

A 5-Year Follow-up Study to Assess Clinical Outcomes of Patients with Diabetes Undergoing Lower Limb Angiography for Significant Peripheral Artery Disease

Yisu Gu · Chatchai Kokar · Catherine Gooday · Darren Morrow ·

Ketan Dhatariya 

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ABSTRACT

Introduction: The optimal management for patients with diabetes and peripheral vascular disease—intermittent claudication or critical limb ischemia (CLI)—remains undetermined.

Methods: In a single-center retrospective analysis, we compared 1- and 5-year amputation-free survival rates in patients

undergoing angiography subsequently treated with medical therapy or revascularization.

Results: 78 patients were included, 56 with CLI (mean age 77 years); 22 with claudication (mean age 75 years). Of the CLI cohort, 30 patients were medically treated. Their 1-year amputation-free survival rate was similar to those treated with revascularization (46.7% versus 50.0%, respectively). 8 patients in the claudicant cohort were treated conservatively. The 1-year amputation-free survival rate was 75.0% for conservative treatment versus 78.6% in those revascularized. Within the CLI cohort, in those conservatively treated 20% underwent major, and 16.7% minor amputations, compared to 15.4% and 23.1% in those revascularized. At 5 years in the claudicant cohort, the amputation-free survival rate was 37.5% with medical treatment, versus 71.4% for those treated with revascularization. For CLI, the 5-year amputation-free survival rate was 10% for conservative treatment, versus 26.9% for revascularization.

Conclusion: We found similar rates of amputation at 1 year for patients treated medically or revascularized. However, at 5 years, the amputation-free survival rate was markedly

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Y. Gu
Department of Medicine, Norfolk and Norwich
University Hospital NHS Foundation Trust, Colney
Lane, Norwich, Norfolk NR4 7UY, UK

C. Kokar
St. George's University School of Medicine,
Grenada, West Indies

C. Gooday · D. Morrow · K. Dhatariya (✉)
Diabetic Foot Clinic, Elsie Bertram Diabetes Centre,
Norfolk and Norwich University Hospital NHS
Foundation Trust, Colney Lane, Norwich,
Norfolk NR4 7UY, UK
e-mail: ketan.dhatariya@nnuh.nhs.uk

D. Morrow
Department of Vascular Surgery, Norfolk and
Norwich University Hospital NHS Foundation Trust,
Colney Lane, Norwich, Norfolk NR4 7UY, UK

higher in revascularized patients compared to those medically managed. Our study highlights the potential role of predicting life expectancy when considering treatment, with the option of surgical treatment offered to those in whom survival is predicted to be longer than 5 years. However, larger studies with matched cohorts are now needed to confirm these findings.

Keywords: Amputation; Angiography; Diabetes; Peripheral vascular disease

INTRODUCTION

The International Diabetes Federation estimates more than 387 million people worldwide were affected by diabetes in 2014, with this number predicted to rise to 592 million by 2035 [1]. Diabetes-related foot disease, in particular foot ulcers, remains one of the main complications caused by a combination of peripheral neuropathy, infection, and peripheral arterial disease (PAD) [2]. Recent data have shown that diabetes is second only to smoking as a cause of PAD [3]. More than one million people a year undergo amputation of the lower limb, with 85% of cases precipitated by a foot ulcer [4]. In England, an estimated £639 million to £662 million (0.6–0.7% of the total National Health Service budget) is spent on the treatment of diabetic foot ulceration and amputation [5]. Aside from the economic burden, there are often considerable social and psychological impacts associated with the diagnosis of diabetes [6].

Infection and PAD form the two major indications for lower limb amputation in diabetes [7, 8]. The Framingham Heart Study (ClinicalTrials.gov identifier, NCT00005121) showed one-fifth of patients with symptomatic PAD suffered also from diabetes, although the

actual prevalence is likely to be higher as most cases of PAD are asymptomatic [9]. The most frequently observed presentation of symptomatic PAD is intermittent claudication; described as a reproducible pain or cramp of the lower limb on walking, which is then relieved by rest. At the other end of the spectrum, a minority of patients will present with features of critical limb ischemia (CLI): rest pain, tissue loss with ulceration and gangrene. Of note, in patients with PAD associated with diabetes, the diseased vessel is often distal, (femoro-popliteal and tibial), whereas PAD secondary to other risk factors (e.g., smoking, hypercholesterolemia), generally occurs in more proximal (aorto-ilio-femoral) vessels [6]. PAD, which progresses faster in the population with diabetes, has been shown in large observational studies to complicate up to half of all diabetic foot ulcer cases, and is an independent risk factor for amputation [6, 10–12]. The prognosis of patients with a diabetic foot ulcer and PAD is poor, with a 50% dying at 5 years, and at 2 years following a major amputation [13].

The Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II) in 2007 and the United Kingdom (UK) National Institute for Health and Clinical Excellence (NICE) in 2012 have published guidelines on the diagnosis and management of PAD [14, 15]. However, evidence-based guidelines for the management of patients with diabetes presenting with PAD is lacking. In 2011, in the UK NICE produced guidance on the management of diabetic foot problems in hospitalized patients but were unable to provide recommendations on the optimal time for either revascularization or orthopedic interventions to prevent amputation due to a lack of evidence [16]. A review by Brownrigg et al. focusing on the evidence-based strategies

for diabetic foot ulceration advised best medical therapy (wound care with debridement, treatment of infection, off-loading with a 6-week period of observation) for patients with diabetes and mild PAD with an ankle-brachial index of ≥ 0.6 [17].

In large ulcers with possible infection, early vascular intervention may be required due to poor outcomes with conservative therapy. Revascularization is also advised for those patients where PAD is contributing to poor wound healing, with the exception of very frail patients or those with an unsalvageable foot [17]. A systematic review in 2012 demonstrated improved rates of limb salvage in patients with diabetes with foot ulcers undergoing revascularization compared to those treated medically; however, the authors concluded that there were insufficient data to recommend one form of revascularization over another [18].

In summary, due to the relatively scarcity of good quality evidence, there remains uncertainty as to the best way to manage patients with diabetes who have a degree of PAD. Our aim was to present a descriptive analysis of the clinical outcome of revascularization versus medical management in patients with claudication and CLI at our own regional multidisciplinary diabetes foot clinic, as measured by their amputation-free survival rate at 1 and 5 years. In particular, to examine how our patient results compare to other similar studies.

MATERIALS AND METHODS

We performed a retrospective analysis of all of our patients attending the tertiary specialist diabetes vascular foot clinic with diabetes who underwent an angiogram of the lower limb

during the 24-month period from January 2009 to December 2010. We retrospectively reviewed their medical notes to record their foot disease history, disease presentation, co-morbidities and medication, intervention, and 1-year clinical outcome. For those patients that were alive and without minor or major amputation at 1 year, we analyzed their disease outcome in terms of amputation-free survival again at 5-year follow-up.

Disease presentation was recorded as claudication or CLI (ulcer, gangrene or rest pain). Intervention was defined as conservative medical management, or revascularization (which included angioplasty, profundoplasty, embolectomy, endarterectomy, or bypass). For medical management, we recorded the reason for this conservative approach as follows: unfit for surgery; patient refusal; joint decision by clinician and patient to treat conservatively; no option for or failed revascularization; and symptom resolution by the time of the procedure. The clinical outcome in the same lower limb was recorded as 'no amputation', 'minor amputation' (trans-metatarsal, forefoot or digits), 'major amputation' (above or below knee) or 'death' (from whatever cause). We calculated the 1- and 5-year amputation-free survival rate to compare the outcome of medical versus surgical intervention in the treatment of claudication and CLI.

Compliance with Ethics Guidelines

Due to the retrospective, anonymous nature of the study, the Norfolk and Norwich University Hospitals NHS Foundation Trust ethics committee classed this as a service improvement exercise and ethical approval was deemed to not be necessary.

RESULTS

A total of 78 patients with diabetes from our specialist clinic underwent lower limb angiography at our institution between January 2009 and December 2010. 56 patients had presentations of CLI, while 22 patients had claudication symptoms only. Table 1 shows the baseline characteristics of the two cohorts. Figure 1a, b illustrates the 1-year outcome of the two cohorts, along with the reason for conservative management and form of revascularization performed. The 8 patients who were treated conservatively in the claudicant cohort included one patient who presented 6 months after their initial presentation of claudication with CLI, resulting in one major above knee amputation.

