of Clinical Outcomes Between Primary Bypass and Secondary Bypass After Failed Plain Balloon Angioplasty in the Bypass versus Angioplasty for Severe Ischaemia of the Limb (BASIL) Trial. Eur J Vasc Endovasc Surg. 2018;55(5):666–71.

189. Farber A, Menard MT, Conte MS, Kaufman JA, Powell RJ, Choudhry NK, et al. Surgery or Endovascular Therapy for Chronic Limb-Threatening Ischemia. N Engl J Med. 2022;387(25):2305–16.

190. Antoniou GA, Georgiadis GS, Antoniou SA, Makar RR, Smout JD, Torella F. Bypass surgery for chronic lower limb ischaemia. Cochrane Database Syst Rev

[Internet]. 2017 Apr 3 [cited 2022 Dec 27]; 4. doi:10.1002/14651858.CD002000.pub3.

191. Bodewes TCF, Darling JD, Deery SE, O'Donnell TFX, Pothof AB, Shean KE, et al. Patient selection and perioperative outcomes of bypass and endovascular intervention as first revascularization strategy for infrainguinal arterial disease. J Vasc Surg. 2018;67(1):206-16.

192. Majmundar M, Patel KN, Doshi R, Anantha-Narayanan M, Kumar A, Reed GW, et al. Comparison of 6-Month Outcomes of Endovascular vs Surgical Revascularization for Patients With Critical Limb Ischemia. JAMA Netw Open [Internet]. 2022 Aug 1 [cited 2022 Dec 28]; 5(8). doi:10.1001/jamanetworkopen.2022.27746.

193. Abu Dabrh AM, Steffen MW, Asi N, Undavalli C, Wang Z, Elamin MB, et al. Bypass surgery versus endovascular interventions in severe or critical limb ischemia. J Vasc Surg. 2016;63(1):244-53.

194. Gray WK, Day J, Horrocks M. Outcomes for Angioplasty and Bypass Lower Limb Revascularisation Procedures for Limb Salvage in England: Findings From the Getting It Right First Time Programme. Eur J Vasc Endovasc Surg. 2020;60(5):711–9.

195. Wong KHF, Zucker BE, Wardle BG, Coughlin PA, Chaplin K, Cheng H-Y, et al. Systematic review and narrative synthesis of surveillance practices after endovascular intervention for lower limb peripheral arterial disease. J Vasc Surg. 2022;75(1):372-80.

196. Mills JL, Wixon CL, James DC, Devine J, Westerband A, Hughes JD. The natural history of intermediate and critical vein graft stenosis: recommendations for continued surveillance or repair. J Vasc Surg. 2001;33(2):273–80.

197. Nguyen LL, Conte MS, Menard MT, Gravereaux EC, Chew DK, Donaldson MC, et al. Infrainguinal vein bypass graft revision: factors affecting long-term outcome. J Vasc Surg. 2004;40(5):916–23.

198. Nather A, Wong KL. Distal amputations for the diabetic foot. Diabet Foot Ankle. [Internet]. 2013 Jul 16 [cited 2022 Dec 28]; 4. doi:10.3402/dfa.v4i0.21288

199. McGuire J, Thomson A, Kennedy PG. The Biomechanics of Diabetic Foot Amputation. Wounds. 2021;33(9):231–6.

200. Yammine K, Hayek F, Assi C. A meta-analysis of mortality after minor amputation among patients with diabetes and/or peripheral vascular disease. J Vasc Surg. 2020;72(6):2197–207.

201. Glaser JD, Bensley RP, Hurks R, Dahlberg S, Hamdan AD, Wyers MC, et al. Fate of the contralateral limb after lower extremity amputation. J Vasc Surg. 2013;58(6):1571-77.

202. Littman AJ, Tseng C-L, Timmons A, Moore K, Landry G, Czerniecki JM, et al. Risk of Ipsilateral Reamputation Following an Incident Toe Amputation Among U.S. Military Veterans With Diabetes, 2005–2016. Diabetes Care. 2020;43(5):1033–40.

203. Shi E, Jex M, Patel S, Garg J. Outcomes of Wound Healing and Limb Loss After Transmetatarsal Amputation in the Presence of Peripheral Vascular Disease. J Foot Ankle Surg. 2019;58(1):47–51.

204. Gabel J, Jabo B, Patel S, Kiang S, Bianchi C, Chiriano J, et al. Analysis of Patients Undergoing Major Lower Extremity Amputation in the Vascular Quality Initiative. Ann Vasc Surg. 2018;46:75–82.

205. Nehler MR, Coll JR, Hiatt WR, Regensteiner JG, Schnickel GT, Klenke WA, et al. Functional outcome in a contemporary series of major lower extremity amputations. J Vasc Surg. 2003;38(1):7–14.

206. National Confidential Enquiry into Patient Outcome and Death. Lower Limb Amputation: Working Together. London: NCEPOD; 2014.

207. Ettema S, Kal E, Houdijk H. General estimates of the energy cost of walking in people with different levels and causes of lower-limb amputation: a systematic review and meta-analysis. Prosthet Orthot Int. 2021;45(5):417–27.

208. Chopra A, Azarbal AF, Jung E, Abraham CZ, Liem TK, Landry GJ, et al. Ambulation and functional outcome after major lower extremity amputation. J Vasc Surg. 2018;67(5):1521–9.

209. Crane H, Boam G, Carradice D, Vanicek N, Twiddy M, Smith GE. Through-knee versus above-knee amputation for vascular and non-vascular major lower limb amputations. Cochrane Database Syst Rev [Internet]. 2021 Dec 14 [cited 2022 Dec 29]; 12. doi:10.1002/14651858.CD013839.pub2

210. van Netten JJ van, Fortington LV, Hinchliffe RJ, Hijmans JM. Early Post-operative Mortality After Major Lower Limb Amputation: A Systematic Review of Population and Regional Based Studies. Eur J Vasc Endovasc Surg. 2016;51(2):248–57.

211. Stern JR, Wong CK, Yerovinkina M, Spindler SJ, See AS, Panjaki S, et al. A Meta-analysis of Long-term Mortality and Associated Risk Factors following Lower Extremity Amputation. Ann Vasc Surg. 2017;42:322–7.

212. Meshkin DH, Zolper EG, Chang K, Bryant M, Bekeny JC, Evans KK, et al. Long-term Mortality After Nontraumatic Major Lower Extremity Amputation: A Systematic Review and Meta-analysis. J Foot Ankle Surg. 2021;60(3):567–76.

213. Thorud JC, Plemmons B, Buckley CJ, Shibuya N, Jupiter DC. Mortality After Nontraumatic Major Amputation Among Patients With Diabetes and Peripheral Vascular Disease: A Systematic Review. J Foot Ankle Surg. 2016;55(3):591–9.

214. Ubbink DT, Vermeulen H. Spinal cord stimulation for non-reconstructable chronic critical leg ischaemia. Cochrane Database Syst Rev [Internet]. 2013 Feb 28 [cited 2022 Dec 29]; 2. doi:10.1002/14651858.CD004001.pub3.

215. Moran PS, Teljeur C, Harrington P, Ryan M. A systematic review of intermittent pneumatic compression for critical limb ischaemia. Vasc Med. 2015;20(1):41–50.

216. Zaki M, Elsherif M, Tawfick W, El Sharkawy M, Hynes N, Sultan S. The Role of Sequential Pneumatic Compression in Limb Salvage in Non-reconstructable Critical Limb Ischemia. Eur J Vasc Endovasc Surg. 2016;51(4):565–71.

217. Vietto V, Franco JV, Saenz V, Cytryn D, Chas J, Ciapponi A. Prostanoids for critical limb ischaemia. Cochrane Database Syst Rev [Internet]. 2018 Jan 10 [cited 2022 Dec 29]; 1. doi:10.1002/14651858.CD006544.pub3.

218. Kranke P, Bennett MH, Martyn-St James M, Schnabel A, Debus SE, Weibel S. Hyperbaric oxygen therapy for chronic wounds. Cochrane Database Syst Rev [Internet]. 2015 Jun 24 [cited 2022 Dec 29]; 6. doi:10.1002/14651858.CD004123.pub4.

219. Stoekenbroek RM, Santema TB, Legemate DA, Ubbink DT, van den Brink A, Koelemay MJW. Hyperbaric oxygen for the treatment of diabetic foot ulcers: a systematic review. Eur J Vasc Endovasc Surg. 2014;47(6):647–55.

220. Smith FB, Bradbury A, Fowkes G. Intravenous naftidrofuryl for critical limb ischaemia. Cochrane Database Syst Rev [Internet]. 2012 Jul 11 [cited 2022 Dec 29]; 7. doi:10.1002/14651858.CD002070.pub2.

221. Forster R, Liew A, Bhattacharya V, Shaw J, Stansby G. Gene therapy for peripheral arterial disease. Cochrane Database Syst Rev [Internet]. 2018 Oct 31 [cited 2022 Dec 29]; 10. doi:10.1002/14651858.CD012058.pub2.

222. Abdul Wahid SF, Ismail NA, Wan Jamaludin WF, Muhamad NA, Abdul Hamid MKA, Harunarashid H, et al. Autologous cells derived from different sources and administered using different regimens for 'no-option' critical lower limb ischaemia patients. Cochrane Database Syst Rev [Internet]. 2018 Aug 29 [cited 2022 Dec 29]; 8. doi:10.1002/14651858.CD010747.pub2.

223. van Reijen NS, Hensing T, Santema TKB, Ubbink DT, Koelemay MJW. Outcomes of Conservative Treatment in Patients with Chronic Limb Threatening Ischaemia: A Systematic Review and Meta-Analysis. Eur J Vasc Endovasc Surg. 2021;62(2):214–24.

224. Verwer MC, Wijnand JGJ, Teraa M, Verhaar MC, de Borst GJ. Long Term Survival and Limb Salvage in Patients With Non-Revascularisable Chronic Limb Threatening Ischaemia. Eur J Vasc Endovasc Surg. 2021;62(2):225–32.

225. Elgzyri T, Larsson J, Thörne J, Eriksson K-F, Apelqvist J. Outcome of ischemic foot ulcer in diabetic patients who had no invasive vascular intervention. Eur J Vasc Endovasc Surg. 2013;46(1):110–7.

226. Shan LL, Yang LS, Tew M, Westcott MJ, Spelman TD, Choong PF, et al. Quality of Life in Chronic Limb Threatening Ischaemia: Systematic Review and Meta-Analysis. Eur J Vasc Endovasc Surg. 2022;64(6):666–83.

227. Rollins KE, Jackson D, Coughlin PA. Meta-analysis of contemporary short- and long-term mortality rates in patients diagnosed with critical leg ischaemia. Br J Surg. 2013;100(8):1002–8.

228. Heikkila K, Loftus IM, Mitchell DC, Johal AS, Waton S, Cromwell DA. Population-based study of mortality and major amputation following lower limb revascularization. Br J Surg. 2018;105(9):1145–54.

229. Birmpili P, Atkins E, Li Q, Johal AS, Waton S, Williams R, et al. Evaluation of the ICD-10 system in coding revascularisation procedures in patients with peripheral arterial disease in England: A retrospective cohort study using national administrative and clinical databases. eClinicalMedicine [Internet]. 2022 Nov 12 [cited 2023 Jan 5]; 55. doi:10.1016/j.eclinm.2022.101738

230. Simons JP, Schanzer A, Flahive JM, Osborne NH, Mills JL, Bradbury AW, et al. Survival prediction in patients with chronic limb-threatening ischemia who undergo infrainguinal revascularization. Eur J Vasc Endovasc Surg. 2019;58(Supp 1):S120-34.

231. Mustapha JA, Katzen BT, Neville RF, Lookstein RA, Zeller T, Miller LE, et al. Propensity Score-Adjusted Comparison of Long-Term Outcomes Among Revascularization Strategies for Critical Limb Ischemia. Circ Cardiovasc Interv [Internet]. 2019 Sep 9 [cited 2023 Jan 5]; 12(9). doi:10.1161/CIRCINTERVENTIONS.119.008097.

232. Vierthaler L, Callas PW, Goodney PP, Schanzer A, Patel VI, Cronenwett J, et al. Determinants of survival and major amputation after peripheral endovascular intervention for critical limb ischemia. J Vasc Surg. 2015;62(3):655-64.

233. Darling JD, McCallum JC, Soden PA, Korepta L, Guzman RJ, Wyers MC, et al. Results for primary bypass versus primary angioplasty/stent for lower extremity chronic limb-threatening ischemia. J Vasc Surg. 2017;66(2):466–75.

234. Heikkilä K, Loftus IM, Waton S, Johal AS, Boyle JR, Cromwell DA. Association of neighbourhood deprivation with risks of major amputation and death following lower limb revascularisation. Atherosclerosis. 2020;306:11–4.

235. Miyata T, Mii S, Kumamaru H, Takahashi A, Miyata H, Japanese Society for Vascular Surgery JAPAN Critical Limb Ischemia Database (JCLIMB) Committee. Risk prediction model for early outcomes of revascularization for chronic limb-threatening ischaemia. Br J Surg. 2021;108(8):941–50.

236. Horrocks M. Vascular Surgery GIRFT Programme National Specialty Report [Internet]. 2018 [cited 2023 Jan 5]. Available from: https://gettingitrightfirsttime.co.uk/wp-content/uploads/2018/02/GIRFT_Vascular_Surgery_Report-March_2018.pdf

237. Vascular Society of Great Britain and Ireland. A Best Practice Clinical Care Pathway for Peripheral Arterial Disease [Internet]. 2019 [cited 2023 Jan 5]. Available from: https://www.vascularsociety.org.uk/_userfiles/pages/files/Document%20Library/PAD%20QIF%20March%202019%20v2.pdf

238. Waton S, Johal A, Birmpili P, Li Q, Cromwell D, Pherwani A, et al. National Vascular Registry: 2020 Annual Report. London: The Royal College of Surgeons of England; 2020.

239. Renton S, Brooks M, Jenkins M, Boyle J, Allen L, Smith L, et al. Provision of services for patients with vascular disease 2021. London: Vascular Society of Great Britain and Ireland; 2021.

240. Nickinson ATO, Bridgwood B, Houghton JSM, Nduwayo S, Pepper C, Payne T, et al. A systematic review investigating the identification, causes, and outcomes of delays in the management of chronic limb-threatening ischemia and diabetic foot ulceration. J Vasc Surg. 2020;71(2):669-81.

241. Li Q, Birmpili P, Johal AS, Waton S, Pherwani AD, Boyle JR, et al. Delays to revascularization for patients with chronic limb-threatening ischaemia. Br J Surg. 2022;109(8):717-26.

242. Nickinson ATO, Dimitrova J, Houghton JSM, Rate L, Dubkova S, Lines H, et al. Does the Introduction of a Vascular Limb Salvage Service Improve One Year Amputation Outcomes for Patients with Chronic Limb-Threatening Ischaemia? Eur J Vasc Endovasc Surg. 2021;61(4):612-9.

243. Peters DH, Adam T, Alonge O, Agyepong IA, Tran N. Implementation research: what it is and how to do it. BMJ [Internet]. 2013 Nov 20 [cited 2023 Jan 6]; 347. doi:10.1136/bmj.f6753

244. Ogrinc G, Davies L, Goodman D, Batalden P, Davidoff F, Stevens D. SQUIRE 2.0 (*Standards for QUality Improvement Reporting Excellence)*: revised publication guidelines from a detailed consensus process. BMJ Qual Saf. 2016;25(12):986–92.

