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The Influence of Subintimal Angioplasty on Level of Amputation and Limb Salvage Rates in Lower Limb Critical Ischaemia: A 15-year Experience

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Objectives. *The aim of this study is to assess the influence of subintimal angioplasty (SIA) on lower limb amputation rate and level in critically ischaemic limbs.*
Methods. *Between January 1989 and March 2004, 1268 patients were admitted for treatment of lower limb critical ischaemia. Eight hundred and twenty-nine patients underwent revascularisation (bypass 671 and angioplasty 158), while 439 patients had primary amputations. A retrospective analysis of a prospectively maintained vascular registry was performed.*
Patients were divided into two groups, those who were admitted prior to the availability of subintimal angioplasty and those treated post-introduction of angioplasty. The two groups were compared with regards to age, sex, diabetes mellitus, ASA grade, Rutherford classification and level of disease. Outcome was assessed by the limb salvage rate, 30-day morbidity and mortality, and length of hospital stay.
Results. *The average number of revascularisation increased with the introduction of subintimal angioplasty, from 53 to 96 per year (p<0.001). The overall limb salvage rate increased significantly from 42 to 70% (p<0.001). The cumulative limb salvage rate following revascularisation rose from 72 to 86% (p<0.001). The level of amputation (AKA:BKA) did not vary significantly. Thirty-day morbidity, mortality and length of hospital stay were significantly lower in the post-angioplasty group.*
Conclusions. *Technical advances have resulted in a steadying of amputation numbers despite an ageing population.*

Keywords: Subintimal angioplasty; Critical limb ischaemia; Amputation; Limb salvage rate; Amputation level.

Introduction

Critical lower limb ischaemia is a major component of the workload of vascular units, and accounted for 86% of total amputations in our institution over the last 15 years, with 35% of patients with CLI being treated with primary amputation. The European consensus document on chronic critical leg ischaemia[1] estimated the incidence of CLI at 50–100 per 100,000 population per year, and this incidence is rising as the age of our population increases.

Options include conservative management, angioplasty, arterial bypass surgery, and amputation. The choice of management is dependant on a number of factors including clinical presentation (Rutherford classification),[2] TASC classification of lesion,[3] and patient fitness for surgery (ASA grade). The Joint Vascular Research Group of the UK found that 60% of patients were suitable for revascularisation, while a further 20% needed an amputation.[4] It is nearly 20 years since, this paper was published and these figures have changed considerably. Evidence has shown that appropriately performed revascularisation leads to high patency rates and significantly reduced amputation rates in specialised vascular and endovascular units.[5,6] The greater cost effectiveness of revascularisation compared to amputation and the fact that it offers a possibility for the patient to maintain independence in daily activities, further stimulates the increase in revascularisation.[7]

We have previously reported a prospective parallel group comparison that suggests subintimal angioplasty improves limb salvage.[8] In this study we aimed to examine our service as a whole, mindful of the fact that the West of Ireland has a higher old (>65 years)

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dependency ratio, at 22.6, than any other region in the country.[1] The aim of this study is to investigate the trends in CLI management in our centre over the last 15 years and to determine if the recent establishment of a specialized vascular and endovascular unit adequately services our aging population and has led to any change in referral pattern, patient numbers and disease presentation. Furthermore, we wished to investigate if the introduction of specialized techniques, in this case subintimal angioplasty, have led to any changes in limb salvage, amputation rate and level of amputation.

Materials and Methods

This is a population based epidemiological analysis, performed in the Western region of Ireland, to which University College Hospital Galway is a tertiary referral centre. Its catchment area is in excess of 750,000. UCHG had one consultant general surgeon with a specialist interest in vascular surgery since, 1987 and has an additional specialist vascular and endovascular consultant surgeon since, 2001. This appointment has led to a change in referral pattern. Patients with CLI, who were traditionally referred to specialized units outside our catchment area for evaluation and treatment, are now being managed within our institution.