Comparison of baseline micro- and macro-vascular complications of the two treatment arms showed the following results. Within the claudicant group, the mean Estimated Glomerular Filtration Rate (eGFR) was slightly lower at 56.6 mL/min/1.73 m² in the no revascularization group, and 65.1 mL/min/1.73 m² in the revascularization group. Conversely, for patients with critical ischemia, the mean eGFR was higher in the medically treated cohort (58.4 versus 53.8 mL/min/1.73 m²).

Amongst the claudicants, for the 8 patients treated medically, 4 had cardiovascular disease [3 with stable angina only, and 1 with previous non ST-Segment elevation myocardial infarction (NSTEMI)/ST segment elevation myocardial infarction (STEMI)], and no patient had previous transient ischemic attack (TIA) or stroke. In comparison, within the 14 patients that underwent revascularization, a higher proportion of patients had cardiovascular disease (7 patients with stable angina only, 6

with STEMI/NSTEMI), and TIA/stroke (4 patients) complications.

For critical ischemia, amongst the 30 patients treated conservatively, 21 had cardiovascular complications (12 stable angina only, 9 STEMI/NSTEMI) and 4 had TIA/stroke. For those 26 patients treated surgically, a slightly higher proportion of patients had cardiovascular (11 stable angina only and 11 NSTEMI/STEMI) and TIA/stroke (8 patients) complications.

With regards to risk factors for arterial disease, similar proportions of claudicant patients were ex- or current smokers within the medical and surgical treatment groups (62.5% versus 57.1%, respectively). For critical ischemia, there was a higher proportion of ex- or current smokers for those patients treated surgically (69.2% versus 36.7%).

Analysis of diabetes related risk factors shows the mean glycated hemoglobin (HbA1c) was lower for patients treated medically in the claudicant cohort (54 versus 62 mmol/mol), but higher in critical ischemia patients treated medically (64 versus 56 mmol/mol). In this study, the majority of patients had Type 2 diabetes, with only 4 patients with Type 1. The proportion of patients on insulin therapy compared to diet or tablet alone was similar for both medically and surgically treated patient cohorts in the claudicant arm (25% versus 28.6%, respectively), but was markedly higher for those patients treated medically within the critical ischemia arm (53.3% versus 15.4%).

Review of baseline surgical status showed 42.9% of patients in the claudicant group treated with revascularization had prior surgery compared to 37.5% of patients treated conservatively. For critical ischemia, patients in the revascularization cohort had slightly higher rates of previous surgical intervention (50%

Table 1 Clinical characteristics of patients treated by conservative and revascularization in the claudication and critical limb ischemia cohorts

Population characteristics	Claudicants (<i>n</i> = 22)		Critical limb ischemia (<i>n</i> = 56)	
	No revascularization (<i>n</i> = 8)	Revascularization (<i>n</i> = 14)	No revascularization (<i>n</i> = 30)	Revascularization (<i>n</i> = 26)
Age (mean, years)	72.1	75.9	77.9	76.3
M/F	6/2	13/1	20/10	12/14
Diabetes				
Type 1/type 2	1/7	0/14	3/27	0/26
Type 2 management				
Diet	1	2	3	10
Tablet	4	8	8	12
Insulin	2	4	16	4
Mean HbA1c (mmol/mol)	54	62	64	56
Mean eGFR (mL/min/1.73 m ²)	56.6	65.1	58.4	53.8
Previous surgical intervention	3/5	6/8	13/17	13/13
Y/N				
Risk factors				
Stable angina	3	7	12	11
Previous STEMI/NSTEMI	1	6	9	11
Previous TIA/stroke	0	4	4	8
Ex or current smoker	5	8	11	18
Concurrent medications				
Aspirin	8	12	18	17
Statin	5	12	21	17
Fibrate	0	0	0	2
ACE/ARB	6	6	16	14
Ulcer and gangrene				
Forefoot			15	12
Midfoot			5	1
Heel			3	1
Ankle			2	1
Leg			2	0
Location unavailable			1	3

Table 1 continued

Population characteristics	Claudicants (<i>n</i> = 22)		Critical limb ischemia (<i>n</i> = 56)	
	No revascularization (<i>n</i> = 8)	Revascularization (<i>n</i> = 14)	No revascularization (<i>n</i> = 30)	Revascularization (<i>n</i> = 26)
Rest pain			2	8

HbA1c glycated hemoglobin, *eGFR* estimated glomerular filtration rate, *STEMI* ST segment elevation myocardial infarction, *NSTEMI* non ST-Segment elevation myocardial infarction, *TIA* transient ischemic attack, *ACE* angiotensin-converting enzyme, *ARB* angiotensin 2 receptor blockers

versus 43.3%). Prior surgery included both amputation and vascular intervention. Data of individual procedural types were unfortunately not collected.