245. Wilson P, Kislov R. Implementation Science. 1st ed. Cambridge: Cambridge University Press; 2022.

246. Proctor E, Silmere H, Raghavan R, Hovmand P, Aarons G, Bunger A, et al. Outcomes for Implementation Research: Conceptual Distinctions, Measurement Challenges, and Research Agenda. Adm Policy Ment Health Ment Health Serv Res. 2011;38(2):65–76.

247. Pinnock H, Barwick M, Carpenter CR, Eldridge S, Grandes G, Griffiths CJ, et al. Standards for Reporting Implementation Studies (StaRI) Statement. BMJ [Internet]. 2017 Mar 6 [cited 2023 Jan 6]; 356. doi:10.1136/bmj.i6795.

248. Proctor EK, Powell BJ, McMillen JC. Implementation strategies: recommendations for specifying and reporting. Implement Sci [Internet]. 2013 Dec 1 [cited 2023 Jan 6];8. doi:10.1186/1748-5908-8-139.

249. Bauer MS, Damschroder L, Hagedorn H, Smith J, Kilbourne AM. An introduction to implementation science for the non-specialist. BMC Psychol [Internet]. 2015 Sep 16 [cited 2023 Jan 6]; 3. doi:10.1186/s40359-015-0089-9.

250. Green CA, Duan N, Gibbons RD, Hoagwood KE, Palinkas LA, Wisdom JP. Approaches to Mixed Methods Dissemination and Implementation Research: Methods, Strengths, Caveats, and Opportunities. Adm Policy Ment Health. 2015;42(5):508–23.

251. Palinkas LA, Aarons GA, Horwitz S, Chamberlain P, Hurlburt M, Landsverk J. Mixed method designs in implementation research. Adm Policy Ment Health. 2011;38(1):44–53.

252. Curran GM, Bauer M, Mittman B, Pyne JM, Stetler C. Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact. Med Care. 2012;50(3):217–26.

253. Landes SJ, McBain SA, Curran GM. An introduction to effectiveness-implementation hybrid designs. Psychiatry Res [Internet]. 2019 Oct [cited 2023 Jan 7]; 280. doi:10.1016/j.psychres.2019.112513

254. Nilsen P. Making sense of implementation theories, models and frameworks. Implement Sci [Internet]. 2015 Apr 21 [cited 2023 Jan 7]; 10. doi:10.1186/s13012-015-0242-0.

255. Damschroder LJ. Clarity out of chaos: Use of theory in implementation research. Psychiatry Res [Internet]. 2020 Jan [cited 2023 Jan 7];283. doi:10.1016/j.psychres.2019.06.036.

256. Esmail R, Hanson HM, Holroyd-Leduc J, Brown S, Strifler L, Straus SE, et al. A scoping review of full-spectrum knowledge translation theories, models, and frameworks. Implement Sci [Internet]. 2020 Feb 14 [cited 2023 Jan 7]; 15. doi:10.1186/s13012-020-0964-5.

257. Kirk MA, Kelley C, Yankey N, Birken SA, Abadie B, Damschroder L. A systematic review of the use of the Consolidated Framework for Implementation Research. Implement Sci [Internet]. 2016 May 17 [cited 2023 Jan 7]; 11. doi:10.1186/s13012-016-0437-z.

258. Cane J, O'Connor D, Michie S. Validation of the theoretical domains framework for use in behaviour change and implementation research. Implement Sci [Internet]. 2012 Apr 24 [cited 2023 Jan 7]; 7. doi:10.1186/1748-5908-7-37.

259. Bergström A, Ehrenberg A, Eldh AC, Graham ID, Gustafsson K, Harvey G, et al. The use of the PARIHS framework in implementation research and practice—a citation analysis of the literature. Implement Sci [Internet]. 2020 Aug 27 [cited 2023 Jan 7]; 15. doi:10.1186/s13012-020-01003-0.

260. D'Lima D, Soukup T, Hull L. Evaluating the Application of the RE-AIM Planning and Evaluation Framework: An Updated Systematic Review and Exploration of Pragmatic Application. Front Public Health. 2021 [cited 2023 Jan 7]; 9. doi:10.3389/fpubh.2021.755738.

261. Greenhalgh T, Robert G, Macfarlane F, Bate P, Kyriakidou O. Diffusion of innovations in service organizations: systematic review and recommendations. Milbank Q. 2004;82(4):581–629.

262. Birken SA, Powell BJ, Shea CM, Haines ER, Alexis Kirk M, Leeman J, et al. Criteria for selecting implementation science theories and frameworks: results from an international survey. Implement Sci [Internet]. 2017 Oct 30 [cited 2023 Jan 8]; 12. doi:10.1186/s13012-017-0656-y.

263. Strifler L, Cardoso R, McGowan J, Cogo E, Nincic V, Khan PA, et al. Scoping review identifies significant number of knowledge translation theories, models, and frameworks with limited use. J Clin Epidemiol. 2018;100:92–102.

264. Birken SA, Rohweder CL, Powell BJ, Shea CM, Scott J, Leeman J, et al. T-CaST: an implementation theory comparison and selection tool. Implement Sci [Internet]. 2018 Nov 22 [cited 2023 Jan 8]; 13. doi:10.1186/s13012-018-0836-4.

265. Lynch EA, Mudge A, Knowles S, Kitson AL, Hunter SC, Harvey G. "There is nothing so practical as a good theory": a pragmatic guide for selecting theoretical approaches for implementation projects. BMC Health Serv Res [Internet]. 2018 Nov 14 [cited 2023 Jan 8]; 18. doi:10.1186/s12913-018-3671-z.

266. Kislov R, Pope C, Martin GP, Wilson PM. Harnessing the power of theorising in implementation science. Implement Sci [Internet]. 2019 Dec 11 [cited 2023 Jan 8]; 14. doi:10.1186/s13012-019-0957-4.

267. Davidoff F, Dixon-Woods M, Leviton L, Michie S. Demystifying theory and its use in improvement. BMJ Qual Saf. 2015;24(3):228–38.

268. Nilsen P, Hasson H. Programme theory. In: Nilsen P, Birken S, editors. Handbook on Implementation Science. Cheltenham: Edward Elgar Publishing; 2020. p. 512-8.

269. W.K. Kellogg Foundation. Logic Model Development Guide. [Internet] W.K. Kellogg Foundation; 2004 [cited 2023 Jan 8]. Available from: https://www.naccho.org/uploads/downloadable-resources/Programs/Public-Health-Infrastructure/KelloggLogicModelGuide_161122_162808.pdf

270. Moullin JC, Dickson KS, Stadnick NA, Albers B, Nilsen P, Broder-Fingert S, et al. Ten recommendations for using implementation frameworks in research and practice. Implement Sci Commun [Internet]. 2020 Apr 30 [cited 2023 Jan 9]; 1. doi:10.1186/s43058-020-00023-7

271. Nilsen P. Overview of theories, models and frameworks in implementation science. In: Nilsen P, Birken S, editors. Handbook on Implementation Science. Cheltenham: Edward Elgar Publishing; 2020. p. 8–31.

272. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ [Internet]. 2014 Mar 7 [cited 2023 Jan 9]; 348. doi:10.1136/bmj.g1687.

273. Skivington K, Matthews L, Simpson SA, Craig P, Baird J, Blazeby JM, et al. A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance. BMJ [Internet]. 2021 Sep 30 [cited 2023 Jan 9]; 374. doi:10.1136/bmj.n2061.

274. Damschroder LJ, Aron DC, Keith RE, Kirsh SR, Alexander JA, Lowery JC. Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. Implement Sci [Internet]. 2009 Aug 7 [cited 2023 Jan 9]; 4. doi:10.1186/1748-5908-4-50.

275. Eccles M, Grimshaw J, Walker A, Johnston M, Pitts N. Changing the behavior of healthcare professionals: the use of theory in promoting the uptake of research findings. J Clin Epidemiol. 2005;58(2):107–12.

276. Ajzen I. The theory of planned behavior. Organ Behav Hum Decis Process. 1991;50(2):179–211.

277. Michie S, Johnston M, Abraham C, Lawton R, Parker D, Walker A. Making psychological theory useful for implementing evidence based practice: a consensus approach. Qual Saf Health Care. 2005;14(1):26-33.

278. Michie S, van Stralen MM, West R. The behaviour change wheel: A new method for characterising and designing behaviour change interventions. Implement Sci [Internet]. 2011 Apr 23 [cited 2023 Jan 9]; 6. doi:10.1186/1748-5908-6-42.

279. Rogers L, De Brún A, McAuliffe E. Defining and assessing context in healthcare implementation studies: a systematic review. BMC Health Serv Res [Internet]. 2020 Jun 29 [cited 2023 Jan 9]; 20. doi:10.1186/s12913-020-05212-7.

280. Nilsen P, Bernhardsson S. Context matters in implementation science: a scoping review of determinant frameworks that describe contextual determinants for implementation outcomes. BMC Health Serv Res [Internet]. 2019 Mar 25 [cited 2023 Jan 10]; 19. doi:10.1186/s12913-019-4015-3.

281. Rogers L, De Brún A, McAuliffe E. Development of an integrative coding framework for evaluating context within implementation science. BMC Med Res Methodol [Internet]. 2020 Jun 15 [cited 2023 Jan 10]; 20. doi:10.1186/s12874-020-01044-5.

282. Watson DP, Adams EL, Shue S, Coates H, McGuire A, Chesher J, et al. Defining the external implementation context: an integrative systematic literature review. BMC Health Serv Res [Internet]. 2018 Mar 27 [cited 2023 Jan 10]; 18. doi:10.1186/s12913-018-3046-5.

283. Li SA, Jeffs L, Barwick M, Stevens B. Organizational contextual features that influence the implementation of evidence-based practices across healthcare settings: a systematic integrative review. Syst Rev [Internet]. 2018 May 5 [cited 2023 Jan 10]; 7. doi:10.1186/s13643-018-0734-5.

284. Santos WJ, Graham ID, Lalonde M, Demery Varin M, Squires JE. The effectiveness of champions in implementing innovations in health care: a systematic review. Implement Sci Commun [Internet]. 2022 Jul 22 [cited 2023 Jan 10]; 3. doi:10.1186/s43058-022-00315-0.

285. Rogers EM. Diffusion of innovations. New York: Free Press; 1983.

286. Dryden-Palmer KD, Parshuram CS, Berta WB. Context, complexity and process in the implementation of evidence-based innovation: a realist informed review. BMC Health Serv Res [Internet]. 2020 Feb 3 [cited 2023 Jan 10]; 20. doi:10.1186/s12913-020-4935-y.

287. Powell BJ, Waltz TJ, Chinman MJ, Damschroder LJ, Smith JL, Matthieu MM, et al. A refined compilation of implementation strategies: results from the Expert Recommendations for Implementing Change (ERIC) project. Implement Sci [Internet]. 2015 Feb 12 [cited 2023 Jan 10]; 10. doi:10.1186/s13012-015-0209-1.

288. Leeman J, Birken SA, Powell BJ, Rohweder C, Shea CM. Beyond "implementation strategies": classifying the full range of strategies used in implementation science and practice. Implement Sci [Internet]. 2017 Nov 3 [cited 2023 Jan 10]; 12. doi:10.1186/s13012-017-0657-x.

289. Powell BJ, Beidas RS, Lewis CC, Aarons GA, McMillen JC, Proctor EK, et al. Methods to Improve the Selection and Tailoring of Implementation Strategies. J Behav Health Serv Res. 2017;44(2):177–94.

290. Waltz TJ, Powell BJ, Fernández ME, Abadie B, Damschroder LJ. Choosing implementation strategies to address contextual barriers: diversity in recommendations and future directions. Implement Sci [Internet]. 2019 Apr 29 [cited 2023 Jan 11]; 14. doi:10.1186/s13012-019-0892-4.

291. Batalden PB, Davidoff F. What is 'quality improvement' and how can it transform healthcare? Qual Saf Health Care. 2007;16(1):2–3.

292. Kohn LT, Corrigan JM, Donaldson MS, editors. To Err is Human: Building a Safer Health System. Washington, DC: National Academies Press; 2000.

293. Hurtado MP, Swift EK, Corrigan JM, editors. Crossing the Quality Chasm: A New Health System for the 21st Century. Washington, DC: National Academies Press; 2001.

294. De Silva D. Improvement collaboratives in Healthcare. [Internet] The Health Foundation; 2014 [cited 2023 Jan 11]. Available from: https://www.health.org.uk/publications/improvement-collaboratives-in-health-care

295. Ovretveit J, Mittman B, Rubenstein L, Ganz DA. Using implementation tools to design and conduct quality improvement projects for faster and more effective improvement. Int J Health Care Qual Assur. 2017;30(8):755–68.

296. Nilsen P, Thor J, Bender M, Leeman J, Gäre BA, Sevdalis N. Improvement science. In: Nilsen P, Birken S, editors. Handbook on Implementation Science. Cheltenham: Edward Elgar Publishing; 2020. p. 389–408.

297. Leeman J, Rohweder C, Lee M, Brenner A, Dwyer A, Ko LK, et al. Aligning implementation science with improvement practice: a call to action. Implement Sci Commun [Internet]. 2021 Sep 8 [cited 2023 Jan 11]; 2. doi:10.1186/s43058-021-00201-1.

298. Balasubramanian BA, Cohen DJ, Davis MM, Gunn R, Dickinson LM, Miller WL, et al. Learning Evaluation: blending quality improvement and implementation research methods to study healthcare innovations. Implement Sci [Internet]. 2015 Mar 10 [cited 2023 Jan 11]; 10. doi:10.1186/s13012-015-0219-z.

299. Wells S, Tamir O, Gray J, Naidoo D, Bekhit M, Goldmann D. Are quality improvement collaboratives effective? A systematic review. BMJ Qual Saf. 2018;27(3):226–40.

300. Schouten LMT, Hulscher MEJL, Everdingen JJE van, Huijsman R, Grol RPTM. Evidence for the impact of quality improvement collaboratives: systematic review. BMJ. 2008;336(7659):1491–4.

301. Institute for Healthcare Improvement. The Breakthrough Series: IHI's Collaborative Model for Achieving Breakthrough Improvement. [Internet] Institute for Healthcare Improvement; 2003 [cited 2023 Jan 12]. Available from:

http://www.ihi.org/resources/Pages/IHIWhitePapers/TheBreakthroughSeriesIHIsCollaborativeModelforAchievingBreakthroughImprovement.aspx

302. Lasker RD, Weiss ES, Miller R. Partnership synergy: a practical framework for studying and strengthening the collaborative advantage. Milbank Q. 2001;79(2):179–205.

303. Bunger AC, Hanson RF, Doogan NJ, Powell BJ, Cao Y, Dunn J. Can Learning Collaboratives Support Implementation By Rewiring Professional Networks? Adm Policy Ment Health. 2016;43(1):79–92.

304. Hulscher MEJL, Schouten LMT, Grol RPTM, Buchan H. Determinants of success of quality improvement collaboratives: what does the literature show? BMJ Qual Saf. 2013;22(1):19–31.