Data recovery

Data was retrieved from our hospital inpatient enquiry (HIPE) department and VascuBase. Follow-up data was obtained from medical records and a phone survey of general practitioners.

Inclusion criteria

Only patients with limb threatening ischaemia, who had some form of intervention, were entered into the study. All patients had rest pain, ulcers, or gangrene caused by peripheral arterial occlusive disease (Rutherford categories 4–6)[2] with an ankle brachial index (ABI) of less than 0.5 or a reduced toe pressure ($<$30–50 mmHg).[3]

Amputation

Major amputation was defined as any amputation above the level of the ankle, i.e. below-knee amputation or above-knee amputation. Trans metatarsal amputation is seen as a minor amputation and known as leg-sparing surgery, which is now performed in preference to repeated ray amputations. Primary amputation was defined as amputation of the ischaemic limb without an antecedent attempt at revascularisation, and was considered in those cases in which the arterial disease was not amenable to reconstruction due to the progressive nature of the underlying atherosclerotic occlusive disease. In patients with no vessel run-off, combined with an ABI less than 0.2 with no digital pressures, vascular reconstruction was deemed impossible and these patients were considered best served by a primary amputation. Secondary amputation was a major amputation, performed on a patient who had some prior attempt at revascularisation, i.e. they were members of either the SIA or bypass groups.

Investigations

Historically, the need for amputation was determined by clinical examination of the leg by the general surgeon on call, occasionally assisted by angiography. ABIs were crudely performed by the surgeon, using hand held Doppler. If an amputation was deemed necessary the most distal level of amputation that will heal was clinically assessed immediately before surgery.

In recent years, modern imaging modalities, such as duplex ultrasound and occasionally MRA, have helped us demonstrate the complete absence of distal vessels by non-invasive means. In 2001 a fully dedicated vascular laboratory was opened in our institution. Since, the ready availability of duplex ultrasound, all patients have received pre-operative ABI measurement and duplex scan as triage for endovascular management, bypass surgery or primary amputation. Patients with heavily calcified crural vessels and patients with echolucent material in their iliac arteries underwent magnetic resonance angiography (MRA).

Subintimal or bypass?

Since 2001, SIA is used as first-line treatment in all suitable patients. The only indications for surgical bypass were the presence of an echolucent shadow in the femoral artery, as visualised on duplex scan, and the absence of a ‘nipple’.[8] Both findings render the lesion unsuitable for subintimal angioplasty. An echolucent shadow in the femoral artery indicates the presence of thrombus and the associated danger of distal embolisation or re-thrombosis.[8] The absence of a nipple (indicating a flush occlusion) makes it difficult to initiate the subintimal dissection plane.[8]

Lesions <5 cm (TASC A or B) are treated by intraluminal angioplasty, as recommended by the TASC working group and were not included in this study.[3] SIA was used for both femeropopliteal and iliac occlusions based on a definition of SIA as endovascular management of arterial occlusive lesions >5 cm in length (i.e. TASC C and D lesions).[3] All lesions treated post-SIA were either TASC C or D, as seen on intra-operative angiogram.

All SIA procedures were performed in theatre using the OEC mobile c-arm imaging system (GE, USA). All patients were brought to the operating theatre on an intention-to-treat basis. If more than one lesion was treated, the patient was assigned to a group as per the most proximal lesion treated.

Since 2001, 80% of the bypass procedures were performed by the dedicated vascular and endovascular surgeon, while the other 20% were divided between two general surgeons, one with vascular interests, and the other who referred his patients to the interventional radiology department for intervention. All of these patients are excluded from the study.

Pre-operative assessment

Since 2001, preoperative cardiorespiratory evaluation is performed on all patients and includes a careful clinical assessment, with all patients undergoing preoperative echocardiography and pulmonary function testing. While general or spinal anesthesia is used in bypass surgery, regional anesthesia with haemodynamic monitoring is used for SIA.

