Are rates of limb salvage following infra-inguinal angioplasty comparable between people with and without diabetes?

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Article points

1. Defining the extent of ischaemia as a result of peripheral arterial occlusive disease in the diabetic foot can be complex.
2. Despite similar demographic data, limb salvage following infra-inguinal angioplasty in diabetic patients is worse than for those without diabetes.
3. Although not yet fully defined, there is a role for infra-inguinal angioplasty in the management of critical limb ischaemia in people with diabetes.

Key words

- Infra-inguinal angioplasty
- Limb salvage
- Peripheral arterial occlusive disease

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The authors sought to establish whether limb salvage following infra-inguinal angioplasty in people with peripheral arterial occlusive disease (PAOD) and diabetes was comparable to rates of limb salvage achieved in patients without diabetes. A retrospective review of a prospectively maintained interventional radiology database was undertaken. Demographic data were comparable, although a greater proportion of the diabetic patients had tissue loss at presentation. Technical success, 30-day mortality and survival at 1 year were similar. Significantly more people with diabetes ultimately required a major limb amputation. This is a reflection of the difficulty of defining critical limb ischaemia in diabetes and the complexity of the diabetic foot. However, for some patients meaningful limb salvage can be achieved and as such there is a role for infra-inguinal angioplasty in the management of PAOD in people with diabetes. It is important that radiologists should be fully integrated members of the multidisciplinary diabetic foot care team.

Critical limb ischaemia (CLI) was defined by the European Working Group on Critical Limb Ischaemia in 1991. The criteria for diagnosis are: (i) ankle systolic pressure of ≤50 mmHg, or a toe systolic pressure of ≤30 mmHg; and either (ii) >2 weeks of recurrent foot pain at rest that requires regular analgesia, or (iii) a non-healing wound or gangrene of the foot or toes. Failure to address CLI may result in limb loss.

Peripheral vascular disease and the diabetic foot

Diagnosing CLI in people with diabetes can be difficult. In the presence of neuropathy, rest pain may not be present, or indeed neuropathy may be painful in the absence of arterial disease (NICE, 2011). Furthermore, foot ulceration among people with diabetes may be the result of multiple injurious processes other than ischaemia.

Thus, for the person with diabetes, it is essential to optimise therapeutic interventions for each disease each component: there should be aggressive drainage of sepsis with debridement of necrotic tissue in conjunction with appropriate antibiotic therapy, good glycaemic control, and meticulous foot care with mechanical protection and pressure relief. If there is evidence of peripheral arterial occlusive disease (PAOD) and clinical concern about the adequacy of distal perfusion, restoration of arterial continuity must be considered. Given the complexity of these issues, it is clear that improving outcome requires a considered multidisciplinary approach to each patient (NICE, 2011).

PAOD in people with diabetes may present in a form indistinguishable from its presentation among people without diabetes, both in terms of symptoms and distribution of disease. However, there are a group of diabetes patients in whom PAOD is present only within the tibial vessels, but to a severe degree (NICE, 2012). The more proximal vessels may also be diseased, or in some cases are remarkably free of atheroma.

Distal disease in particular offers a challenge to the clinician, as therapeutic options may be limited. Thus, outcome for people with diabetes and POAD (across a variety of presentations) is worse than for those with POAD and no diabetes diagnosis (Jude et al, 2001; 2010).

Tools for revascularisation

Arterial revascularisation may be achieved by open surgical bypass or angioplasty. There is increasing evidence supporting the use of infra-inguinal angioplasty in people with severe lower-limb ischaemia (Tsetis and Belli 2004; Loftus et al, 2004; Faglia et al, 2005; Aarts et al, 2006; Hussey et al, 2008; Conrad et al, 2009; *Figure 1*). The multicentre, randomised controlled BASIL (Bypass versus Angioplasty in Severe Ischaemia of the Leg) Trial (Adam et al, 2005) provided further robust evidence for this intervention, reporting similar medium-term rates of limb salvage with infra-inguinal angioplasty and surgical bypass. The investigators also found angioplasty to be associated with lower procedure-related morbidity, mortality and cost.

Despite these positive findings, the role of endovascular intervention in people with PAOD and diabetes has yet to be fully defined (Classen et al, 2011; Hinchcliffe et al, 2012). While advances in endovascular technology allow for the successful treatment of more distal and complex arterial lesions, the impact that we make on the natural history of the disease process for this patient group remains uncertain and requires further investigation.