In the claudicant group, the 1-year amputation-free survival rate for medical therapy was 75% versus 78.6% in those patients treated with revascularization. The 5-year amputation-free survival was 37.5% for conservative treatment, versus 71.4% for those treated with revascularization.

For the CLI cohort, 46.7% of patients had a 1-year amputation-free survival rate in the cohort of patients treated conservatively compared to 50% in the patients treated with revascularization. Of the 56 patients presenting with CLI, 15.4% underwent a major amputation at 1-year follow-up in the revascularization group compared to 20% in the conservative arm. For minor amputations, the rate was 23.1% for revascularization versus 16.7% for conservative therapy. The 5-year amputation-free survival rate was 10% in the conservative arm compared to 26.9% for those treated with revascularization.

Finally, within the revascularization cohort, a distinction can be made between endovascular procedures and bypass surgery. Subgroup analysis shows the endovascular route results in a 1-year amputation-free survival rate of 75% versus 100% for bypass surgery in claudicants. At 5 years, however, the

amputation-free survival rate was higher at 33.3% for the endovascular procedures, versus 0% for bypass. For critical ischemia, the outcomes are more comparable, with 1 year amputation-free survival rates of 52.9% for endovascular procedures and 44.4% for bypass surgery. Five-year amputation-free survival rates were 17.6% for endovascular versus 22% for bypass procedures.

The data we present here are descriptive only, with no attempts at statistical analysis due to the small sample size and retrospective nature of the study, which made any further comparisons between the cohorts unreliable.

DISCUSSION

In this study, we demonstrate revascularization to be a more effective treatment for claudicants and patients with CLI, with approximately double the amputation-free survival rate at 5 years. However, our study has also demonstrated similar amputation outcomes at 1-year follow-up for patients treated with either medical or revascularization therapy for both presentations of claudication and CLI.

Our results at 1 year would suggest that conservative management of CLI and claudication is as effective as surgical intervention in terms of limb preservation. For patients, this would mean a similar clinical outcome without the risks and complications of