Adjuvant pharmacological treatment

All patients in the post-SIA group were treated with aspirin, pravastatin and cardioselective beta-blocker peri- and postoperatively. Post-operatively we add clopidogrel for 1 year. This 'magic bullet' aims to reduce cardiovascular morbidity and mortality, and failures due to thrombosis, myo-intimal hyperplasia, or further progression of atherosclerosis. We have previously shown that this treatment statistically improves the overall outcome of high-risk patients with peripheral vascular disease.[42]

Follow-up

Prior to 2001, patients were seen at 1 and 6 months post-discharge for clinical assessment and ABI measurement. However, this was not fixed and varied per patient. A surveillance programme was initiated in 2001, and the post-SIA group were seen at 6-weeks, 3 months, 6 months, 9 months and yearly thereafter. This programme allows for early detection and management of restenosis and consequently high assisted primary patency and secondary patency rates. It consists of ABI measurement and duplex scanning of the entire length of the graft, with calculation of peak systolic velocities and the velocity ratios across all identified lesions. A stenosis of between 50 and 75% on duplex scan, together with a drop in ABI of >0.15, in the presence of deterioration in clinical status, was taken as an indication for re-intervention.[3,8]

Treatment analysis

The patients were divided into two groups depending on whether they were treated prior to or post the availability of subintimal angioplasty (SIA) in 2001. The two groups were compared with respect to age, sex, ASA grade, Rutherford classification, level of disease and the presence of diabetes mellitus. Outcome was assessed by the limb salvage rate, 30-day morbidity and mortality, and length of hospital stay. As per HIPE records hospital stay included the total time spent for each hospital stay. This included time spent under other consultants during the same visit, prior to referral to the vascular team; time spent on pre-operative anaesthetic assessment and optimisation; time spent managing co-morbid conditions; and time spent awaiting placement in nursing homes and respite facilities.

Statistical analysis

Cumulative limb salvage rates were calculated separately for the pre- and post-SIA groups using actuarial life table projections. Cumulative limb salvage rates were calculated for the surgical bypass and SIA groups using the same method. If a patient had undergone more than one procedure, follow-up was started from the first procedure. Also if the patient underwent more than one major amputation, the first amputation was counted as the event.

Demographic differences were assessed with Pearson's chi-squared test for categorical variables and the *t*-test for continuous variables. Multivariate analysis was performed with a Cox proportional hazards model to determine the effect of patient demographics (i.e. age, sex, diabetes and other co-morbidities), disease presentation and treatment modality on

Table 1. Patient demographics

	Pre-SIA	Post-SIA
Number	938	330
M:F	64:26%	57:43%
Age	73	72
Diabetes mellitus	23%	21%
ASA grade III:IV	60:40%	58:42%

amputation-free survival rate. All p-values were considered significant at 0.05. Statistical analyses were performed with SPSS 12.0.1 for windows software.

Results

Over a 15 year, period from 1989 to 2004, 1268 patient were treated for critical limb ischaemia. Eight hundred twenty-nine patients (65%) underwent attempts at revascularisation. Six hundred seventy-one patients had peripheral bypass surgery and 158 had peripheral endovascular procedures. In the same period 439 patients had primary amputations. Only 19% of patients were lost to follow-up. Thirty-three percent (221 patients) of those who had bypass surgery went on to have a secondary amputation, while 5% (eight patients) of those who had subintimal angioplasty eventually lost their limb.

The patients were divided into two groups, depending on whether they presented prior to or since, the availability of SIA (Table 1). There was no statistical difference between the two groups with respect to age, sex, ASA grade or the presence of diabetes. The differences between the two groups in the presentation (Rutherford classification) and level of the disease did not reach statistical significance (Table 2).

Limb salvage rates

The limb salvage rate was steady and averaged at 42% prior to the introduction of SIA. The limb salvage rate (70%) increased dramatically in 2001 with the introduction of SIA (Fig. 1).