305. Loftus IM, Paraskevas KI, Johal A, Waton S, Heikkila K, Naylor AR, et al. Delays to Surgery and Procedural Risks Following Carotid Endarterectomy in the UK National Vascular Registry. Eur J Vasc Endovasc Surg. 2016;52(4):438–43.

306. Moja L, Piatti A, Pecoraro V, Ricci C, Virgili G, Salanti G, et al. Timing matters in hip fracture surgery: patients operated within 48 hours have better outcomes. A meta-analysis and meta-regression of over 190,000 patients. PLoS One [Internet]. 2012 Oct 3 [cited 2020 Oct 2]; 7(10). doi:10.1371/journal.pone.0046175.

307. Elgzyri T, Larsson J, Nyberg P, Thörne J, Eriksson KF, Apelqvist J. Early Revascularization after Admittance to a Diabetic Foot Center Affects the Healing Probability of Ischemic Foot Ulcer in Patients with Diabetes. Eur J Vasc Endovasc Surg. 2014;48(4):440–6.

308. Noronen K, Saarinen E, Albäck A, Venermo M. Analysis of the Elective Treatment Process for Critical Limb Ischaemia with Tissue Loss: Diabetic Patients Require Rapid Revascularisation. Eur J Vasc Endovasc Surg. 2017;53(2):206–13.

309. Kuhrij LS, Meershoek AJA, Karthaus EG, Vahl AC, Hamming JF, Nederkoorn PJ, et al. Factors Associated with Hospital Dependent Delay to Carotid Endarterectomy in the Dutch Audit for Carotid Interventions. Eur J Vasc Endovasc Surg. 2019;58(4):495–501.

310. Armitage P, Matthews JNS, Berry G. Statistical Methods in Medical Research. 4th ed. Oxford: Blackwell Science; 2002. Chapter 19, Statistical Methods in Epidemiology; p. 648–716.

311. Zou G. A modified poisson regression approach to prospective studies with binary data. Am J Epidemiol. 2004;159(7):702–6.

312. Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. PLoS Med [Internet]. 2015 Oct 6 [cited 2020 Oct 2]; 12(10). doi:10.1371/journal.pmed.1001885.

313. Sheehan KJ, Sobolev B, Villán Villán YF, Guy P. Patient and system factors of time to surgery after hip fracture: a scoping review. BMJ Open [Internet]. 2017 Aug 21 [cited 2020 Oct 3]; 7(8). doi:10.1136/bmjopen-2017-016939.

314. Ryan DJ, Yoshihara H, Yoneoka D, Egol KA, Zuckerman JD. Delay in Hip Fracture Surgery: An Analysis of Patient-Specific and Hospital-Specific Risk Factors. J Orthop Trauma. 2015;29(8):343–8.

315. Trenner M, Kuehnl A, Salvermoser M, Reutersberg B, Geisbuesch S, Schmid V, et al. High Annual Hospital Volume is Associated with Decreased in Hospital Mortality and Complication Rates Following Treatment of Abdominal Aortic Aneurysms: Secondary Data Analysis of the Nationwide German DRG Statistics from 2005 to 2013. Eur J Vasc Endovasc Surg. 2018;55(2):185–94.

316. Poorthuis MHF, Brand EC, Halliday A, Bulbulia R, Bots ML, de Borst GJ. High Operator and Hospital Volume Are Associated With a Decreased Risk of Death and Stroke After Carotid Revascularization: A Systematic Review and Meta-analysis. Ann Surg. 2019;269(4):631–41.

317. Goka EA, Phillips P, Poku E, Essat M, Woods HB, Walters SJ, et al. The Relationship between Hospital or Surgeon Volume and Outcomes in Lower Limb Vascular Surgery in the United Kingdom and Europe. Ann Vasc Surg. 2017;45:271–86.

318. Chen Y-F, Armoiry X, Higenbottam C, Cowley N, Basra R, Watson SI, et al. Magnitude and modifiers of the weekend effect in hospital admissions: a systematic review and meta-analysis. BMJ Open [Internet]. 2019 Jun 4 [cited 2020 Oct 3]; 9(6). doi:10.1136/bmjopen-2018-025764.

319. Arulkumaran N, Harrison DA, Brett SJ. Association between day and time of admission to critical care and acute hospital outcome for unplanned admissions to adult general critical care units: cohort study exploring the 'weekend effect'. Br J Anaesth. 2017;118(1):112–22.

320. Palmer WL, Bottle A, Davie C, Vincent CA, Aylin P. Dying for the weekend: a retrospective cohort study on the association between day of hospital presentation and the quality and safety of stroke care. Arch Neurol. 2012;69(10):1296–302.

321. Sorita A, Ahmed A, Starr SR, Thompson KM, Reed DA, Prokop L, et al. Off-hour presentation and outcomes in patients with acute myocardial infarction: systematic review and meta-analysis. BMJ [Internet]. 2014 Jan 21 [cited 2020 Oct 3]. 348. doi:10.1136/bmj.f7393.

322. Jairath V, Kahan BC, Logan RF, Hearnshaw SA, Travis SP, Murphy MF, et al. Mortality from acute upper gastrointestinal bleeding in the United kingdom: does it display a 'weekend effect'? Am J Gastroenterol. 2011;106(9):1621–8.

323. Jehan F, Khan M, Kulvatunyou N, Hamidi M, Gries L, Zeeshan M, et al. Day of Hospital Admission and Effect on Outcomes: The Weekend Effect in Acute Gallstone Pancreatitis. J Surg Res. 2019;233:192–8.

324. Dasenbrock HH, Pradilla G, Witham TF, Gokaslan ZL, Bydon A. The impact of weekend hospital admission on the timing of intervention and outcomes after surgery for spinal metastases. Neurosurgery. 2012;70(3):586–93.

325. Orandi BJ, Selvarajah S, Orion KC, Lum YW, Perler BA, Abularrage CJ. Outcomes of nonelective weekend admissions for lower extremity ischemia. J Vasc Surg. 2014;60(6):1572-9.

326. Ricci WM, Brandt A, McAndrew C, Gardner MJ. Factors affecting delay to surgery and length of stay for patients with hip fracture. J Orthop Trauma. 2015;29(3):e109-14.

327. Bray BD, Cloud GC, James MA, Hemingway H, Paley L, Stewart K, et al. Weekly variation in health-care quality by day and time of admission: a nationwide, registry-based, prospective cohort study of acute stroke care. Lancet. 2016;388(10040):170–7.

328. Sun J, Girling AJ, Aldridge C, Evison F, Beet C, Boyal A, et al. Sicker patients account for the weekend mortality effect among adult emergency admissions to a large hospital trust. BMJ Qual Saf. 2019;28(3):223–30.

329. Walker AS, Mason A, Quan TP, Fawcett NJ, Watkinson P, Llewelyn M, et al. Mortality risks associated with emergency admissions during weekends and public holidays: an analysis of electronic health records. Lancet. 2017;390(10089):62–72.

330. Potgieter R, Hindley H, Mitchell D, McCleary J. Delivering a National Quality Improvement Programme for Patients with Abdominal Aortic Aneurysms. London: Vascular Society of Great Britain and Ireland; 2012.

331. National Institute for Health and Care Excellence. Stroke and transient ischaemic attack in over 16s: diagnosis and initial management. [Internet] NICE; 2019 [cited 2020 Oct 4]. Available from: https://www.nice.org.uk/guidance/ng128

332. Taylor M, Hopman W, Yach J. Length of stay, wait time to surgery and 30-day mortality for patients with hip fractures after the opening of a dedicated orthopedic weekend trauma room. Can J Surg. 2016;59(5):337–41.

333. Ambler GK, Mariam NBG, Sadat U, Coughlin PA, Loftus IM, Boyle JR. Weekend effect in non-elective abdominal aortic aneurysm repair. BJS Open. 2017;1(5):158–64.

334. O'Donnell TFX, Li C, Swerdlow NJ, Liang P, Pothof AB, Patel VI, et al. The Weekend Effect in AAA Repair. Ann Surg. 2019;269(6):1170–5.

335. Galyfos G, Sigala F, Bazigos G, Filis K. Weekend effect among patients undergoing elective vascular surgery. J Vasc Surg. 2019;70(6):2038–45.

336. Gillies MA, Lone NI, Pearse RM, Haddow C, Smyth L, Parks RW, et al. Effect of day of the week on short- and long-term mortality after emergency general surgery. Br J Surg. 2017;104(7):936–45.

337. McCallum IJ, McLean RC, Dixon S, O'Loughlin P. Retrospective analysis of 30-day mortality for emergency general surgery admissions evaluating the weekend effect. Br J Surg. 2016;103(11):1557–65.

338. Hoehn RS, Go DE, Dhar VK, Kim Y, Hanseman DJ, Wima K, et al. Understanding the 'Weekend Effect' for Emergency General Surgery. J Gastrointest Surg. 2018;22(2):321–8.

339. Melnychuk M, Morris S, Black G, Ramsay AIG, Eng J, Rudd A, et al. Variation in quality of acute stroke care by day and time of admission: prospective cohort study of weekday and weekend centralised hyperacute stroke unit care and non-centralised services. BMJ Open [Internet]. 2019 Nov 7 [cited 2020 Oct 4]; 9(11). doi:10.1136/bmjopen-2018-025366.

340. Black GB, Ramsay AIG, Baim-Lance A, Eng J, Melnychuk M, Xanthopoulou P, et al. What does it take to provide clinical interventions with temporal consistency? A qualitative study of London hyperacute stroke units. BMJ Open

[Internet]. 2019 Nov 7 [cited 2020 Oct 4]; 9(11). doi:10.1136/bmjopen-2018-025367.

341. Meacock R, Doran T, Sutton M. What are the Costs and Benefits of Providing Comprehensive Seven-day Services for Emergency Hospital Admissions? Health Econ. 2015;24(8):907–12.

342. Almasri J, Adusumalli J, Asi N, Lakis S, Alsawas M, Prokop LJ, et al. A systematic review and meta-analysis of revascularization outcomes of infrainguinal chronic limb-threatening ischemia. J Vasc Surg. 2018;68(2):624–33.

343. Simons JP, Goodney PP, Flahive J, Hoel AW, Hallett JW, Kraiss LW, et al. A comparative evaluation of risk-adjustment models for benchmarking amputation-free survival after lower extremity bypass. J Vasc Surg. 2016;63(4):990–7.

344. Brothers TE, Zhang J, Mauldin PD, Tonnessen BH, Robison JG, Vallabhaneni R, et al. Predicting outcomes for infrapopliteal limb-threatening ischemia using the Society for Vascular Surgery Vascular Quality Initiative. J Vasc Surg. 2016;63(1):114-24.

345. Kreutzburg T, Peters F, Kuchenbecker J, Marschall U, Lee R, Kriston L, et al. The GermanVasc Score: A Pragmatic Risk Score Predicts Five Year Amputation Free Survival in Patients with Peripheral Arterial Occlusive Disease. Eur J Vasc Endovasc Surg. 2021;61(2):248–56.

346. Herbert A, Wijlaars L, Zylbersztejn A, Cromwell D, Hardelid P. Data Resource Profile: Hospital Episode Statistics Admitted Patient Care (HES APC). Int J Epidemiol. 2017;46(4):1093–1093i.

347. NHS Digital. National Clinical Coding Standards ICD-10 5th Edition. Leeds: NHS Digital; 2021.

348. Jauhari Y, Gannon MR, Dodwell D, Horgan K, Clements K, Medina J, et al. Construction of the secondary care administrative records frailty (SCARF) index

and validation on older women with operable invasive breast cancer in England and Wales: a cohort study. BMJ Open [Internet]. 2020 May 5 [cited 2022 Oct 10]; 10(5). doi:10.1136/bmjopen-2019-035395.

349. Armitage JN, van der Meulen JH, Royal College of Surgeons Co-morbidity Consensus Group. Identifying co-morbidity in surgical patients using administrative data with the Royal College of Surgeons Charlson Score. Br J Surg. 2010;97(5):772–81.

350. Ministry of Housing, Communities & Local Government. English Indices of Deprivation 2019. [Internet] Ministry of Housing, Communities & Local Government; 2019 [cited 2022 Oct 10]. Available from: https://www.gov.uk/government/statistics/english-indices-of-deprivation-2019

351. NHS Digital. National Clinical Coding Standards OPCS-4.8 Reference Book. Leeds: NHS Digital; 2017.

352. Office for National Statistics. Deaths [Internet]; 2022 [cited 2022 Oct 10]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths

353. Conroy RM. What Hypotheses do "Nonparametric" Two-Group Tests Actually Test? Stata J. 2012;12(2):182–90.

354. Birmpili P, Johal A, Li Q, Waton S, Chetter I, Boyle JR, et al. Factors associated with delays in revascularization in patients with chronic limb-threatening ischaemia: population-based cohort study. Br J Surg. 2021;108(8):951–9.

355. Bottle A, Aylin P. Mortality associated with delay in operation after hip fracture: observational study. BMJ. 2006;332(7547):947–51.

356. Moxey PW, Hofman D, Hinchliffe RJ, Poloniecki J, Loftus IM, Thompson MM, et al. Delay Influences Outcome after Lower Limb Major Amputation. Eur J Vasc Endovasc Surg. 2012;44(5):485–90.

357. Benson RA, Meecham LA, Hewitt CA, Bradbury AW. Comparison of Immediate and Long-term Outcomes in Men and Women Undergoing Revascularisation for Chronic Limb Threatening Ischaemia in the Bypass vs. Angioplasty in Severe Ischaemia of the Leg (BASIL-1) Trial. Eur J Vasc Endovasc Surg. 2019;58(2):224–8.

358. Wübbeke LF, Naves CCLM, Daemen J-WHC, Jacobs MJ, Mees BME. Editor's Choice – Mortality and Major Amputation after Revascularisation in Octogenarians Versus Non-Octogenarians with Chronic Limb Threatening Ischaemia: A Systematic Review and Meta-Analysis. Eur J Vasc Endovasc Surg. 2020;60(2):231–41.

359. Holt PJE, Poloniecki JD, Thompson MM. Multicentre study of the quality of a large administrative data set and implications for comparing death rates. Br J Surg. 2012;99(1):58–65.

360. Burns EM, Rigby E, Mamidanna R, Bottle A, Aylin P, Ziprin P, et al. Systematic review of discharge coding accuracy. J Public Health (Oxf). 2012;34(1):138–48.

361. Bamber JR, Stephens TJ, Cromwell DA, Duncan E, Martin GP, Quiney NF, et al. Effectiveness of a quality improvement collaborative in reducing time to surgery for patients requiring emergency cholecystectomy. BJS Open. 2019;3(6):802–11.

362. Aggarwal G, Peden CJ, Mohammed MA, Pullyblank A, Williams B, Stephens T, et al. Evaluation of the Collaborative Use of an Evidence-Based Care Bundle in Emergency Laparotomy. JAMA Surg [Internet]. 2019 May 1 [cited 2022 Jan 20]; 154(5). doi: 10.1001/jamasurg.2019.0145.

363. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370(9596):1453-7.