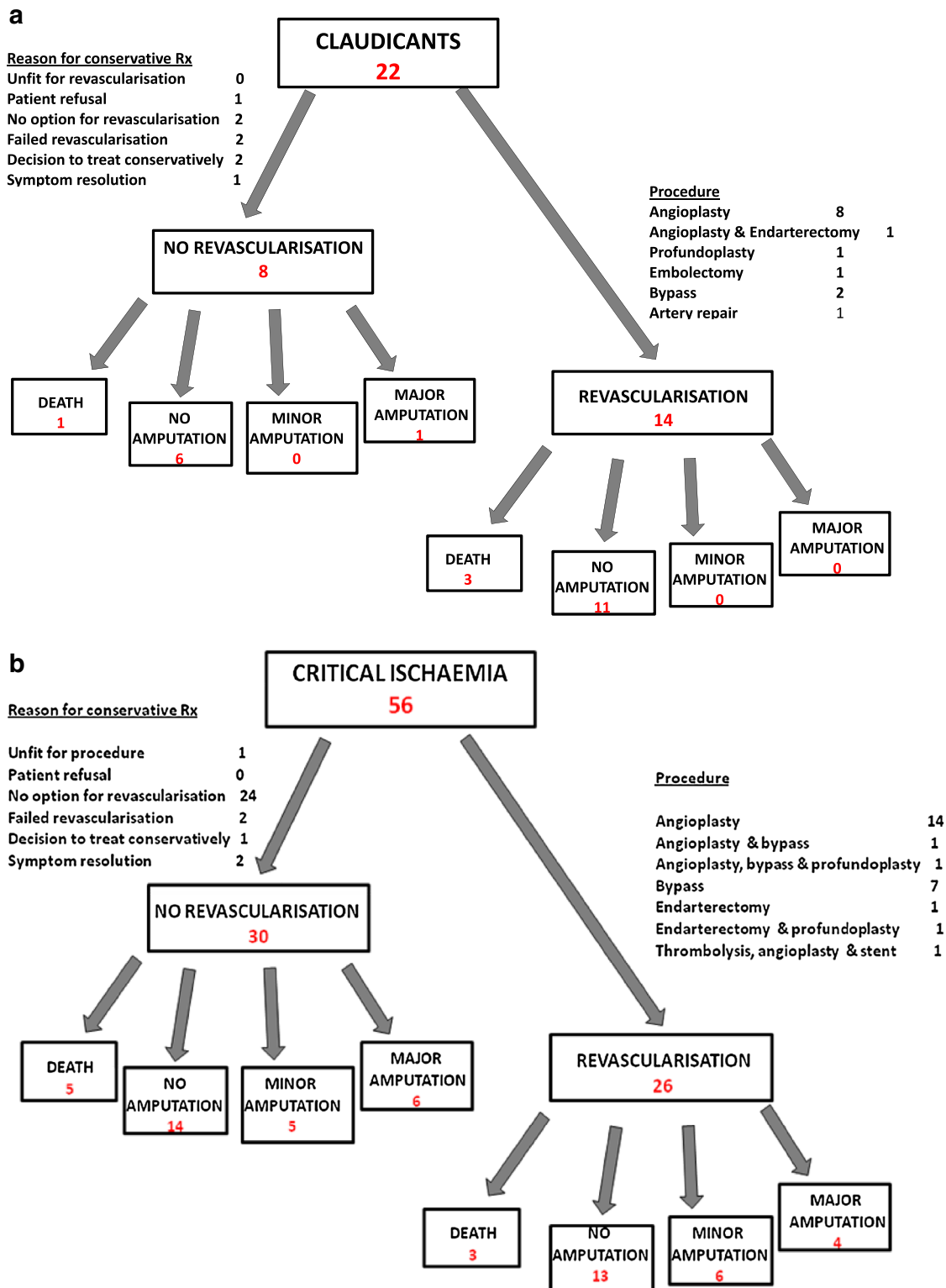


Fig. 1 a, b One-year clinical outcome of patients treated by medical versus revascularization for presentations of critical limb ischemia and claudication

surgery, and a financial benefit for the health system. Our data are in contrast to previous work that has shown better rates of limb salvage for patients undergoing vascular intervention [18, 19]. The results of these reviews also reflect the current UK national and international guidelines for the management of PAD—although it must be acknowledged that these guidelines are not specific to diabetes [14]. The TASC II and 2012 NICE guidelines on intermittent claudication recommend initial conservative treatment with a supervised exercise program and modification of risk factors, with a plan for angioplasty and possible bypass surgery if these measures prove to be unsuccessful [14, 15]. For CLI, NICE recommends revascularization therapy over conservative measures, as assessed by a dedicated vascular multidisciplinary team [15]. TASC II is also in favor of revascularization over conservative measures for CLI if the patient is fit for surgery [14]. In addition, the guideline recommends best medical management or amputation if there is intolerable pain or spreading infection [14]. Nevertheless, whilst the findings of the current study are in contrast to these guidelines, they are in accordance with 2 other studies that show that best medical management for the diabetic foot at 1 year is associated with similar outcomes as revascularization [20, 21]. Elgzyri et al. conducted a prospective study of 602 patients with diabetes who all presented to a multidisciplinary foot center with foot ulcers, but who were deemed to be unsuitable for revascularization [20]. These authors demonstrated limb salvage rates of 56% and 77%, respectively, at 1 year, with significant healing with conservative measures or with minor amputation alone [20, 21].