Table 2. Disease presentation

	Pre-SIA (%)	Post-SIA (%)
Rutherford classification		
6	36	31
5	17	16
4	47	53
Level of disease (principal lesion treated)		
Aorto-iliac	28	27
Femero-popliteal	71	66
Infra-popliteal	1	7

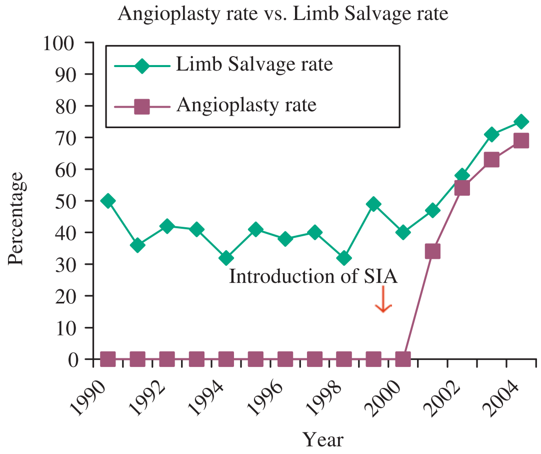

Fig. 1.

Cumulative limb salvage rates

The 1 and 3 year cumulative limb salvage rates following revascularisation are significantly higher in the post-SIA group (85.6%, SE 2.24%; 85.6% SE, 2.30%) when compared to the rates at the same time intervals in the pre-SIA (71.9%, SE 1.95%; 68.1%, SE 2.09%) (Fig. 2).

The cumulative limb salvage rate following SIA angioplasty is 97.8% (SE 1.10%) at 1 year and 97.2% (SE 1.26%) at 3 years. The corresponding rates, at 70.8% (SE 1.86%) and 67.7% (SE 1.97%), respectively, are substantially lower following bypass surgery (Figs. 3 and 4).

Study endpoints (Table 8)

The limb salvage rate has increased significantly since, the introduction of SIA ($p<0.0001$), but the level of amputation has not changed. Thirty-day morbidity and mortality were significantly lower in the post-SIA

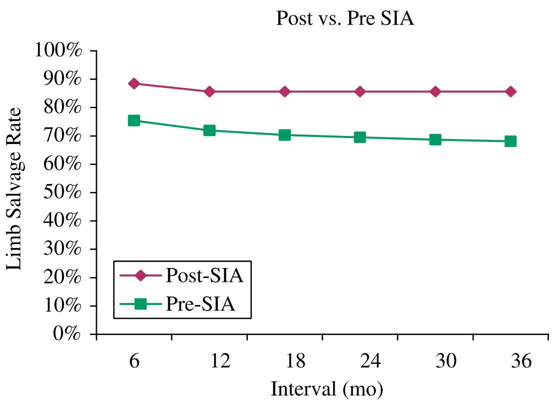

Fig. 2.

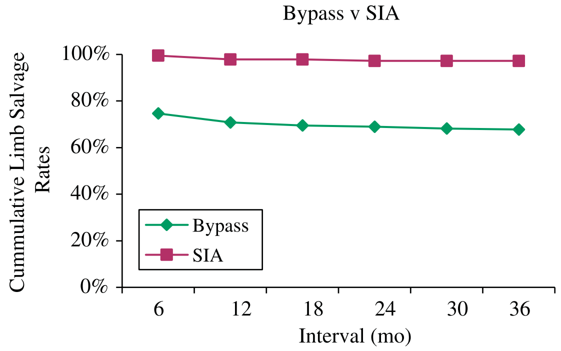

Fig. 3. Limb salvage rates for total bypass and SIA procedures.

group ($p<0.001$, $p=0.005$), as was the mean length of stay ($p<0.0001$).