364. Public Health England. NHS Acute (Hospital) Trust Catchment Populations [Internet]. 2021 [cited 2022 Jan 20]. Available from: https://app.powerbi.com/view?r=eyJrIjoiODZmNGQ0YzItZDAwZi00MzFiLWE4Nz

AtMzVmNTUwMThmMTVlIiwidCI6ImVlNGUxNDk5LTRhMzUtNGIyZS1hZDQ3LTVmM2NmOWRlODY2NiIsImMiOjh9

365. Ovretveit J. Understanding the conditions for improvement: research to discover which context influences affect improvement success. BMJ Qual Saf. 2011;20(Supp 1):i18–23.

366. Taylor SL, Dy S, Foy R, Hempel S, McDonald KM, Ovretveit J, et al. What context features might be important determinants of the effectiveness of patient safety practice interventions? BMJ Qual Saf. 2011;20(7):611–7.

367. World Health Organisation(WHO). WHO announces COVID-19 outbreak a pandemic [Internet]; 2020 Mar 12 [cited 2022 Jan 11]. Available from: https://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/news/news/2020/3/who-announces-covid-19-outbreak-a-pandemic

368. Birmpili P, Li Q, Johal AS, Waton S, Atkins E, Boyle JR, et al. Outcomes of Surgery for Patients with Peripheral Arterial Disease During the COVID-19 Pandemic in the United Kingdom: A Population Based Study. Eur J Vasc Endovasc Surg [Internet]. 2023 Feb 10 [cited 2023 Mar 2]. doi: 10.1016/j.ejvs.2023.02.002.

369. Vascular Services Quality Improvement Programme. NVR-PAD-CLI-Self-Analysis-Guide. [Internet] Vascular Services Quality Improvement Programme; 2020 [cited 2022 Jan 20]. Available from: https://www.vsqip.org.uk/content/uploads/2020/09/NVR-PAD-CLI-Self-Analysis-Guide.pdf

370. Vascular Services Quality Improvement Programme. Quality Improvement Resources [Internet]; 2021 [cited 2022 Jan 21]. Available from: https://www.vsqip.org.uk/resources/quality-improvement/quality-improvement-resources/

371. Healthcare Quality Improvement Partnership (HQIP). National Vascular Registry (NVR) [Internet]; 2021 [cited 2022 Jan 21]. Available from: https://www.hqip.org.uk/a-z-of-nca/national-vascular-registry

372. Mills T, Lawton R, Sheard L. Advancing complexity science in healthcare research: the logic of logic models. BMC Med Res Methodol [Internet]. 2019 Mar 12 [cited 2022 Jan 21]; 19. doi:10.1186/s12874-019-0701-4.

373. Lilford RJ, Chilton PJ, Hemming K, Girling AJ, Taylor CA, Barach P. Evaluating policy and service interventions: framework to guide selection and interpretation of study end points. BMJ [Internet]. 2010 Aug 27 [cited 2022 Jan 21]; 341. doi:10.1136/bmj.c4413.

374. Kontopantelis E, Doran T, Springate DA, Buchan I, Reeves D. Regression based quasi-experimental approach when randomisation is not an option: interrupted time series analysis. BMJ [Internet]. 2015 Jun 9 [cited 2022 Jan 21]; 350. doi:10.1136/bmj.h2750.

375. Portela MC, Pronovost PJ, Woodcock T, Carter P, Dixon-Woods M. How to study improvement interventions: a brief overview of possible study types. BMJ Qual Saf. 2015;24(5):325–36.

376. Toma M, Dreischulte T, Gray NM, Campbell D, Guthrie B. Balancing measures or a balanced accounting of improvement impact: a qualitative analysis of individual and focus group interviews with improvement experts in Scotland. BMJ Qual Saf. 2018;27(7):547–56.

377. Dimick JB, Ryan AM. Methods for evaluating changes in health care policy: the difference-in-differences approach. JAMA. 2014;312(22):2401–2.

378. Hilbe JM. Negative Binomial Regression. 2nd ed. Cambridge: Cambridge University Press; 2011.

379. Shaaban AN, Peleteiro B, Martins MRO. Statistical models for analyzing count data: predictors of length of stay among HIV patients in Portugal using a multilevel model. BMC Health Serv Res [Internet]. 2021 Apr 21 [cited 2022 Jan 21]; 21. doi:10.1186/s12913-021-06389-1.

380. Benneyan JC, Lloyd RC, Plsek PE. Statistical process control as a tool for research and healthcare improvement. Qual Saf Health Care. 2003;12(6):458–64.

381. Mheen PJM de, Woodcock T. Grand rounds in methodology: four critical decision points in statistical process control evaluations of quality improvement initiatives. BMJ Qual Saf. 2023;32(1):47-54.

382. Stephens TJ, Bamber JR, Beckingham IJ, Duncan E, Quiney NF, Abercrombie JF, et al. Understanding the influences on successful quality improvement in emergency general surgery: learning from the RCS Chole-QuIC project. Implement Sci [Internet]. 2019 Aug 23 [cited 2022 Jan 22]; 14. doi:10.1186/s13012-019-0932-0.

383. Peden CJ, Stephens T, Martin G, Kahan BC, Thomson A, Rivett K, et al. Effectiveness of a national quality improvement programme to improve survival after emergency abdominal surgery (EPOCH): a stepped-wedge cluster-randomised trial. Lancet. 2019;393(10187):2213–21.

384. Huddart S, Peden CJ, Swart M, McCormick B, Dickinson M, Mohammed MA, et al. Use of a pathway quality improvement care bundle to reduce mortality after emergency laparotomy. Br J Surg. 2015;102(1):57–66.

385. Feinberg J, Flynn L, Woodward M, Pennell C, Higham H, Morgan L, et al. Improving emergency surgical care for patients with right iliac fossa pain at a regional scale: A quality improvement study using the Supported Champions implementation strategy. Int J Surg. 2018;57:105–10.

386. National Collaborating Centre for Chronic Conditions (Great Britain). Stroke: National Clinical Guideline for Diagnosis and Initial Management of Acute Stroke and Transient Ischaemic Attack (TIA). London: Royal College of Physicians; 2008.

387. Public Health England. AAA screening: monitoring waiting times to surgery [Internet]; 2019 Apr 12 [cited 2022 Jan 22]. Available from: https://www.gov.uk/government/publications/aaa-screening-waiting-times-standards/aaa-screening-monitoring-waiting-times-to-surgery

388. Institute for Government. Timeline of UK government coronavirus lockdowns and restrictions [Internet]; 2022 Dec 9 [cited 2023 Jan 15]. Available from: https://www.instituteforgovernment.org.uk/charts/uk-government-coronavirus-lockdowns

389. The Vascular Society for Great Britain and Ireland. COVID-19 Virus and Vascular Surgery [Internet]; 2020 Mar 20 [cited 2022 Jan 11]. Available from: https://www.vascularsociety.org.uk/professionals/news/113/covid19_virus_and_vascular_surgery

390. Lee KS, Ranganathan S, Choong AMTL, Ng JJ. A scoping review on the changes in vascular surgical practice during the early phases of the COVID-19 pandemic. Semin Vasc Surg. 2021;34(3):63–73.

391. Garin O. Ceiling Effect. In: Michalos AC, editor. Encyclopedia of Quality of Life and Well-Being Research. Dordrecht: Springer Netherlands; 2014. p. 631–3.

392. Aron DC, Tseng C-L, Soroka O, Pogach LM. Balancing measures: identifying unintended consequences of diabetes quality performance measures in patients at high risk for hypoglycemia. Int J Qual Health Care. 2019;31(4):246–51.

393. Lipska KJ, Ross JS, Miao Y, Shah ND, Lee SJ, Steinman MA. Potential overtreatment of diabetes mellitus in older adults with tight glycemic control. JAMA Intern Med. 2015;175(3):356–62.

394. Kanwar M, Brar N, Khatib R, Fakih MG. Misdiagnosis of community-acquired pneumonia and inappropriate utilization of antibiotics: side effects of the 4-h antibiotic administration rule. Chest. 2007;131(6):1865–9.

395. Bhatia RS, Austin PC, Stukel TA, Schull MJ, Chong A, Tu JV, et al. Outcomes in patients with heart failure treated in hospitals with varying admission rates: population-based cohort study. BMJ Qual Saf. 2014;23(12):981–8.

396. Bellosta R, Piffaretti G, Bonardelli S, Castelli P, Chiesa R, Frigerio D, et al. Regional Survey in Lombardy, Northern Italy, on Vascular Surgery Intervention

Outcomes During The COVID-19 Pandemic. Eur J Vasc Endovasc Surg. 2021;61(4):688–97.

397. Lou JY, Kennedy KF, Menard MT, Abbott JD, Secemsky EA, Goodney PP, et al. North American lower-extremity revascularization and amputation during COVID-19: Observations from the Vascular Quality Initiative. Vasc Med. 2021;26(6):613–23.

398. Langley GJ, Moen RD, Nolan KM, Nolan TW, Norman CL, Provost LP. The improvement guide: a practical approach to enhancing organisational performance. 2nd ed. San Francisco: Josey-Bass; 2009.

399. Ramanadhan S, Revette AC, Lee RM, Aveling EL. Pragmatic approaches to analyzing qualitative data for implementation science: an introduction. Implement Sci Commun [Internet]. 2021 Jun 29 [cited 2022 Jun 15]; 2. doi:10.1186/s43058-021-00174-1.

400. Palinkas LA, Mendon SJ, Hamilton AB. Innovations in Mixed Methods Evaluations. Annu Rev Public Health. 2019;40(1):423–42.

401. Qualitative Research in Implementation Science (QUALRIS). Qualitative methods in implementation science. [Internet] Division of Cancer Control and Population Sciences, National Cancer Institute; 2020 Sep 10 [cited 2022 Jun 15]. Available from: https://cancercontrol.cancer.gov/sites/default/files/2020-09/nci-dccps-implementationscience-whitepaper.pdf

402. Madill A, Jordan A, Shirley C. Objectivity and reliability in qualitative analysis: Realist, contextualist and radical constructionist epistemologies. Br J Psychol. 2000;91(1):1–20.

403. Sharma A, Minh Duc NT, Luu Lam Thang T, Nam NH, Ng SJ, Abbas KS, et al. A Consensus-Based Checklist for Reporting of Survey Studies (CROSS). J Gen Intern Med. 2021;36(10):3179–87.

404. O'Brien BC, Harris IB, Beckman TJ, Reed DA, Cook DA. Standards for Reporting Qualitative Research: A Synthesis of Recommendations. Acad Med. 2014;89(9):1245–51.

405. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. Int J Qual Health Care. 2007;19(6):349–57.

406. Berger R. Now I see it, now I don't: researcher's position and reflexivity in qualitative research. Qual Res. 2015;15(2):219–34.

407. Subramani S. Practising reflexivity: Ethics, methodology and theory construction. Methodol Innov [Internet]. 2019 Jul 10 [cited 2022 Jun 15]; 12(2). doi:10.1177/2059799119863276

408. Malthouse R, Roffey-Barentsen J, Watts M. Reflectivity, reflexivity and situated reflective practice. Prof Dev Educ. 2014;40(4):597–609.

409. Consolidated Framework for Implementation Research (CFIR). Interview Guide Tool [Internet]; 2021 [cited 2021 Apr 30]. Available from: https://cfirguide.org/tools/

410. Patton MQ. Qualitative research and evaluation methods: integrating theory and practice. 4th ed. Thousand Oaks, CA: SAGE; 2015.

411. Palinkas LA, Horwitz SM, Green CA, Wisdom JP, Duan N, Hoagwood K. Purposeful Sampling for Qualitative Data Collection and Analysis in Mixed Method Implementation Research. Adm Policy Ment Health. 2015;42(5):533–44.

412. van Rijnsoever FJ. (I Can't Get No) Saturation: A simulation and guidelines for sample sizes in qualitative research. PLoS One [Internet]. 2017 Jul 26 [cited 2022 Jun 16]; 12(7). doi:10.1371/journal.pone.0181689

413. Guest G, Namey E, Chen M. A simple method to assess and report thematic saturation in qualitative research. PLoS One [Internet]. 2020 May 5 [cited 2022 Jun 16]; 15(5). doi:10.1371/journal.pone.0232076

414. Malterud K, Siersma VD, Guassora AD. Sample Size in Qualitative Interview Studies: Guided by Information Power. Qual Health Res. 2016;26(13):1753–60.

415. Guest G, Bunce A, Johnson L. How Many Interviews Are Enough?: An Experiment with Data Saturation and Variability. Field Methods. 2006;18(1):59–82.

416. Hennink M, Kaiser BN. Sample sizes for saturation in qualitative research: A systematic review of empirical tests. Soc Sci Med [Internet]. 2021 Nov 2 [cited 2022 Jun 16]; 292. doi:10.1016/j.socscimed.2021.114523.

417. Vasileiou K, Barnett J, Thorpe S, Young T. Characterising and justifying sample size sufficiency in interview-based studies: systematic analysis of qualitative health research over a 15-year period. BMC Med Res Methodol [Internet]. 2018 Nov 21 [cited 2022 Jun 16]; 18. doi:10.1186/s12874-018-0594-7.

418. Hennink MM, Kaiser BN, Marconi VC. Code Saturation Versus Meaning Saturation: How Many Interviews Are Enough? Qual Health Res. 2017;27(4):591–608.

419. Baker SE, Edwards R. How many qualitative interviews is enough? Expert voices and early career reflections on sampling and cases in qualitative research. [Internet] National Centre for Research Methods; 2012 [cited 2022 Jun 16]. Available from: http://eprints.ncrm.ac.uk/2273/4/how_many_interviews.pdf

420. Hamilton AB, Finley EP. Qualitative methods in implementation research: An introduction. Psychiatry Res [Internet]. 2019 Aug 10 [cited 2022 Jun 16]; 280. doi:10.1016/j.psychres.2019.112516.

421. Information Commissioner's Office. Guide to the UK General Data Protection Regulation (UK GDPR) [Internet]; 2022 [cited 2022 Jun 17]. Available from: https://ico.org.uk/for-organisations/guide-to-data-protection/guide-to-the-general-data-protection-regulation-gdpr/

422. Damschroder LJ, Goodrich DE, Robinson CH, Fletcher CE, Lowery JC. A systematic exploration of differences in contextual factors related to implementing the

MOVE! weight management program in VA: A mixed methods study. BMC Health Serv Res [Internet]. 2011 Sep 30 [cited 2022 Jun 17]; 11. doi:10.1186/1472-6963-11-248.

423. Damschroder LJ, Lowery JC. Evaluation of a large-scale weight management program using the consolidated framework for implementation research (CFIR). Implement Sci [Internet]. 2013 May 10 [cited 2022 Jun 17]; 8. doi:10.1186/1748-5908-8-51.

424. Damschroder LJ, Reardon CM, Sperber N, Robinson CH, Fickel JJ, Oddone EZ. Implementation evaluation of the Telephone Lifestyle Coaching (TLC) program: organizational factors associated with successful implementation. Transl Behav Med. 2017;7(2):233–41.

425. King ES, Moore CJ, Wilson HK, Harden SM, Davis M, Berg AC. Mixed methods evaluation of implementation and outcomes in a community-based cancer prevention intervention. BMC Public Health [Internet]. 2019 Aug 5 [cited 2022 Jun 17]; 19. doi:10.1186/s12889-019-7315-y.