Aim

The aim of this retrospective review was to establish whether meaningful limb salvage with infra-inguinal angioplasty was as achievable among people with and without diabetes and CLI characterised by clinically significant PAOD. Permission was granted by local clinicians to evaluate these outcome data.

Methods

Background

At the authors' centre, people with CLI considered candidates for arterial reconstruction are discussed at a multidisciplinary meeting where arterial imaging is reviewed. An "angioplasty first" approach is favoured, particularly in cases of infra-geniculate disease or significant medical comorbidity. Infra-inguinal angioplasty is performed by an interventional radiologist under local anaesthesia within an endovascular suite.

Data collection

Data for this retrospective review were derived from a prospectively maintained interventional radiology database between October 2010 and December 2012. People with and without diabetes who had clinically significant PAOD were identified and imaging reviewed. Basic demographic data and indication for intervention (i.e. Fontaine classification [Dormandy and Rutherford, 2000; Fontaine stages III and IV are used to describe people with rest pain and tissue loss, respectively) were retrieved from local electronic health records

People with (i) intermittent claudication, or (ii) concurrent supra-inguinal arterial disease where the proximal lesion had not already been previously (and adequately) corrected at the time of presentation, were excluded.

Technical success was reported by the clinician performing the angioplasty and was defined as radiological improvement of the target lesion on completion of the procedure. Subsequent angioplasty failure was identified clinically and confirmed with either arterial duplex or angiography. Major limb amputation was defined as transtibial or transfemoral amputation – digital amputations were excluded. Thirty-day mortality was also recorded. Survival was recorded from the point of intervention to the time of final follow-up.

Analysis

Summary data is expressed as mean with standard deviation (SD) for normally distributed data or median and interquartile range (IQR) for non-parametric data. Data analysis was performed using SPSS.

Results

During the review period, 237 infra-inguinal angioplasties were performed. Demographic data

Figure 1. Complex tibial lesion shown (a) before and (b) after successful infra-inguinal angioplasty.

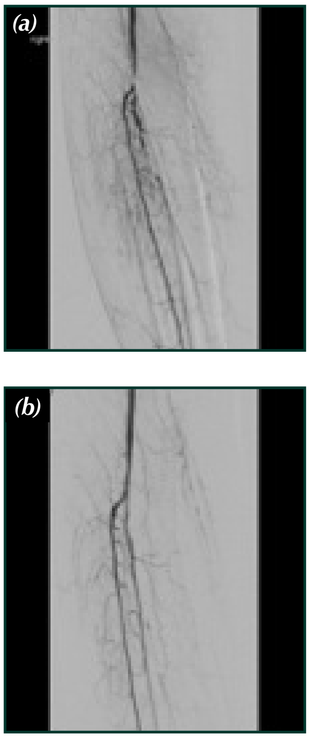


Table 1. Demographic, indication for intervention and diagnostic imaging data.

	Diabetes	Without diabetes
Demographic data		
Patients (*n*)	105	132
Mean age (years [range])	69 [37–88]	69 [33–93]
Men (*n* [%])	65 [62]	76 [58]
Indication for intervention (*n* [%])		
Rest pain†	45 [43]	80 [61]
Tissue loss‡	60 [57]	52 [39]
Diagnostic arterial imaging (*n* [%])		
MR angiography	64 [61]	80 [61]
CT angiography	29 [28]	36 [27]
Arterial duplex	6 [5.5]	13 [10]
Digital subtraction angiography	6 [5.5]	3 [2]

†Fontaine stage III; ‡Fontaine stage IV; CT, computerised tomography; MR, magnetic resonance.

were similar for those with and without diabetes (*Table 1*), with the exception of the indication for intervention; a greater proportion of people with diabetes patients had intervention for tissue loss. Median follow-up was 381 days (IQR: 232–615 days).

Where possible procedures were completed transluminally (88%). In 21 cases subintimal angioplasty was performed. Stenting of the femoro-popliteal segment was performed selectively at the discretion of the clinician performing the procedure (16%), all of which were deployed in the femoro-popliteal segment. No drug-eluting balloons were used in this cohort.