Treatment analysis

The patients were also divided into groups depending on mode of treatment (Table 3). While there were more men in the primary amputation and bypass groups, there were significantly more women in the subintimal angioplasty group ($p<0.01$). The mean age of the bypass group was significantly lower than either of the other groups ($p<0.01$), and the proportion of octogenarians in the angioplasty group was significantly higher than in the bypass group ($p<0.01$). The ASA grade was similar among the groups ($p=0.17$). The clinical presentation of the disease was significantly worse in the primary amputation group ($p<0.001$) when compared to either of the other two groups and significantly worse in the SIA group when compared to the bypass group ($p=0.0012$). There were a significantly higher percentage of diabetics in the primary amputation group ($p<0.05$).

The mean length of hospital stay needed for the primary procedure was significantly lower in the SIA group when compared to either the bypass or primary amputation groups ($p<0.01$). This level of significance remains even when the mean total number days spent in hospital for all admissions is taken into account. The mean number of admissions per patient was the same for the SIA and bypass groups, but the average number of procedures per patient was significantly increased in the bypass group when compared to the SIA group ($p<0.0001$) (Table 4).

Thirty-day morbidity and 30-day mortality were significantly lower in the SIA group than in either of the other two groups ($p<0.001$ for both) (Table 5).

A significantly higher proportion of patients in the SIA group were fit to be discharged home than in either of the other two groups ($p<0.01$). More patients were discharged to a nursing home in the primary amputation group than in the other groups ($p<0.01$), while the number of patients who died before discharge was significantly lower in the SIA group than in either of the other two groups [$p<0.05$ (bypass); $p<0.01$ (primary amputation)] (Table 6).

Using multivariate analysis the factors that were shown to increase the overall risk of amputation were renal failure and diabetes (Table 9).

Table 3. Patient demographics according to mode of treatment

	Primary amputation	Bypass	SIA
Number	439	671	158
M:F	63:37%	67:33%	46:54%
Mean age	76	70	73
Octogenarians	41%	17%	35%
ASA grade III:IV	37:63%	40:60%	25:75%
Diabetes mellitus	32%	18%	16%

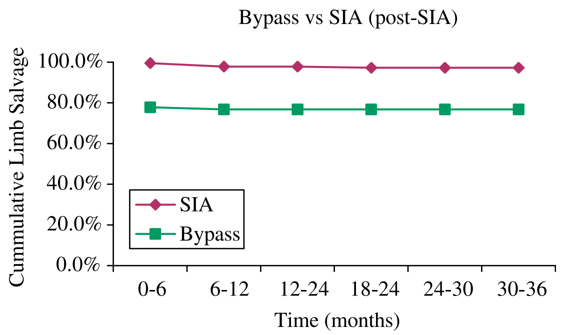

Fig. 4. Limb salvage rates for bypass and SIA procedures done after 2001.

Discussion

In view of the poor outcome associated with CLI, the European consensus document recommends revascularisation for the treatment of CLI if there is over 25% chance of patient survival and limb salvage for 1 year.[1]

Table 4. Comparison of length of stay between treatment modalities

	Primary amputation	Bypass	SIA
Mean length of stay for primary procedure (days)	49	36	17
Mean length of stay for all admissions	50	45	23
Mean no. of admissions	1	1.3	1.3
Mean no. of procedures	1	1.6	1.3

Table 5. 30-day morbidity and mortality

	Primary amputation (%)	Bypass surgery (%)	Subintimal angioplasty (%)
30-day mortality	19	12	4
30-day morbidity	49	32	19

However, it is impossible to accurately predict the longevity of any individual patient, and to date, there have been no prospective studies or clinical trials that have confirmed criteria that allow us to differentiate patients with CLI at high risk for early mortality, for whom revascularisation may be irrelevant, from those patients who are likely to survive a number of years and in whom aggressive attempts at limb salvage would be appropriate. On a population level, however, the efficacy of vascular surgery has been previously demonstrated[9–12] and it has been shown that an increase in vascular reconstructions correlates with an increase in limb salvage rates.[13–16] No study before this has examined the specific role of subintimal angioplasty on amputation trends in critical limb ischaemia.