426. Gale RC, Wu J, Erhardt T, Bounthavong M, Reardon CM, Damschroder LJ, et al. Comparison of rapid vs in-depth qualitative analytic methods from a process evaluation of academic detailing in the Veterans Health Administration. Implement Sci [Internet]. 2019 Feb 1 [cited 2022 Jun 17]; 14. doi:10.1186/s13012-019-0853-y.

427. Holdsworth LM, Safaeinili N, Winget M, Lorenz KA, Lough M, Asch S, et al. Adapting rapid assessment procedures for implementation research using a team-based approach to analysis: a case example of patient quality and safety interventions in the ICU. Implement Sci [Internet]. 2020 Feb 22 [cited 2022 Jun 17]; 15. doi:10.1186/s13012-020-0972-5.

428. Ritchie J, Lewis J. Qualitative research practice: a guide for social science students and researchers. London: SAGE; 2003.

429. Nowell LS, Norris JM, White DE, Moules NJ. Thematic Analysis: Striving to Meet the Trustworthiness Criteria. Int J Qual Methods [Internet]. 2017 Oct 2 [cited 2022 Jun 17]; 16. doi:10.1177/1609406917733847

430. QSR International. NVivo 12 [software]. Melbourne, Australia: QSR International Pty Ltd; 2018.

431. Allsop DB, Chelladurai JM, Kimball ER, Marks LD, Hendricks JJ. Qualitative Methods with Nvivo Software: A Practical Guide for Analyzing Qualitative Data. Psych. 2022;4(2):142–59.

432. Dalkin S, Forster N, Hodgson P, Lhussier M, Carr SM. Using computer assisted qualitative data analysis software (CAQDAS; NVivo) to assist in the complex process of realist theory generation, refinement and testing. Int J Soc Res Methodol. 2021;24(1):123–34.

433. Maher C, Hadfield M, Hutchings M, de Eyto A. Ensuring Rigor in Qualitative Data Analysis: A Design Research Approach to Coding Combining NVivo With Traditional Material Methods. Int J Qual Methods [Internet]. 2018 Jul 10 [cited 2022 Jun 18]; 17. doi:10.1177/1609406918786362

434. Gale NK, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. BMC Med Res Methodol [Internet]. 2013 Sep 18 [cited 2022 Jun 18]; 13. doi:10.1186/1471-2288-13-117.

435. Fereday J, Muir-Cochrane E. Demonstrating Rigor Using Thematic Analysis: A Hybrid Approach of Inductive and Deductive Coding and Theme Development. Int J Qual Methods. 2006;5(1):80–92.

436. Keith RE, Crosson JC, O'Malley AS, Cromp D, Taylor EF. Using the Consolidated Framework for Implementation Research (CFIR) to produce actionable findings: a rapid-cycle evaluation approach to improving implementation. Implement Sci [Internet]. 2017 Feb 10 [cited 2022 Jun 18];12. doi:10.1186/s13012-017-0550-7.

437. Hill JN, Locatelli SM, Bokhour BG, Fix GM, Solomon J, Mueller N, et al. Evaluating broad-scale system change using the Consolidated Framework for Implementation Research: challenges and strategies to overcome them. BMC Res Notes [Internet]. 2018 Aug 4 [cited 2022 Jun 18]; 11. doi:10.1186/s13104-018-3650-9.

438. Safaeinili N, Brown-Johnson C, Shaw JG, Mahoney M, Winget M. CFIR simplified: Pragmatic application of and adaptations to the Consolidated Framework for Implementation Research (CFIR) for evaluation of a patient-centered care transformation within a learning health system. Learn Health Syst [Internet]. 2019 Sep 26 [cited 2022 Jun 18]; 4. doi:10.1002/lrh2.10201

439. Brennan LA, Brady JE, Drummond KL, Wiltsey-Stirman S, Gutner CA, Iverson KM. Mental health clinician perspectives regarding factors impacting implementation of evidence-based psychotherapies in Veterans Health Administration community-based outpatient clinics. Gen Hosp Psychiatry. 2022;75:54–60.

440. Averill JB. Matrix Analysis as a Complementary Analytic Strategy in Qualitative Inquiry. Qual Health Res. 2002;12(6):855–66.

441. Nevedal AL, Reardon CM, Opra Widerquist MA, Jackson GL, Cutrona SL, White BS, et al. Rapid versus traditional qualitative analysis using the Consolidated Framework for Implementation Research (CFIR). Implement Sci [Internet]. 2021 Jul 2 [cited 2022 Jun 19]; 16. doi:10.1186/s13012-021-01111-5.

442. Braun V, Clarke V. Reflecting on reflexive thematic analysis. Qual Res Sport Exerc Health. 2019;11(4):589–97.

443. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol. 2006;3(2):77–101.

444. Miles MB, Huberman AM, Saldana J. Qualitative Data Analysis: A Methods Sourcebook. London: SAGE; 2018.

445. Farmer T, Robinson K, Elliott SJ, Eyles J. Developing and implementing a triangulation protocol for qualitative health research. Qual Health Res. 2006;16(3):377–94.

446. Morse JM. Critical Analysis of Strategies for Determining Rigor in Qualitative Inquiry. Qual Health Res. 2015;25(9):1212–22.

447. Campbell JL, Quincy C, Osserman J, Pedersen OK. Coding In-depth Semistructured Interviews: Problems of Unitization and Intercoder Reliability and Agreement. Sociol Methods Res. 2013;42(3):294–320.

448. O'Connor C, Joffe H. Intercoder Reliability in Qualitative Research: Debates and Practical Guidelines. Int J Qual Methods [Internet]. 2020 Jan 22 [cited 2022 Jun 19]; 19. doi:10.1177/1609406919899220

449. Polit DF, Beck CT. Nursing research: generating and assessing evidence for nursing practice. 9th ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2012.

450. Mays N, Pope C. Qualitative research in health care. Assessing quality in qualitative research. BMJ. 2000;320(7226):50–2.

451. Alvesson M, Sköldberg K. Reflexive Methodology: New Vistas for Qualitative Research. London: SAGE; 2018.

452. Tracy SJ. Qualitative Quality: Eight "Big-Tent" Criteria for Excellent Qualitative Research. Qual Inq. 2010;16(10):837–51.

453. Potgieter R, Hindley H, Mitchell D, Wyatt MG. National Abdominal Aortic Aneurysm Quality Improvement Programme (AAAQIP) interim report 2011. London: Vascular Society of Great Britain & Ireland; 2011.

454. Lee HC, Bennett MV, Crockett M, Crowe R, Gwiazdowski SG, Keller H, et al. Comparison of Collaborative Versus Single-Site Quality Improvement to Reduce NICU Length of Stay. Pediatrics [Internet]. 2018 Jun 13 [cited 2022 Jun 20]; 142. doi:10.1542/peds.2017-1395.

455. Hemmila MR, Cain-Nielsen AH, Jakubus JL, Mikhail JN, Dimick JB. Association of Hospital Participation in a Regional Trauma Quality Improvement Collaborative With Patient Outcomes. JAMA Surg. 2018;153(8):747–56.

456. Wenger E. Communities of practice: learning, meaning and identity. Cambridge: Cambridge University Press; 1998.

457. Nembhard IM. Learning and Improving in Quality Improvement Collaboratives: Which Collaborative Features Do Participants Value Most? Health Serv Res. 2009;44:359–78.

458. Stephens TJ, Peden CJ, Pearse RM, Shaw SE, Abbott TEF, Jones EL, et al. Improving care at scale: process evaluation of a multi-component quality improvement intervention to reduce mortality after emergency abdominal surgery (EPOCH trial). Implement Sci [Internet]. 2018 Nov 13 [cited 2022 Jun 20]; 13. doi:10.1186/s13012-018-0823-9.

459. Bunger AC, Doogan N, Hanson RF, Birken SA. Advice-seeking during implementation: a network study of clinicians participating in a learning collaborative. Implement Sci [Internet]. 2018 Jul 28 [cited 2022 Jun 20]; 13. doi:10.1186/s13012-018-0797-7.

460. Brandrud AS, Nyen B, Hjortdahl P, Sandvik L, Helljesen Haldorsen GS, Bergli M, et al. Domains associated with successful quality improvement in healthcare – a nationwide case study. BMC Health Serv Res [Internet]. 2017 Sep 13 [cited 2022 Jun 20]; 17. doi:10.1186/s12913-017-2454-2.

461. Lengnick-Hall R, Willging CE, Hurlburt MS, Aarons GA. Incorporators, Early Investors, and Learners: a longitudinal study of organizational adaptation during EBP implementation and sustainment. Implement Sci [Internet]. 2020 Sep 10 [cited 2022 Jun 21]; 15. doi:10.1186/s13012-020-01031-w.

462. Rogers L, De Brún A, Birken SA, Davies C, McAuliffe E. Context counts: a qualitative study exploring the interplay between context and implementation success. J Health Organ Manag. 2021;35(7):802-24.

463. Meza RD, Triplett NS, Woodard GS, Martin P, Khairuzzaman AN, Jamora G, et al. The relationship between first-level leadership and inner-context and implementation outcomes in behavioral health: a scoping review. Implement Sci [Internet]. 2021 Jul 6 [cited 2022 Jun 21]; 16. doi:10.1186/s13012-021-01104-4.

464. Aarons GA, Ehrhart MG, Farahnak LR, Sklar M. Aligning Leadership Across Systems and Organizations to Develop a Strategic Climate for Evidence-Based Practice Implementation. Annu Rev Public Health. 2014;35(1):255–74.

465. Pannick S, Sevdalis N, Athanasiou T. Beyond clinical engagement: a pragmatic model for quality improvement interventions, aligning clinical and managerial priorities. BMJ Qual Saf. 2016;25(9):716–25.

466. Birken SA, DiMartino LD, Kirk MA, Lee S-YD, McClelland M, Albert NM. Elaborating on theory with middle managers' experience implementing healthcare innovations in practice. Implement Sci [Internet]. 2016 Jan 4 [cited 2022 Jun 21]; 11. doi:10.1186/s13012-015-0362-6.

467. Birken S, Clary A, Tabriz AA, Turner K, Meza R, Zizzi A, et al. Middle managers' role in implementing evidence-based practices in healthcare: a systematic review. Implement Sci [Internet]. 2018 Dec 12 [cited 2022 Jun 21];13. doi:10.1186/s13012-018-0843-5.

468. Urquhart R, Kendell C, Folkes A, Reiman T, Grunfeld E, Porter G. Factors influencing middle managers' commitment to the implementation of innovations in cancer care. J Health Serv Res Policy. 2019;24(2):91–9.

469. Williams NJ, Wolk CB, Becker-Haimes EM, Beidas RS. Testing a theory of strategic implementation leadership, implementation climate, and clinicians' use of evidence-based practice: a 5-year panel analysis. Implement Sci [Internet]. 2020 Feb 7 [cited 2022 Jun 21]; 15. doi:10.1186/s13012-020-0970-7.

470. White J, Grant K, Sarkies M, Haines T, Evidence Translation in Allied Health (EviTAH) Group. Translating evidence into practice: a longitudinal qualitative

exploration of allied health decision-making. Health Res Policy Syst [Internet]. 2021 Mar 18 [cited 2022 Jun 21] ;19. doi:10.1186/s12961-020-00662-1.

471. Shortell SM, Marsteller JA, Lin M, Pearson ML, Wu SY, Mendel P, et al. The role of perceived team effectiveness in improving chronic illness care. Med Care. 2004;42(11):1040-8.

472. Swaithes L, Dziedzic K, Sharp CA, Ellis B, Walsh N. Context, context, context: how has covid-19 changed implementation globally and how can we 'lock in' learning? Rheumatology. 2020;59(8):1804–7.

473. Becker SJ, Garner BR, Hartzler BJ. Is necessity also the mother of implementation? COVID-19 and the implementation of evidence-based treatments for opioid use disorders. J Subst Abuse Treat [Internet]. 2020 Nov 22 [cited 2022 Jun 22]; 122. doi:10.1016/j.jsat.2020.108210.

474. Wensing M, Sales A, Armstrong R, Wilson P. Implementation science in times of Covid-19. Implement Sci [Internet]. 2020 Jun 8 [cited 2022 Jun 22]; 15. doi:10.1186/s13012-020-01006-x.

475. Piat M, Wainwright M, Cherkas D, Leblanc S, Sofouli E, Rivest MP, et al. Identifying and understanding the contextual factors that shaped mid-implementation outcomes during the COVID-19 pandemic in organizations implementing mental health recovery innovations into services. Implement Sci Commun [Internet]. 2021 Sep 15 [cited 2022 Jun 22]; 2. doi:10.1186/s43058-021-00206-w.

476. Bruns EJ, Parker EM, Hensley S, Pullmann MD, Benjamin PH, Lyon AR, et al. The role of the outer setting in implementation: associations between state demographic, fiscal, and policy factors and use of evidence-based treatments in mental healthcare. Implement Sci [Internet]. 2019 Nov 13 [cited 2022 Jun 22]; 14. doi:10.1186/s13012-019-0944-9.

477. NHS England and NHS Improvement. Commissioning for Quality and Innovation (CQUIN) 2022/23 Annex: Indicator specifications [Internet]; 2022 Jan 12 [cited

2022 Jun 22]. Available from: https://www.england.nhs.uk/publication/combined-ccg-icb-and-pss-commissioning-for-quality-and-innovation-cquin-indicator-specification/

478. American College of Surgeons. COVID-19: recommendations for management of elective surgical procedures [Internet]; 2020 [cited 2022 Jan 11]. Available from: https://www.facs.org/covid-19/clinical-guidance/elective-surgery

479. Natarajan JP, Mahenthiran AK, Bertges DJ, Huffman KM, Eldrup-Jorgensen J, Lemmon GW. Effects of coronavirus disease 2019 on the Society for Vascular Surgery Vascular Quality Initiative arterial procedure registry. J Vasc Surg. 2021;73(6):1852–7.

480. Benson RA, Nandhra S. Outcomes of Vascular and Endovascular Interventions Performed During the Coronavirus Disease 2019 (COVID-19) Pandemic. Ann Surg. 2021;273(4):630–5.

481. San Norberto EM, De Haro J, Peña R, Riera L, Fernández-Caballero D, Sesma A, et al. Outcomes After Vascular Surgery Procedures in Patients with COVID-19 Infection: A National Multicenter Cohort Study (COVID-VAS). Ann Vasc Surg. 2021;73:86–96.

482. Kahlberg A, Mascia D, Bellosta R, Attisani L, Pegorer M, Socrate AM, et al. Vascular Surgery During COVID-19 Emergency in Hub Hospitals of Lombardy: Experience on 305 Patients. Eur J Vasc Endovasc Surg. 2021;61(2):306–15.

483. Mascia D, Kahlberg A, Melloni A, Rinaldi E, Melissano G, Chiesa R. Single-Center Vascular Hub Experience after 7 weeks of COVID-19 Pandemic in Lombardy (Italy). Ann Vasc Surg. 2020;69:90–9.

484. Bellosta R, Bissacco D, Rossi G, Pirrelli S, Lanza G, Frigerio D, et al. Differences in hub and spoke vascular units practice during the novel Coronavirus-19 (COVID-19) outbreak in Lombardy, Italy. J Cardiovasc Surg Torino. 2021;62(1):71–8.