A trend towards more distal angioplasty among those with diabetes was notes, and these lesions tended to be more complex (*Table 2*). Multi-level intervention was performed more often among those with diabetes (27.6% vs 19.7%).

Table 2. Location of primary target lesion.

Primary target lesion (*n* [%])	Diabetes	Without diabetes
Superficial femoral artery	52 [49.5]	75 [56.8]
Popliteal artery	18 [17.1]	26 [19.7]
Tibial vessels	35 [33.3]	31 [23.5]

Early outcome and follow-up data following angioplasty are summarised in *Table 3*. Technical success, 30-day mortality and further attempts at limb salvage were similar across the groups.

Figure 2 shows the trend for major limb amputation following angioplasty using Kaplan Meier analysis. Patients with diabetes were significantly more likely to have had a major limb amputation performed (P=0.005). Most major limb amputations in both cohorts will occurred within 12 months of the initial intervention. Thereafter, the incidence of major limb amputation plateaued.

Survival at follow-up was not significantly different between those with and without diabetes (P=0.25; *Figure 3*).

Discussion

Surgical bypass has been considered the standard of care for patients with CLI for a number of years. Although excellent limb salvage has been demonstrated with this technique, open surgical procedures can be associated with significant morbidity (White and Gray, 2007). There is now robust data demonstrating that angioplasty is a lower risk alternative to open surgical revascularisation for the management of CLI, with similar levels of medium-term limb salvage achieved (Adam et al, 2005).

Data presented here suggest that good rates of short and medium-term limb salvage can be achieved with infra-inguinal angioplasty for people without diabetes, at rates comparable to those achived in the BASIL Trial (84% vs 84%). Two-year survival for this cohort also compare favourably with the the BASIL Trial data (72% vs 70%).

Table 3. Outcome following angioplasty according to indication and diabetes.

Variable	Diabetes (*n*=105)		Without diabetes (*n*=132)	
Indication for intervention	Rest pain† (*n*=45)	Tissue loss‡ (*n*=60)	Rest pain† (*n*=80)	Tissue loss‡ (*n*=52)
Technical success (*n* [%])	40 [88.8]	60 (100%)	70 (92.3%)	52 (100%)
30-day mortality (*n* [%])	2 [4.4]	0	0	1 [1.9]
Further attempt at limb salvage	6 [13.3]	17 [28]	24 [30]	10 [19]
Major amputation at 12 months	9 [20]	26 [43]	18 [13.6]	11 [21]

†Fontaine stage III; ‡Fontaine stage IV.

Figure 2. Kaplan Meier analysis of time spent free from major limb amputation in relation to survival for people with and without diabetes following infra-inguinal angioplasty.

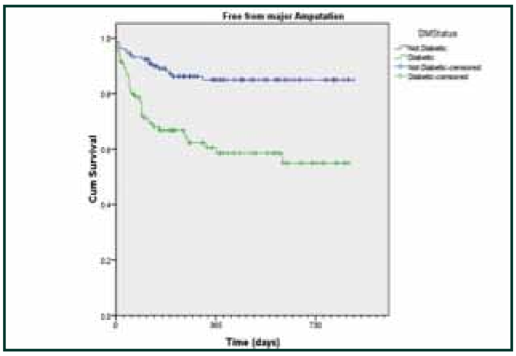
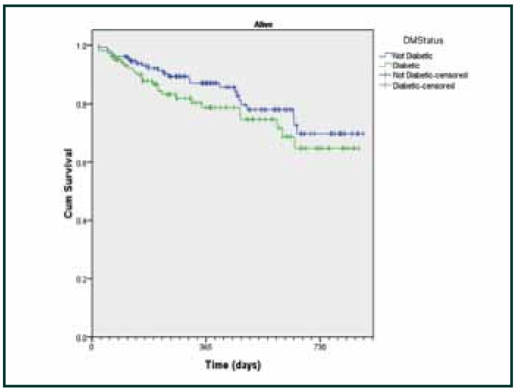


Figure 3. Kaplan Meier analysis of survival among people with and without diabetes following infra-inguinal angioplasty.