Studies that have examined the association between revascularisation procedures and amputation rate, in an attempt to identify the population-based therapeutic effectiveness of revascularisation to treat CLI[17–22] have assumed that if revascularisation procedures avert the need for amputation in some patients, then a negative correlation should exist between rates of amputation and revascularisation procedures.[18] This is not necessarily the case and while many population-based studies have reported decreased rate of amputation in association with increased use of revascularisation procedures,[17,23,24] other studies showed no change in lower extremity amputation rate.[17,23–27] Al-Omran *et al*.[18] found in a retrospective population-based cohort study over an 8-year period, that the revascularisation rate remained stable, with a reduction in the use of bypass surgery and increased use of angioplasty. This is in contrast to our study, in which the number of attempted revascularisations has effectively doubled since, the introduction of subintimal angioplasty from an average of 53 per year (SE $\pm$2.27) to 96 per year (SE $\pm$13.69) ($p=0.0001$). This increase in the number of revascularisations has not resulted in a parallel rise in the number of secondary amputations. In fact the proportion of revascularisations ending with secondary amputations has significantly reduced ($p<0.01$). In addition the number of primary amputations has remained steady since, 1989, averaging at 32 per year (SE $\pm$ 2.172). The adoption of SIA, within a new, dedicated specialized vascular unit, has resulted in an increase in peripheral revascularisation, with an increased limb salvage rate but no decline in the number of lower-extremity amputations.

Table 6. Discharge details

	Primary amputation (%)	Bypass (%)	SIA (%)
Home	57	79	86
Nursing home	19	5	4
Other hospital	5	4	5
RIP	18	10	3
Other	1	2	2

Although the number of patients presenting has dramatically increased, no difference exists in the grade of disease being treated since, 2001 (Table 2), which is not surprising if one follows the strict criteria for definition of CLI.[3] The establishment of a specialized vascular unit, and the availability of new specialized techniques has led to a sudden and dramatic increase in the diagnosis of peripheral vascular disease, and expanded indications for procedural interventions. So, although the incidence of CLI within our catchment area has not suddenly and dramatically changed, the number of patients being referred to our service, who were traditionally referred outside our catchment area for evaluation and treatment, has substantially increased.

In general the ratio of below-knee (BK) to above-knee (AK) is near 1 and has not changed over the years, even with a rise in revascularisation rates.[3] The rationale for primary below-knee amputation assumes that patients will ambulate successfully with prosthesis. Studies on the rate of rehabilitation following lower limb amputation have shown that, while most above knee amputees are wheelchair bound or bed-ridden, and in need of full-time care, up to 80% of patients with below knee amputations can achieve full ambulation with the aid of prosthesis.[19] However, with a population that is aging, increasingly obese, and with extensive co-morbid conditions, ambulation for all patients with BK amputations may be impractical.[20] One review on the functional outcome in a contemporary series of major lower extremity amputations found that, in a population that is clinically and physiologically severely ill, a significant number of amputees are unable to regain bipedal gait despite aggressive rehabilitation.[21] But despite a low rate of postoperative ambulation, most patients remain living in the community.

Previous studies by our group have shown that SIA can achieve symptomatic patency rates of 95% and a reduction in length of hospital stay by minimally invasive means.[8] In this study, SIA was successfully used in a group in which over one third were octogenarians (Table 3). With a cumulative 1-year limb salvage rate of 97% and a mean length of hospital stay less than half that of other treatment modalities. The mean number of admissions was the same as the bypass group but the length of hospital stay for total admissions was significantly lower in the SIA group, as was the average number of procedures per patient and the 30-day mortality rate (Tables 7 and 8). Any of these alone or in combination add to an overall reduction in the cost per patient. One British study estimated the median costs of treating critical ischaemia to be 6611 pounds for angioplasty, 6766 pounds for bypass, and 10,162 pounds for primary amputation.[28] The authors concluded that, with the median cost of managing a patient following amputation almost twice that of successful limb salvage, an aggressive revascularisation policy was justified, and this conclusion has been echoed by our group and others (Table 4).[8,29,30]