485. Boschetti GA, Di Gregorio S, Mena Vera JM, Pane B, Spinella G, Palombo D, et al. COVID-19 Impact on Vascular Surgery Practice: Experience From an Italian University Regional Hub Center for Vascular Pathology. Ann Vasc Surg. 2021;74:73–9.

486. Waton S, Johal A, Birmpili P, Li Q, Cromwell D, O'Neill R, et al. National Vascular Registry: 2021 Annual Report [Internet]. London: The Royal College of Surgeons of England; 2021 [cited 2022 Jan 15]. Available from: https://www.vsqip.org.uk/reports/2021-annual-report/

487. Ball S, Banerjee A, Berry C, Boyle JR, Bray B, Bradlow W, et al. Monitoring indirect impact of COVID-19 pandemic on services for cardiovascular diseases in the UK. Heart. 2020;106(24):1890–7.

488. Björses K, Blomgren L, Holsti M, Jonsson M, Smidfelt K, Mani K. The Impact of Covid-19 on Vascular Procedures in Sweden 2020. Eur J Vasc Endovasc Surg. 2021;62(1):136–7.

489. Martelli E, Sotgiu G, Saderi L, Martelli AR, Settembrini AM. The Impact of the First 11 Months of the COVID-19 Pandemic on Vascular Patients' Care and Hospitalisation Rate in the Vascular Surgery Divisions of Southern Italy. Eur J Vasc Endovasc Surg. 2022;64(2):274–5.

490. Liu C, You J, Zhu W, Chen Y, Li S, Zhu Y, et al. The COVID-19 Outbreak Negatively Affects the Delivery of Care for Patients With Diabetic Foot Ulcers. Diabetes Care. 2020;43(10):125–6.

491. Schuivens PME, Buijs M, Boonman-de Winter L, Veen EJ, de Groot HGW, Buimer TG, et al. Impact of the COVID-19 Lockdown Strategy on Vascular Surgery Practice: More Major Amputations than Usual. Ann Vasc Surg. 2020;69:74–9.

492. Caruso P, Longo M, Signoriello S, Gicchino M, Maiorino MI, Bellastella G, et al. Diabetic Foot Problems During the COVID-19 Pandemic in a Tertiary Care Center: The Emergency Among the Emergencies. Diabetes Care. 2020;43(10):123–4.

493. Sena G, Gallelli G. An increased severity of peripheral arterial disease in the COVID-19 era. J Vasc Surg. 2020;72(2):758.

494. Ng JJ, Gan TRX, Niam JY, Menon RK, Ho P, Dharmaraj RB, et al. Experience from a Singapore tertiary hospital with restructuring of a vascular surgery practice in response to national and institutional policies during the COVID-19 pandemic. J Vasc Surg. 2020;72(4):1166–72.

495. de Mestral C, Gomez D, Wilton AS, Lee DS, Albalawi Z, Austin PC, et al. A Population-Based Analysis of Diabetes-Related Care Measures, Foot Complications, and Amputation During the COVID-19 Pandemic in Ontario, Canada. JAMA Netw Open [Internet]. 2022 Jan 4 [cited 2022 Jan 15]; 5. doi:10.1001/jamanetworkopen.2021.42354.

496. Valabhji J, Barron E, Vamos EP, Dhatariya K, Game F, Kar P, et al. Temporal Trends in Lower-Limb Major and Minor Amputation and Revascularization Procedures in People With Diabetes in England During the COVID-19 Pandemic. Diabetes Care. 2021;44(6):133–5.

497. Ho VT, Eberhard AV, Asch SM, Leeper NJ, Fukaya E, Arya S, et al. US National Trends in Vascular Surgical Practice During the COVID-19 Pandemic. JAMA Surg. 2021;156(7):681–3.

498. Carreras G, Lugo A, Stival C, Amerio A, Odone A, Pacifici R, et al. Impact of COVID-19 lockdown on smoking consumption in a large representative sample of Italian adults. Tob Control. 2022;31(5):615-22.

499. Duarte A, Gouveia EMR, Lopes A, Rato JP, Valente J, Pedro LM. Lessons Learned from the Impact of the COVID-19 Pandemic in a Vascular Surgery Department and Preparation for Future Outbreaks. Ann Vasc Surg. 2021;73:97-106.

500. Jongkind V, Earnshaw JJ, Bastos Gonçalves F, Cochennec F, Debus ES, Hinchliffe R, et al. Editor's Choice - Update of the European Society for Vascular Surgery (ESVS) 2020 Clinical Practice Guidelines on the Management of Acute Limb

Ischaemia in Light of the COVID-19 Pandemic, Based on a Scoping Review of the Literature. Eur J Vasc Endovasc Surg. 2022;63(1):80–9.

501. COVIDSurg Collaborative. Mortality and pulmonary complications in patients undergoing surgery with perioperative SARS-CoV-2 infection: an international cohort study. Lancet. 2020;396(10243):27–38.

502. Ambler GK, Thomas-Jones E, Edwards AGK, Twine CP. Prognostic Risk Modelling for Patients Undergoing Major Lower Limb Amputation: An Analysis of the UK National Vascular Registry. Eur J Vasc Endovasc Surg. 2020;59(4):606-613.

503. Dovell G, Rogers CA, Armstrong R, Harris RA, Hinchliffe RJ, Mouton R. The Effect of Mode of Anaesthesia on Outcomes After Elective Endovascular Repair of Abdominal Aortic Aneurysm. Eur J Vasc Endovasc Surg. 2020;59(5):729-738.

504. Pouncey AL, Sweeting MJ, Bicknell C, Powell JT. Sex-specific differences in the standard of care for infrarenal abdominal aortic aneurysm repair, and risk of major adverse cardiovascular events and death. Br J Surg. 2023;110(4):481-488.

505. Costa ML, Griffin XL, Achten J, Metcalfe D, Judge A, Pinedo-Villanueva R, et al. World Hip Trauma Evaluation (WHiTE): framework for embedded comprehensive cohort studies. BMJ Open [Internet]. 2016 Oct 21 [cited 2023 Jul 6];6. doi: 10.1136/bmjopen-2016-011679

506. Oxford Clinical Trials Research Unit (OCTRU). WHiTE Platform [Internet]; 2023 [cited 2023 Jul 6]. Available from: https://white-platform.octru.ox.ac.uk/

507. Lensen S, Macnair A, Love SB, Yorke-Edwards V, Noor NM, Martyn M, et al. Access to routinely collected health data for clinical trials - review of successful data requests to UK registries. Trials [Internet]. 2020 May 12 [cited 2023 Jul 6]; 21. doi: 10.1186/s13063-020-04329-8.

Appendices

Appendix 1: ICD-10 diagnosis codes related to peripheral arterial disease (PAD) and diabetes in HES

Condition	ICD-10 code
PAD	I70 Atherosclerosis (excluding I70.21) I73 Other peripheral vascular diseases I74 Arterial embolism and thrombosis I77.1 Stricture of artery I77.9 Other unspecified disorders of arteries and arterioles E10.5 Type 1 diabetes mellitus with peripheral circulatory complications E11.5 Type 2 diabetes mellitus with peripheral circulatory complications E13.5 Other specified diabetes mellitus with peripheral circulatory complications E14.5 Unspecified diabetes mellitus with peripheral circulatory complications
PAD with tissue loss	I70.21 Atherosclerosis of arteries of extremities with gangrene M86 Osteomyelitis L89 Decubitus ulcer and pressure area L97 Ulcer of lower limb, not elsewhere classified L98.4 Chronic ulcer of skin, not elsewhere classified R02 Gangrene, not elsewhere classified
Diabetes mellitus	E10 Type 1 diabetes mellitus E11 Type 2 diabetes mellitus E12 Malnutrition-related diabetes mellitus E13 Other specified diabetes mellitus E14 Unspecified diabetes mellitus

Emergency admission codes	
21	Accident and emergency department
22	General Practitioner
23	Bed bureau
24	Consultant clinic
28	Other emergency (eg. transfer from another provider)
2A	Accident and Emergency Department of another provider
2B	Emergency transfer of an admitted patient from another Hospital
2D	Other emergency admission
81	Transfer of admitted patient from other Hospital other than in an emergency

Excluded: Elective admission (11, 12, 13), Maternity-related (31, 32, 82, 83, 2C), Not known/not applicable (98, 99)

Appendix 2: Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures (OPCS) version 4.8 codes used in the study to capture endovascular and surgical lower limb revascularisation procedures

OPCS Codes	Description
Open surgical revascularisation	
L161	Emergency bypass of aorta by anastomosis of axillary artery to femoral artery
L162	Bypass of aorta by anastomosis of axillary artery to femoral artery NEC
L163	Bypass of aorta by anastomosis of axillary artery to bilateral femoral arteries
L168	Other specified extra-anatomic bypass of aorta
L169	Unspecified extra-anatomic bypass of aorta
L206	Emergency bypass of bifurcation of aorta by anastomosis of aorta to iliac artery
L216	Bypass of bifurcation of aorta by anastomosis of aorta to iliac artery
L501	Emergency bypass of common iliac artery by anastomosis of aorta to common iliac artery
L502	Emergency bypass of iliac artery by anastomosis of aorta to external iliac artery
L503	Emergency bypass of artery of leg by anastomosis of aorta to common femoral artery
L504	Emergency bypass of artery of leg by anastomosis of aorta to deep femoral artery
L505	Emergency bypass of iliac artery by anastomosis of iliac artery to iliac artery
L506	Emergency bypass of artery of leg by anastomosis of iliac artery to femoral artery
L508	Other specified other emergency bypass of iliac artery
L509	Unspecified other emergency bypass of iliac artery
L511	Bypass of common iliac artery by anastomosis of aorta to common iliac artery
L512	Bypass of iliac artery by anastomosis of aorta to external iliac artery
L513	Bypass of artery of leg by anastomosis of aorta to common femoral artery
L514	Bypass of artery of leg by anastomosis of aorta to deep femoral artery
L515	Bypass of iliac artery by anastomosis of iliac artery to iliac artery
L516	Bypass of artery of leg by anastomosis of iliac artery to femoral artery
L518	Other specified other bypass of iliac artery
L519	Unspecified other bypass of iliac artery
L521	Endarterectomy of iliac artery and patch repair of iliac artery
L522	Endarterectomy of iliac artery
L528	Other specified reconstruction of iliac artery
L529	Unspecified reconstruction of iliac artery
L538	Other specified open operations on iliac artery

L539	Other unspecified open operations on iliac artery
L581	Emergency bypass of femoral artery by anastomosis of femoral to femoral artery
L582	Emergency bypass of femoral artery by anastomosis of femoral artery to popliteal artery using prosthesis
L583	Emergency bypass of femoral artery by anastomosis of femoral artery to popliteal artery using vein graft
L584	Emergency bypass of femoral artery by anastomosis of femoral artery to tibial artery using prosthesis
L585	Emergency bypass of femoral artery by anastomosis of femoral artery to tibial artery using vein graft
L586	Emergency bypass of femoral artery by anastomosis of femoral artery to peroneal artery using prosthesis
L587	Emergency bypass of femoral artery by anastomosis of femoral artery to peroneal artery using vein graft
L588	Other specified other emergency bypass of femoral artery
L589	Unspecified other emergency bypass of femoral artery
L591	Bypass of femoral artery by anastomosis of femoral artery to femoral artery
L592	Bypass of femoral artery by anastomosis of femoral artery to popliteal artery using prosthesis
L593	Bypass of femoral artery by anastomosis of femoral artery to popliteal artery using vein graft
L594	Bypass of femoral artery by anastomosis of femoral artery to tibial artery using prosthesis
L595	Bypass of femoral artery by anastomosis of femoral artery to tibial artery using vein graft
L596	Bypass of femoral artery by anastomosis of femoral artery to peroneal artery using prosthesis
L597	Bypass of femoral artery by anastomosis of femoral artery to peroneal artery using vein graft
L598	Other specified other bypass of femoral artery
L599	Unspecified other bypass of femoral artery
L601	Endarterectomy of femoral artery and patch repair of femoral artery
L602	Endarterectomy of femoral artery
L603	Profundaplasty of femoral artery and patch repair of deep femoral artery
L604	Profundaplasty of femoral artery
L608	Other specified reconstruction of femoral artery
L609	Unspecified reconstruction of femoral artery
L651	Revision of reconstruction involving aorta
L652	Revision of reconstruction involving iliac artery
L653	Revision of reconstruction involving femoral artery
L658	Other specified revision of reconstruction of artery
L659	Unspecified revision of reconstruction of artery

L681	Endarterectomy and patch repair of artery
L682	Endarterectomy
L683	Repair of artery using prosthesis
L684	Repair of artery using vein graft
L688	Other specified repair of other artery
L689	Unspecified repair of other artery
Endovascular revascularisation	
L541	Percutaneous transluminal angioplasty of iliac artery
L544	Percutaneous transluminal insertion of stent into iliac artery
L548	Other specified transluminal operations on iliac artery
L549	Unspecified transluminal operations on iliac artery
L631	Percutaneous transluminal angioplasty of femoral artery
L635	Percutaneous transluminal insertion of stent into femoral artery
L638	Other specified transluminal operations on femoral artery
L639	Unspecified transluminal operations on femoral artery
L662	Percutaneous transluminal stent reconstruction of artery
L665	Percutaneous transluminal balloon angioplasty of artery
L667	Percutaneous transluminal placement of peripheral stent in artery
L668	Other specified other therapeutic transluminal operations on artery
L669	Unspecified other therapeutic transluminal operations on artery
L711	Percutaneous transluminal angioplasty of artery
L718	Other specified therapeutic transluminal operations on other artery
L719	Unspecified therapeutic transluminal operations on other artery
Artery of intervention	
Z38.1	Common iliac artery
Z38.2	Internal iliac artery
Z38.3	Common femoral artery
Z38.4	Deep femoral artery
Z38.5	Superficial femoral artery
Z38.6	Popliteal artery
Z97.1	Anterior tibial artery
Z97.2	Posterior tibial artery
Z97.3	Peroneal artery
Z97.4	Dorsalis pedis artery
Z97.5	External iliac artery
Z97.6	Iliac artery not elsewhere captured
Z97.7	Tibial artery not elsewhere captured

Appendix 3: CFIR Framework with CFIR construct definitions

I.	**Innovation Characteristics**	
A.	Intervention Source	Perception of key stakeholders about whether the innovation is externally or internally developed.
B.	Evidence Strength & Quality	Stakeholders' perceptions of the quality and validity of evidence supporting the belief that the innovation will have desired outcomes.
C.	Relative Advantage	Stakeholders' perception of the advantage of implementing the innovation versus an alternative solution.
D.	Adaptability	The degree to which an innovation can be adapted, tailored, refined, or reinvented to meet local needs.
E.	Trialability	The ability to test the innovation on a small scale in the organization, and to be able to reverse course (undo implementation) if warranted.
F.	Complexity	Perceived difficulty of the innovation, reflected by duration, scope, radicalness, disruptiveness, centrality, and intricacy and number of steps required to implement.
G.	Design Quality & Packaging	Perceived excellence in how the innovation is bundled, presented, and assembled.
H.	Cost	Costs of the innovation and costs associated with implementing the innovation including investment, supply, and opportunity costs.
II.	**Outer Setting**	
A.	Needs & Resources of Those Served by the Organization	The extent to which the needs of those served by the organization (e.g., patients), as well as barriers and facilitators to meet those needs, are accurately known and prioritized by the organization.
B.	Cosmopolitanism	The degree to which an organization is networked with other external organizations.
C.	Peer Pressure	Mimetic or competitive pressure to implement an innovation, typically because most or other key peer or competing organizations have already implemented or are in a bid for a competitive edge.
D.	External Policy & Incentives	A broad construct that includes external strategies to spread innovations including policy and regulations (governmental or other central entity), external mandates, recommendations and guidelines, pay-for-performance, collaboratives, and public or benchmark reporting.