In terms of the nature of amputation, i.e. major versus minor, within the CLI cohort, we demonstrate a modest reduction in major amputation rates in the revascularization cohort compared to conservative therapy at 1 year. However, this is at the expense of a higher rate of minor amputations in this group. Whether this outcome is acceptable is dependent on the needs of the individual patient, the quality of the prosthesis and the success of rehabilitation. A large prospective study examining the long-term prognosis of 189 patients with diabetes undergoing major and minor amputations showed 93% of patients returned to living independently following a minor amputation compared to 61% having a major amputation. More patients with minor amputations also regained their original walking capacity in comparison to patients after major amputations [22]. Although revascularization lowers the rate of major amputations in patients presenting with CLI, a longer follow-up period may be necessary to ascertain the significance of the higher rate of minor amputations, as many of these cases may eventually progress to major amputation. A recent study to demonstrate this phenomena in patients with diabetes showed an average interval from minor to major amputation of 591.0 and 559.6 days for mild-to-moderate and severe PAD, respectively. Thus, a longer follow-up of our patients beyond the 365 days may show a similar outcome for those who underwent a minor amputation [23].

A number of factors may account for the differences at 1 year between our results and the findings of other published data in terms of clinical outcome between revascularization and conservative therapy. Our sample size was relatively small; thus between-group

comparisons were more difficult and we make no statement about statistical significance between the groups. Compared to other similar published studies, many of which follow up patients for many years, or until wound healing or death, our 1-year follow-up period is relatively short. Indeed for a number of our patients, minor or major amputations occurred at 13 or 14 months following their initial angiogram, but these were not included due to the 12-month follow-up criteria. In addition, our analysis included the results of 78 patients at our regional diabetes foot center. However, similar studies examining the outcomes of diabetes and peripheral vascular disease, for example the EURODIALE study and the BASIL trials (National Institute of Health Research HTA—96/05/01), are large multicenter trials with data for hundreds of patients. Thus, if our study were to be extended to involve larger populations with matched cohorts, the amputation-free survival rate of medical versus revascularization at 1 year may be different to the current values.

In addition, larger multicenter trials would also allow subgroup analysis of data. Of interest, the distinction between endovascular procedures and more invasive bypass surgery is a clinically significant one: the endovascular route is less invasive, can be performed under local anesthesia as a day case, and can be performed more than once. Results of subgroup analysis for critical ischemia in this study show comparable one- and 5-year amputation-free survival rates for the two revascularization routes; however, small cohorts make further analysis of data unreliable.

Within the CLI cohort, we recorded also the location of ulcer and gangrene for patients treated by conservative and revascularization (Table 1). Location was recorded as forefoot (hallux and toes), mid-foot (to include

metatarsals, dorsal and plantar surfaces of the foot), heel, ankle, leg or location unavailable. The majority of such lesions occurred on the forefoot of both treatment arms. The very small numbers of ulcers and gangrene occurring elsewhere in the lower limb make any further analysis of the relationship between location and rate of amputation unreliable.

In addition, as a retrospective study, the data collected are limited to the information already available from previously documented events, rather than prospectively collecting information specific to this study question. Prospective data collection may provide a more detailed account of disease presentation, co-morbidities, and medication history of the patient.

Recent studies show the outcome of a diabetic foot ulcer is not only affected by the severity of ischemia, but also by the extent of tissue loss, the presence of infection, and certain co-morbidities of the patient [24]. For example, there is evidence that the presence of stroke and the microvascular complications of diabetes are strongly associated with lower limb amputation. However, the rate of amputation in patients with and without coronary artery disease and/or myocardial infarction was not significantly different [25, 26]. In our study, despite aggressive revascularization therapy, the 1-year amputation-free survival rate is similar for claudicant patients treated by both medical and surgical approaches. The absence of superiority of revascularization may be partly explained by the differing patient characteristics of the two treatment arms. For example, there is a higher prevalence of previous TIA/stroke (4 versus 0 patients), and a higher mean HbA1c (62 versus 54 mmol/mol), within the cohort treated with revascularization compared to those treated medically. As discussed above, could patients with a history

of cerebrovascular disease and poorly controlled diabetes, and therefore, a greater likelihood of microvascular complications, be more likely to progress to amputation regardless of aggressive therapy?

In a similar fashion, patients with chronic kidney disease (eGFR <60 ml/min) and those treated with renal dialysis have a higher rate of below- and above-knee amputations in comparison with diabetic patients without renal disease [27]. In our study, within the group of patients presenting with CLI, the mean eGFR is lower for those patients treated surgically in comparison to those treated medically (53.8 versus 58.4 mL/min/1.73 m²). In our study, the degree of tissue loss, presence of infection, and severity of ischemia were not recorded. The use of randomization or matching techniques to take into account these confounding factors is difficult to perform in our current study population due to the relatively small sample size. Nevertheless, patients with diabetes who have certain co-morbidities associated with higher rates of amputation may warrant an earlier and more intensive treatment approach for long-term limb preservation. In a similar fashion, all patients, whether treated with conservative or surgical measures, would benefit from tight glycemic and blood pressure control to reduce both the microvascular complications and thus rates of lower extremity amputation.