The incidence of diabetes, especially type 2, in our population is increasing as our population ages.[31,32] Diabetes is known to be associated with increased calcification, multi-level disease and infrapopliteal lesions, as well as a mortality rate up to ten times higher than in non-diabetics.[28] However, it has been shown that diabetics can benefit from a bypass operation to the same degree as non-diabetics in terms of patency and limb salvage.[33] Although subintimal angioplasty has been shown to successfully achieve recanalization of long occluded arterial segments,[8,34,35] its specific role in diabetic patients has not been widely studied. We found that diabetics were more likely to have an amputation than non-diabetics ($p=0.029$), a finding reflected in previous studies.[36] However, in those patients deemed suitable for revascularisation, there was no statistical significant difference in the limb salvage rate between diabetic and non-diabetic patients. This is again in accordance with other studies.[34] However, diabetics were more likely to have an amputation after bypass surgery than after SIA ($p<0.05$). Our high limb salvage rate in diabetics following SIA is helped by a number of factors, including a strict protocol in diabetic patients of primary transmetatarsal amputation rather than repeated digital amputations. This is based on clinical experience and recognition of the biomechanical factors that are specific to diabetics,[37] such as plantar fascia abnormalities and increased vertical plantar pressures under the metatarsal heads of the forefoot, which lead to a more rigid foot.

Table 7. Comparison of length of stay pre- and post SIA

	Pre-SIA	Post-SIA
Mean length of stay for primary procedure (days)	43	22
Mean length of stay for all admissions (days)	49	27
Mean no. of admissions	1.2	1.2
Mean no. of procedures	1.8	2

Table 8. Primary endpoints

	Pre-SIA (%)	Post-SIA (%)
Limb salvage rate	42	70
AKA:BKA	40:60	60:40
30-day morbidity	38	21
30-day mortality	16	7

Our data showed an unequivocal shift in patients to our practice with CLI, characterized by increasing age, an increased proportion of women, and a higher prevalence of diabetes mellitus and renal disease. Using multivariate analysis, the co-morbid factors that had negative impact on limb salvage were diabetes ($p-0.029$) and renal insufficiency ($p=0.006$), factors well recognized by other authors.[33]

Although the literature is consistent regarding a lack of significant effect of diabetes and advanced age on revascularisation results, the question of gender-based differences in outcome remains controversial.[38,39] We found no significant association between gender, major adverse events or risk of amputation.[40] Women were on average older than their male counterparts (75 vs. 71 years, $p<0.0001$), but unlike previous studies there was no corresponding disimprovement in disease pattern.[41]

CLI has major implications for health costs and most vascular units workload, but our results show that despite a changing patient population with increased co-morbidity, more advanced ischemia, and a need for greater technical complexity, technical advances have resulted in a steadying of amputation numbers. SIA has broadened our indications for intervention but yet the need for primary amputation still exists, suggesting that patients undergoing vascular reconstruction and those undergoing primary

Table 9. Cox proportional hazards model: risk factors for major amputation

Risk factor	Risk ratio	95% confidence interval	p
Age > 80 years	1.294	0.921–1.820	0.138
Male gender	1.103	0.783–1.554	0.575
Heart disease	0.925	0.535–1.595	0.778
Diabetes mellitus	1.610	1.395–1.941	0.029*
Renal failure	2.253	1.257–4.039	0.006*
SIA	0.774	0.582–1.028	0.077

* Significant at $p<0.05$ level.

amputation may represent different population categories. The later category mostly consists of patients presenting too late, with tissue loss too extensive to enable limb salvage. Risk of amputation following revascularisation procedures is positively associated with type of procedure, and diabetic and renal status. SIA plays a major role in the initial management of CLI, because it is cost effective, minimally invasive, associated with a high limb salvage rate, and is preferred by patients.

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