Despite the demographic data being not significantly different between those with and without diabetes in this series presented here –and despite similarly levels of technical success, 30-day mortality and survival – a clear difference in major limb amputation at 12 months was observed between the diabetes and non-diabetes cohorts. Subsequent sub-group analysis demonstrates suggests that the increased requirement for major limb amputation in the diabetes cohort exists irrespective of presentation (Fontaine stage III: diabetes 20% vs non-diabetes 13.6%; Fontaine stage IV: diabetes 43% vs non-diabetes 21%).

People with diabetes in the present series had more distal arterial disease and were more likely to have complex multi-level lesions than those without diabetes. Given that the durability of infra-inguinal angioplasty interventions for tibial vessel disease is uncertain, with one small study demonstrating significant early recoil (Baumann et al, 2014), this could explain the poorer amputation outcomes for those with diabetes.

It was not possible from the records available to gauge the extent of tissue loss among those classified as Fontaine stage IV, or to what extent sepsis was present, but certainly these factors may have prejudiced outcome in the diabetes cohort.

Another consideration is endothelial dysfunction (often referred to as small vessel disease), which is highly prevalent among those with diabetes (Hadi and Suwaidi, 2007) and probably contributed to the greater proportion of major limb amputations performed in the diabetes group reported here. A study of people with established renal dysfunction (a group that frequently have POAD and endothelial dysfunction) describe limb salvage rates of 68.9% at 1 year, and 84% of that cohort had a diagnosis of diabetes (Orimoto et al, 2013).

The NICE guidelines (2012) recommend that revascularisation should be considered if clinically appropriate to avoid amputation. However, three people with diabetes and tissue loss (Fontaine stage IV) included in the present study required a major limb amputation within 7 days of infra-inguinal angioplasty. Critical review of these cases suggests that these people may have been better served by a primary amputation.

In clinical practice, it is difficult to predict which of those with diabetes and foot ulceration will improve with revascularisation, and which will not. Thus, we must determine how people with diabetes and CLI can be appropriate triaged for primary amputation or revascularisation. This question remains unanswered by the current literature.

Defining what constitutes successful outcome in this patient cohort is worthy of consideration. Thirty-day survival, primary patency, secondary patency, limb salvage and survival are the variables most commonly described in vascular literature. Given their binary nature, these variables make for easily measurable endpoints. However, for patients, improved health-related quality of life is often more important (Fitzpatrick et al, 1992). As such clinical end points such as a reduction in the number of

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hospital admissions as a result of foot sepsis, a reduction in the requirement for analgesia or antibiotic therapy, ulcer healing and recurrence maybe more meaningful. Evaluating the efficacy of CLI interventions against these variables should be an aim of future investigations.

At present, there is limited randomised controlled trial evidence to support the use of infra-inguinal angioplasty in diabetic foot care. The absence of medium- and long-term outcome data for this intervention have been highlighted by NICE (2011), but endovascular therapy would appear to have clinical utility in this group. Continued industry investment and the further development of endovascular techniques and technology has resulted in a small number of studies reporting excellent limb salvage results. Acin et al's (2012) results support primary stenting of long femoro-popliteal segment stenoses, and Schmidt et al (2014) are exploring the utility of excimer laser atherectomy for long femoro-popliteal segment stent occlusions, with good early results. Fanelli et al (2012) suggest that drug eluting balloons that incorporate agents such as paclitaxel may reduce the rate of arterial restenosis following angioplasty, the therapeutic effects of which are being explored with positive early data (Liistro et al, 2013). The significant question relates to whether these outcomes can be replicated outwith trial settings (many of which have are industry sponsored). These innovations require to be explored with further independent, randomised, controlled trials.

It is difficult to assess the degree of bias in the present series. The "angioplasty first" approach means that angioplasty will be attempted in cases that would be deemed medically unfit for bypass or in whom there is no usable conduit. Whether these patients could have been managed surgically, and whether this would have influenced outcome, is unclear.

Conclusion

Data presented here suggest that infra-inguinal angioplasty is a low-risk intervention. Limb salvage at 2 years in those with without diabetes was found to be comparable to previously published trial data. Among those with diabetes, limb salvage rates following infra-inguinal angioplasty are poorer than for those without diabetes. This reflects the difficulties in defining CLI in people with diabetes and highlights the complexity of diabetic foot care.

Although it is as yet not fully defined, there is a role for infra-inguinal angioplasty in the management of CLI in people with diabetes. As such, it is important that radiologists are fully integrated members of the multidisciplinary diabetic foot care team. ■

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