A comment needs to be made about the apparent lack of use of adjuvant therapies (Table 1), in particular statins, in our cohort. Many of these individuals also had some underlying wound infections. Our standardized antibiotic protocol advocates the use of clarithromycin or fucidin at times [28]. The use of either of these drugs necessitates the stopping of statin therapy to avoid potential interaction and subsequent rhabdomyolysis.

Finally, the success of revascularization therapy for lower limb PAD was traditionally reported in terms of arterial patency and limb salvage. However, there remain questions as to if these are accurate predictors of functional outcome for the patient—in particular improved mobility and independence. Taylor et al. in 2006 examined both the technical outcome of reconstruction patency and limb salvage, as well as the functional outcome of ambulation and maintenance of independent living, for 841 patients with CLI at a University Medical Center [29]. Results of that study suggested some patients—in particular those with dementia—may have had a technically satisfactory outcome, including limb salvage, but may not have experienced any improved functional outcome. That group of patients overall performed worse than those patients who lost their limbs, in terms of survival, ambulation, and independent living [29]. Thus, despite achieving arterial patency and long-term limb salvage, some patients may still suffer from functional disabilities that result in both a reduced sense of well-being for the individual, as well as a significant financial burden on the healthcare system. In this context, despite similar amputation-free survival rates for our two cohorts at 1 year, it is necessary also to assess how this compares with the functional outcome for our patients in terms of maintenance of mobility and quality of life. Our data are in agreement with recent guidance from the International Working Group of the Diabetic Foot who recommends that “revascularization should be avoided in patients in whom, from the patient perspective; the risk–benefit ratio for the probability of success is unfavorable” [30]. In line with the above, it would be interesting to assess length and frequency of hospital admission for the

patients in this study as these factors can also have a significant impact on quality of life.

We acknowledge that our data have their limitations. It is retrospective in nature, a relatively small sample size and a relatively short follow-up period. We have also not described in detail the nature of the severity of the PAD. Our study is also similar to previous work because our subjects lack matching between the 2 groups. In addition, there is an absence of correlation between the clinical endpoints and functional outcomes. It is imperative to take into consideration significant baseline patient characteristics such as glycaemic control, renal function, and other micro/macro-vascular risk factors, when comparing medical versus revascularization therapy on amputation-free survival outcomes. Unfortunately due to small sample size and retrospective nature of our study, matching of the treatment arms was not performed. Future studies taking into account such confounding factors will enable more reliable conclusions to be drawn.

Thus, our data suggest similar outcomes for medically and surgically managed patients with PAD at 1 year and superior outcomes for surgery at 5-year follow-up; however, firm conclusions cannot be drawn at present due significant patient differences of the two treatment arms. Baseline renal function, diabetic control, and vascular complications should also be taken into account when predicting for patient survival. Nevertheless, a risk stratification model should be implemented because patients with certain risk factors strongly associated with lower limb amputation, for example, microvascular complications of diabetes, may still be best managed with a more intensive approach.

CONCLUSION

In summary, our study suggests that best medical management for PAD in diabetes may be as effective as surgical intervention at 1-year follow-up in terms of limb salvage for patients with claudication and CLI. We show that patients presenting with CLI treated conservatively at our diabetic foot center do not necessarily progress rapidly to amputation at 1 year. In contrast, at 5 years, patients treated surgically have a much higher amputation-free survival rate for both types of PAD. Although limiting surgery to those patients predicted to have a longer life expectancy may be feasible, with reductions in the costs of surgery and avoidance of potentially unnecessary surgical risks, larger studies are now needed to confirm this.

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Compliance with ethics guidelines. Because of the retrospective, anonymous nature of the study, the Norfolk and Norwich University Hospitals NHS Foundation Trust ethics committee classed this as a service

improvement exercise and ethical approval was deemed not to be necessary.

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