III.	**Inner Setting**	
A.	Structural Characteristics	The social architecture, age, maturity, and size of an organization.
B.	Networks & Communications	The nature and quality of webs of social networks, and the nature and quality of formal and informal communications within an organization.
C.	Culture	Norms, values, and basic assumptions of a given organization.
D.	Implementation Climate	The absorptive capacity for change, shared receptivity of involved individuals to an innovation, and the extent to which use of that innovation will be rewarded, supported, and expected within their organization.
1.	Tension for Change	The degree to which stakeholders perceive the current situation as intolerable or needing change.
2.	Compatibility	The degree of tangible fit between meaning and values attached to the innovation by involved individuals, how those align with individuals' own norms, values, and perceived risks and needs, and how the innovation fits with existing workflows and systems.
3.	Relative Priority	Individuals' shared perception of the importance of the implementation within the organization.
4.	Organizational Incentives & Rewards	Extrinsic incentives such as goal-sharing, awards, performance reviews, promotions, and raises in salary, and less tangible incentives such as increased stature or respect.
5.	Goals & Feedback	The degree to which goals are clearly communicated, acted upon, and fed back to staff, and alignment of that feedback with goals.
6.	Learning Climate	A climate in which: 1. Leaders express their own fallibility and need for team members' assistance and input; 2. Team members feel that they are essential, valued, and knowledgeable partners in the change process; 3. Individuals feel psychologically safe to try new methods; and 4. There is sufficient time and space for reflective thinking and evaluation.
E.	Readiness for Implementation	Tangible and immediate indicators of organizational commitment to its decision to implement an innovation.
1.	Leadership Engagement	Commitment, involvement, and accountability of leaders and managers with the implementation of the innovation.

2.	Available Resources	The level of resources organizational dedicated for implementation and on-going operations including physical space and time.
3.	Access to Knowledge & Information	Ease of access to digestible information and knowledge about the innovation and how to incorporate it into work tasks.
IV.	**Characteristics of Individuals**	
A.	Knowledge & Beliefs about the Innovation	Individuals' attitudes toward and value placed on the innovation, as well as familiarity with facts, truths, and principles related to the innovation.
B.	Self-efficacy	Individual belief in their own capabilities to execute courses of action to achieve implementation goals.
C.	Individual Stage of Change	Characterization of the phase an individual is in, as s/he progresses toward skilled, enthusiastic, and sustained use of the innovation.
D.	Individual Identification with Organization	A broad construct related to how individuals perceive the organization, and their relationship and degree of commitment with that organization.
E.	Other Personal Attributes	A broad construct to include other personal traits such as tolerance of ambiguity, intellectual ability, motivation, values, competence, capacity, and learning style.
V.	**Process**	
A.	Planning	The degree to which a scheme or method of behaviour and tasks for implementing an innovation are developed in advance, and the quality of those schemes or methods.
B.	Engaging	Attracting and involving appropriate individuals in the implementation and use of the innovation through a combined strategy of social marketing, education, role modelling, training, and other similar activities.
1.	Opinion Leaders	Individuals in an organization that have formal or informal influence on the attitudes and beliefs of their colleagues with respect to implementing the innovation.
2.	Formally Appointed Internal Implementation Leaders	Individuals from within the organization who have been formally appointed with responsibility for implementing an innovation as coordinator, project manager, team leader, or other similar role.
3.	Champions	"Individuals who dedicate themselves to supporting, marketing, and 'driving through' an [implementation]", overcoming indifference or resistance that the innovation may provoke in an organization.

4.	External Change Agents	Individuals who are affiliated with an outside entity who formally influence or facilitate innovation decisions in a desirable direction.
5.	Key Stakeholders	Individuals from within the organization that are directly impacted by the innovation, e.g., staff responsible for making referrals to a new program or using a new work process.
6.	Innovation Participants	Individuals served by the organization that participate in the innovation, e.g., patients in a prevention program in a hospital.
C.	Executing	Carrying out or accomplishing the implementation according to plan.
D.	Reflecting & Evaluating	Quantitative and qualitative feedback about the progress and quality of implementation accompanied with regular personal and team debriefing about progress and experience.

Appendix 4: Interview guide

Interview question	CFIR construct
How did you first hear about the peripheral arterial disease quality improvement framework and the effort to implement it and why did you decide to participate in the programme? *Probing: Who made the decision to participate and why, what was your motivation? Do you think there is a benefit in implementing it? Are you aware of any units that have implemented the recommendations and have seen improvements?*	Intervention source Evidence strength Tension for change
What is your view on each of the components of the programme, so the webinars, the data collection in the NVR, the performance reports and the online resources? *Probing: Did you use any of the ideas that other centres shared during the webinars? Did you contact any of the other centre leads to discuss or share resources or information?*	Design Quality and Packaging
Did you get anything out of participating in this collaborative/programme?	Relative advantage
What more could we offer to participating units as part of the programme?	Evaluating
Can you describe the pathway that a patient presenting with CLTI follows in your network and the changes you have made to the pathway as part of the PAD QIP?	Executing
How did you decide what changes to make and how did you go about implementing the changes? *Probing: For example, did you do an audit or did you have meetings with stakeholders?*	Planning Executing
If team leader: Who did you involve in the decision-making process and the implementation? *Probing: Did you build a team and who did you include in that team? Was this formal part of yours and their job plan?* If not the team leader: What is your involvement in the implementation of the PAD QIP in your organisation and what is your view on the changes? *Probing: Do you believe you were right to get involved and that you made a contribution to the team?*	Team structure Teamwork Engaging

Had you set specific goals and did the implementation go according to plan? How did you monitor progress? *Probing: Please describe how frequently and the format in which information was provided, and what decisions / actions the information contributed to. Did you use the performance reports sent every 4 months or local data collection in addition to the NVR?*	Planning Executing
How was the participation in the programme and the changes made received by your team? *Probing: What was the experience of the team members and other colleagues regarding these changes? Have you involved other colleagues outside your department? Which ones and in what way? Were they interested in participating? Did they understand the purpose of the changes, did they engage, did they find the changes helpful or not, were they supportive? Did they think it is worthwhile? Did it affect their working routine?*	Team beliefs Team compatibility Team culture
How is your relationship with other specialties involved in the patient pathway? (eg. IR, anaesthetics, theatre management) Did the intervention affect your working relationships?	Networks/ Communication
How was progress, decisions and feedback shared with the team? Have you held any meetings where you presented the results?	Reflecting and Evaluating
What is your opinion on the new CLTI pathway? How did the changes affect the patients, your own work, the team and the organisation overall? *Probing: Were there costs associated with the changes? How well the changes fit with existing practices in your centre?*	Knowledge/ beliefs about Intervention Patient needs Cost
Did you seek support at senior organisational level or from stakeholders or key people and how did you approach them/convince them? Who supported it and what kind of support did they give? *Probing: Who were the key people who you tried to get on board and how did you approach them?. What strategies did you use to sell the idea? What was the stakeholder involvement? Did the stakeholders understand the purpose of the programme? What did they think of it?*	Leadership engagement Engaging
How did the resources, the priorities and the incentives in your organisation affect your efforts to implement changes in the CLTI patient pathway? *Probing: Did you have the necessary resources (time and material)? Was reducing time to revascularisation considered a priority in your organisation?*	Relative Priority Organisational Incentives and Rewards

Were there other competing priorities or organisational challenges at the same time? Were there any incentives in your organisation to help ensure that the changes would be successful?	Available Resources
What were the main difficulties you faced when you tried to make changes to the vascular service as part of the programme?	N/A
What was the main factor that helped you make changes to the vascular service?	N/A
What do you think could be improved? Are there any further changes you would like to make in the future?	Evaluating
What was the impact of COVID, positive or negative, on your implementation efforts?	N/A
Is there anything I should have asked you that I did not ask you?	N/A

Appendix 5: Survey questions

Organisation: (drop down menu from a list of the 13 early adopter Trusts)

Department: Vascular Surgery, Interventional Radiology, Other

Occupation: Doctor, Specialist nurse, Administrator

Please rate the following components of the PAD QIP	Not useful	Moderately useful	Very useful	Did not use/ attend
Webinars (for sharing practice)	**1**	**2**	**3**	**0**
Online quality improvement resources	**1**	**2**	**3**	**0**
Electronic data collection system (NVR)	**1**	**2**	**3**	**0**
Quarterly performance reports	**1**	**2**	**3**	**0**

Which of the following reflects the stage of implementation of the PAD QIP your organisation is in?	Choose one
I participate in the PAD QIP but have not decided on any changes yet	**1**
I have decided what changes to do but have not implemented them yet	**2**
I have made some changes to reach the PAD QIP timelines as a trial	**3**
I have integrated the changes into routines and promote its use to others	**4**

Please rate how much you agree or disagree with the following statements		Completely disagree	Disagree	Neither agree nor disagree	Agree	Completely agree
1	I have access to information and materials about the PAD QIP.					
2	The supporting materials and resources for the PAD QIP are informative.					
3	The supporting materials and resources for the PAD QIP will help/have helped with its implementation.					
4	I have good knowledge about the PAD QIP and what it entails.					
5	The PAD QIP is complicated to implement.					
6	The PAD QIP is adaptable to my local setting.					
7	I understand why the PAD QIP is being used in my organisation					
8	There is strong evidence indicating that changes planned/implemented in my organisation as part of the PAD QIP will reduce time-to-revascularisation for CLTI patients.					
9	The new practices planned/implemented as part of the PAD QIP are better than previous practices.					
10	The changes planned/implemented as part of the PAD QIP are associated with high costs for the organisation.					
11	I think there is a strong need for service changes to shorten time-to-revascularisation.					
12	The service changes that will be/were made as part of the PAD QIP meet the needs of the patients with CLTI treated by the vascular service in my region.					
13	I believe that participation in the PAD QIP will be/is effective in reducing time-to-revascularisation in my organisation.					
14	I have positive feelings about changes being implemented in my organisation as part of the PAD QIP.					
15	I am confident that I will be/am able to successfully implement changes as part of the PAD QIP.					
16	The PAD QIP allows me to network with colleagues in similar positions in other organisations and exchange information.					
17	Networking with colleagues outside my organisation will help/ helps with the implementation of changes in my setting.					

Please rate how much you agree or disagree with the following statements		Completely disagree	Disagree	Neither agree nor disagree	Agree	Completely agree
18	The fact that other organisations are participating in the PAD QIP has influenced my decision to participate as well.					
19	Participating in the PAD QIP and making service changes would provide an advantage to my organisation compared to other organisations in the UK.					
20	National policy and recommendations have influenced my decision to participate in the PAD QIP.					
21	Financial incentives have influenced my decision to participate in the PAD QIP.					
22	My colleagues and other stakeholders in my organisation think that there is a strong need for service changes to shorten time-to-revascularisation.					
23	My colleagues feel confident about implementing changes as part of the PAD QIP.					
24	I have good working relationship with colleagues outside my department who are involved in the PAD QIP.					
25	New ideas are embraced and used to make improvements in my team.					
26	I am involved in the decision-making process about what changes will be/are being implemented in my organisation as part of the PAD QIP.					
27	My team has set specific goals related to the implementation of changes as part of the PAD QIP.					
28	A plan is in place in my organisation about the implementation of changes as part of the PAD QIP.					
29	Changes as part of the PAD QIP are being implemented according to plan.*					
30	My team adjusts the changes we plan according to the PAD QIP quarterly performance reports.*					
31	My team adjusts the changes we plan according to locally measured performance indicators.*					
32	The progress with the PAD QIP is fed back to the team members.					
33	The infrastructure of my organisation (size, age, workload, participation in vascular network) will help/helps with the implementation of changes as part of the PAD QIP.					
34	New ideas are embraced and used to make improvements in my organisation. My organisation encourages trying new approaches, innovation and changes.					

Please rate how much you agree or disagree with the following statements		Completely disagree	Disagree	Neither agree nor disagree	Agree	Completely agree
35	My organisation has a good track-record of implementing changes.					
36	My organisation provides resources that allow the implementation of changes as part of the PAD QIP.					
37	Shortening time-to-revascularisation for patients with CLTI is a high-priority initiative for my department.					
38	There are incentives in my organisation to help ensure that the implementation of changes as part of the PAD QIP is successful.					
39	The implementation of changes as part of the PAD QIP aligns with the goals of my organisation.					
40	Changes that will be/are made as part of the PAD QIP fit well with the existing work processes and practices in my organisation.					
41	There is at least one individual in my organisation who champions and leads the implementation of changes as part of the PAD QIP.					
42	Key stakeholders are involved in the decision-making process about implementation of the changes.					
43	Leaders in my organisation are aware of the PAD QIP but are not involved in the implementation.					
44	Leaders in my organisation support participation in the PAD QIP and implementation of changes.					
45	Influential individuals in my organisation support making changes as part of the PAD QIP.					

Questions indicated with asterisk are only shown if implementation stage 3 or 4 is selected.

Appendix 6: Interview codebook

This codebook includes code definitions and coding criteria.

Intervention Characteristics	
A. Intervention Source	Definition: Perception of key stakeholders about whether the intervention is externally or internally developed. Inclusion Criteria: Include statements about the source of the intervention and the extent to which interviewees view the change as internal to the organization, e.g., an internally developed program, or external to the organization, e.g., a program coming from the outside.
B. Evidence Strength & Quality	Definition: Stakeholders' perceptions of the quality and validity of evidence supporting the belief that the intervention will have desired outcomes. Inclusion Criteria: Include statements regarding awareness of evidence and the strength and quality of evidence, as well as the absence of evidence or a desire for different types of evidence, such as pilot results instead of evidence from the literature.
C. Relative Advantage	Definition: Stakeholders' perception of the advantage of implementing the intervention versus an alternative solution. Inclusion Criteria: Include statements that demonstrate the intervention is better (or worse) than existing programs, *and statements about what problems/issues the intervention has caused.* Exclusion Criteria: Exclude statements that demonstrate a strong need for the intervention and code to Tension for Change.
D. Adaptability	Definition: The degree to which an intervention can be adapted, tailored, refined, or reinvented to meet local needs. Inclusion Criteria: Include statements regarding the (in)ability to adapt the intervention to their context, e.g., complaints about the rigidity of the protocol. Exclusion Criteria: Statements that the intervention did or did not need to be adapted to Compatibility.
E. Complexity	Definition: Perceived difficulty of the intervention, reflected by duration, scope, radicalness, disruptiveness, centrality, and intricacy and number of steps required to implement.

	Inclusion Criteria: Code statements regarding the complexity of the intervention itself. Exclusion Criteria: Exclude statements regarding the complexity of implementation and code to the appropriate CFIR code, e.g., difficulties related to space are coded to Available Resources and difficulties related to engaging participants in a new program are coded to Engaging.
F. Design Quality & Packaging	Definition: Perceived excellence in how the intervention is bundled, presented, and assembled. Inclusion Criteria: Include statements regarding the quality of the materials and packaging.
a. NVR data collection*	Definition: Opinions about the data collection method used during the programme (National Vascular Registry and the development of a new specific database on REDCap)
b. Online resources*	Definition: Opinions and use of online resources about Quality Improvement
c. Performance reports*	Definition: Opinions and suggestions about the quarterly performance reports that were sent to the local program leads
d. Webinars meetings*	Definition: Opinions and suggestions about the online webinars and the face-to-face meetings that were conducted as part of the programme and where clinicians from all participating centres met.
e. PAD QIP overall*	Definition: Opinions about the usefulness, aim, purpose of the programme overall, as this was perceived by the participants
f. PAD QIP suggestions*	Definition: Suggestions and ideas about how the programme could be improved in the future and what more it can offer to participants.
G. Cost	Definition: Costs of the intervention and costs associated with implementing the intervention including investment, supply, and opportunity costs. Inclusion Criteria: Include statements related to the cost of the intervention and its implementation
Outer Setting	
A. Needs & Resources of Those Served by the Organization	Definition: The extent to which the needs of those served by the organization (e.g., patients), as well as barriers and facilitators to meet those needs, are accurately known and prioritized by the organization. Inclusion Criteria: Include statements demonstrating (lack of) awareness of the needs and resources of those served by

	the organization, such as statements about: 1. Perceived need for the intervention based on the needs of those served by the organization and if the intervention will meet those needs; 2. Barriers and facilitators of those served by the organization to participating in the intervention; 3. Participant feedback on the intervention, i.e., satisfaction and success in a program. In addition, include statements that capture whether or not awareness of the needs and resources of those served by the organization influenced the implementation or adaptation of the intervention. Exclusion Criteria: Exclude statements that demonstrate a strong need for the intervention and/or that the current situation is untenable and code to Tension for Change.
B. Cosmopolitanism	Definition: The degree to which an organization is networked with other external organizations. Inclusion Criteria: Include descriptions of outside group memberships and networking done outside the organization.
C. Peer Pressure	Definition: Mimetic or competitive pressure to implement an intervention, typically because most or other key peer or competing organizations have already implemented or are in a bid for a competitive edge. Inclusion Criteria: Include statements about perceived pressure or motivation from other entities or organizations in the local geographic area or system to implement the intervention.
D. External Policy & Incentives	Definition: A broad construct that includes external strategies to spread interventions including policy and regulations (governmental or other central entity), external mandates, recommendations and guidelines, pay-for-performance, collaboratives, and public or benchmark reporting. Inclusion Criteria: Include descriptions of external performance measures from the system.
Inner Setting – Team**	
A. Team structure**	Definition: Team size, turnover/stability, workload
B. Teamwork**	Definition: The quality of communication within the team and relationships amongst its members.
C. Culture**	Definition: The norms, values and assumptions of the team, the degree of autonomy given to staff and their perceptions of change.

D. Compatibility**	Definition: Whether the intervention fits with the existing workflows of the team.
E. Team beliefs**	Definition: Beliefs and perceptions of the team about the intervention.
Inner Setting - Organisation	
A. Structural Characteristics	Definition: The social architecture, age, maturity, and size of an organization. *Additionally, the vascular network configuration, and issues that arise due to this, i.e. service relocation to a different hospital, large catchment area, information about the Spoke hospitals served by that arterial centre.*
B. Networks & Communications	Definition: The quality of communications within an organization and relationships amongst its members. Inclusion Criteria: This includes communication between departments or specialties, *including the relationship between the Vascular Surgery and the Interventional Radiology departments and teams.* Include statements about general networking, communication, and relationships in the organization, such as descriptions of meetings, email groups, or other methods of keeping people connected and informed, and statements related to team formation, quality, and functioning. Exclusion Criteria: Exclude statements related to engagement strategies and outcomes, e.g., how key stakeholders became engaged with the intervention and what their role is in implementation, and code to Engaging. Exclude descriptions of outside group memberships and networking done outside the organization and code to Cosmopolitanism.
C. Culture, merged with Learning Climate	Definition: Norms, values, and basic assumptions of a given organization, the degree of autonomy given to staff and their perceptions of change. Learning climate is a climate in which: 1. Leaders express their own fallibility and need for team members' assistance and input; 2. Team members feel that they are essential, valued, and knowledgeable partners in the change process; 3. Individuals feel psychologically safe to try new methods; and 4. There is sufficient time and space for reflective thinking and evaluation. Inclusion Criteria: Inclusion criteria, and potential sub-codes, will depend on the framework or definition used for "culture."

D. Implementation Climate	Definition: The absorptive capacity for change, shared receptivity of involved individuals to an intervention, and the extent to which use of that intervention will be rewarded, supported, and expected within their organization. Inclusion Criteria: Include statements regarding the general level of receptivity to implementing the intervention.
a. Tension for Change	Definition: The degree to which stakeholders perceive the current situation as intolerable or needing change. Inclusion Criteria: Include statements that (do not) demonstrate a strong need for the intervention and/or that the current situation is untenable, e.g., statements that the intervention is absolutely necessary or that the intervention is redundant with other programs. Exclusion Criteria: Exclude statements regarding specific needs of individuals that demonstrate a need for the intervention, but do not necessarily represent a strong need or an untenable status quo, and code to Needs and Resources of Those Served by the Organization.
b. Relative Priority	Definition: Individuals' shared perception of the importance of the implementation within the organization. Inclusion Criteria: Include statements that reflect the relative priority of the intervention, e.g., statements related to change fatigue in the organization due to implementation of many other programs. Exclusion Criteria: Exclude or double code statements regarding the priority of the intervention based on compatibility with organizational values to Compatibility, e.g., if an intervention is not prioritized because it is not compatible with organizational values.
E. Organisational Leadership Engagement	Definition: Commitment, involvement, and accountability of leaders and managers with the implementation of the intervention, *including whether frontline leaders/managers (Consultants, departmental managers, divisional managers) are committed and involved in the implementation.* Inclusion Criteria: Include statements regarding the level of engagement of organizational leadership. Exclusion Criteria: Exclude or double code statements regarding leadership engagement to Engaging.
F. Available Resources	Definition: The level of organizational resources dedicated for implementation and on-going operations including

	physical space and time, human (staffing), financial, technological. Inclusion Criteria: Include statements related to the presence or absence of resources specific to the intervention that is being implemented.
Characteristics of Individuals	
A. Beliefs and knowledge about the Intervention	Definition: Individuals' attitudes toward and value placed on the intervention, as well as familiarity with facts, truths, and principles related to the intervention. *Inclusion Criteria: Include beliefs about the local changes to the service, that are not captured under "Relative Advantage". Beliefs about the PAD QIP as a collaborative quality improvement programme are captured under "Design Quality & Packaging".*
B. Self-efficacy	Definition: Individual belief in their own capabilities to execute courses of action to achieve implementation goals. *Inclusion Criteria: Include comments about their personal contribution to the local implementation and their ability to make changes*
C. Individual Stage of Change	Definition: *How each person got involved, how they found out about the programme, if they volunteered or if they were allocated this job.* Characterization of the phase an individual is in, as s/he progresses toward skilled, enthusiastic, and sustained use of the intervention.
Process	
E. Planning	Definition: The degree to which a scheme or method of behavior and tasks for implementing an intervention are developed in advance, and the quality of those schemes or methods. Inclusion Criteria: Include evidence of pre-implementation diagnostic assessments and planning, as well as refinements to the plan.
a. Local future plans*	Definition: The specific plans that participants have made for changes in their centre in the future. Include changes already planned but also aspirational ones.
F. Engaging	Definition: Attracting and involving appropriate individuals in the implementation and use of the intervention through a combined strategy of social marketing, education, role modeling, training, and other similar activities. Inclusion Criteria: Include statements related to engagement strategies and outcomes, i.e., if and how staff and intervention

	participants became engaged with the intervention and what their role is in implementation. Both strategies and outcomes are coded here. This construct includes the sub-constructs of • Opinion Leaders, • Formally Appointed internal implementation leaders, • Champions ("Individuals who dedicate themselves to supporting, marketing, and 'driving through' an [implementation]", overcoming indifference or resistance that the intervention may provoke in an organization), • External change agents, • Key stakeholders (Individuals from within the organization that are directly impacted by the intervention, e.g., staff responsible for making referrals to a new program or using a new work process)
G. Executing	Definition: Carrying out the implementation according to plan. Inclusion Criteria: Statements demonstrating how implementation occurred with respect to the implementation plan.
a. Local pathway changes*	Definition: Changes that were implemented in each vascular unit to reach the improvement goal, i.e. reduce time to revascularisation
H. Reflecting & Evaluating	Definition: Quantitative and qualitative feedback about the progress and quality of implementation accompanied with regular personal and team debriefing about progress and experience. Inclusion Criteria: Include statements that refer to the implementation team's (lack of) assessment of the progress toward and impact of implementation, as well as the interpretation of outcomes related to implementation. Reflecting and Evaluating is part of the implementation process; it likely ends when implementation activities end. It does not require goals be explicitly articulated; it can focus on descriptions of the current state with real-time judgment, though there may be an implied goal (e.g., we need to implement the intervention) when the implementation team discusses feedback in terms of adjustments needed to complete implementation.
a. Data collection*	Definition: Methods by which data were collected in the organization, e.g. through local databases, using the online NVR system. This includes the use of data coordinators/data clerks.

COVID-19*	
A. COVID positive effect*	Definition: The effect that the COVID-19 pandemic had on implementation efforts that facilitated change. Inclusion Criteria: Statements on the effect of COVID that were perceived as facilitating the implementation effort or having a positive effect on patients or the delivery of patient care.
B. COVID negative effect*	Definition: The effect that the COVID-19 pandemic had on implementation efforts that hindered change. Inclusion Criteria: Statements on the effect of COVID, that were perceived as hindering the implementation effort or having a negative effect on patients or the delivery of patient care
Main facilitating factor*	Definition: The main factor that the participants think helped them implement changes in their organization. May include double coding statements that fit in CFIR constructs.
Main difficulty*	Definition: The main factor that the participants think hindered their efforts to implement changes in their organization. May include double coding statements that fit in CFIR constructs.
A. Other difficulties*	Definition: Factors that are perceived as hindering the implementation efforts of the participants, apart from the main one. May include double coding statements that fit in CFIR constructs.

* These codes were developed inductively by the research team.

** Team level determinants were added in the CFIR framework as described by Rogers et al., because the existing constructs did not clearly separate the team and organization-level determinants.

Text in italics indicates changes to the definition or the inclusion criteria made by the researcher.

Glossary

AAA QIP: Abdominal Aortic Aneurysm quality improvement programme

ABPI: Ankle-brachial pressure index

ACEI: Angiotensin-converting enzyme inhibitors

AFS: Amputation-free survival

AKA: Above-knee amputation

AKI: Acute kidney injury

ALI: Acute limb ischaemia

AP: Ankle pressure

ARB: angiotensin receptor blockers

ASA: American Society of Anaesthesiologists

BASIL: Bypass versus Angioplasty in Severe Ischaemia of the Leg (trial)

BIC: Bayesian information criterion

BKA: Below-knee amputation

BMI: Body mass index

BMS: Bare metal stent

CAQDAS: Computer Assisted Qualitative Data Analysis Software

CFIR: Consolidated Framework for Implementation Research

CHF: Chronic heart failure

CI: Confidence interval

CKD: Chronic kidney disease

CLI: Chronic limb ischaemia

CLTI: chronic limb-threatening ischaemia

COPD: Chronic obstructive pulmonary disease

COVID-19: Coronavirus 19 disease

CTA: Computed tomography angiography

CWD: Continuous wave Doppler

DAPT: Dual antiplatelet therapy

DBP: Diastolic blood pressure

DCB: Drug-coated balloon

DES: Drug-eluting stent

DFU: Diabetic foot ulcers

DID: difference in difference (analysis)

DSA: Digital subtraction angiography

DUS: Duplex ultrasound

ERIC: Expert Recommendations for Implementing Change

FA: Framework analysis

FTE: Full-time equivalent

GBD: Global Burden of Diseases, Injuries, and Risk Factors Study

GDPR: General Data Protection Regulations

GIRFT: Getting it Right First Time

GLASS: Global Limb Anatomic Staging System

GSV: Great saphenous vein

HDL-C: High density lipoprotein cholesterol

HES: Hospital Episode Statistics

HIC: High-income countries

HQIP: Healthcare quality improvement partnership

HR: Hazard ratio

ICD-10: International Classification of Diseases 10th revision

IDSA: Infectious Diseases Society of America

IHD: Ischaemic Heart Disease

IMD: Index of multiple deprivation

IQR: Interquartile range

IR: Interventional radiology

IRR: Incidence rate ratio

IS: Implementation Science

IWGDF: International Working Group on the Diabetic Foot

LDL-C: Low-density lipoprotein cholesterol

LMIC: Low and middle-income countries

LOS: Length of stay

LSOA: Lower super-output area

MACE: Major adverse cardiovascular events

MALE: Major adverse limb events

MDT: Multidisciplinary team

MRA: Magnetic resonance angiography

NCEPOD: National Confidential Enquiry into Patient Outcome and Death

NHS: National Health Service

NICE: National Institute for Health and Care Excellence

NRT: Nicotine replacement therapy

NVR: National Vascular Registry

ONS: Office for National Statistics

OPCS: Office of Population Censuses and Surveys (classification)

OR: Odds ratio

PAD: Peripheral Arterial Disease

PAD QIP: Peripheral Arterial Disease Quality Improvement Programme

PAD: Peripheral Arterial Disease

PARIHS: Promoting Action on Research Implementation in Health Services

PBA: Plain balloon angioplasty

PDSA: Plan-Do-Study-Act (cycle)

PSV: Peak systolic velocity

PTFE: polytetrafluoroethylene

QI: Quality Improvement

QIC: Quality Improvement Collaborative

QIF: Quality Improvement Framework

RCS CCI: Royal College of Surgeons Charlson Comorbidity Index

RCS: Royal College of Surgeons of England

RCT: Randomised controlled trial

RE-AIM: Reach Effectiveness Adoption Implementation Maintenance

RR: Risk ratio

RRR: Relative risk ratio

SBP: Systolic blood pressure

SCARF: Secondary Care Administrative Records Frailty (index)

SFA: superficial femoral artery

SGLT-2: sodium-glucose co-transporter 2

SINBAD: Site, Ischaemia, Neuropathy, Bacterial infection and Depth

SPC: Statistical process control

STROBE: strengthening the reporting of observational studies in epidemiology

SVS: Society for Vascular Surgery

TASC: Trans-Atlantic Inter-Society Consensus

TBPI: toe-brachial pressure index

$TcPO_2$: Transcutaneous partial pressure of oxygen

TDF: Theoretical Domains Framework

TMF: Theories, models and frameworks

TP: Toe pressure

UK: United Kingdom

VSGBI: Vascular Society of Great Britain and Ireland

WIfI: Wound, Ischaemia and foot Infection (classification)