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Analysis of the Elective Treatment Process for Critical Limb Ischaemia with Tissue Loss: Diabetic Patients Require Rapid Revascularisation

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WHAT PAPER ADDS

Delay in the treatment of critical limb ischaemia with tissue loss has rarely been investigated, even if the common conception is that these patients require treatment without delay. In this retrospective study, the whole treatment process from referral to revascularisation in all its diversity and complexity is presented. The impact of delay and how rapid revascularisation is essential for diabetic patients is demonstrated.

Objectives: The number of elderly people is increasing; inevitably, the result will be more patients with critical limb ischaemia (CLI) in the future. Tissue loss in CLI is related to a high risk of major amputation. The aim of this study was to analyze the treatment process from referral to revascularisation, to discover possible delays and reasons behind them, and to distinguish patients benefitting the most from early revascularisation.

Methods: A retrospective analysis was performed of 394 consecutive patients with a combined 447 affected limbs, referred to the outpatient clinic during 2010—2011 for tissue loss of suspected ischaemic origin.

Results: For 246 limbs revascularisation was scheduled. After changes in the initial treatment strategy, endovascular treatment (ET) was performed on 221 and open surgery (OS) on 45 limbs. Notably there was crossover after ET in 17.0% of the procedures, and re-revascularisations were required in 40.1% after ET and 31.1% after OS. The median time from referral to revascularisation was 43 days (range 1—657 days) with no significant difference between ET and OS. For 29 (11.8%) patients the ischaemic limb required an emergency operation scheduled at the first visit to the outpatient clinic. For 25 (10.2%) patients the situation worsened while waiting for elective revascularisation and an emergency procedure was performed. Diabetic patients formed the majority of the study population, with 159 diabetic feet undergoing revascularisation. In multivariate analysis, diabetes was associated with poor limb salvage. When revascularisation was achieved within 2 weeks, no difference was seen in limb salvage. However, when the delay from first visit to revascularisation exceeded 2 weeks, limb salvage was significantly poorer in diabetic patients.

Conclusions: Diabetic ulcers always require vascular evaluation, and when ischaemia is suspected the diagnostics should be organised rapidly to ensure revascularisation without delay, according to this study within 2 weeks from the first evaluation.

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INTRODUCTION

Ulcer formation in an ischaemic limb is a sign of critical limb ischaemia (CLI), the most severe form of peripheral artery disease (PAD). The prevalence of CLI and ischaemic ulcers is rising with the aging population and the growing number of diabetic patients. PAD is estimated to affect 9—24%[1—3] of diabetic patients during their lifetime, and analogously 8—25%[1,4] of diabetic patients are estimated to develop a foot ulcer.

Diabetic foot ulcers and their treatment trajectories have been widely investigated, but studies concerning delay in revascularisation are scarce.[5,6] The primary care centres play a vital role in the early detection of inadequate arterial blood supply in a diabetic foot,[7,8] which is crucial for patient prognosis.[9,10] Once PAD is suspected, a vascular surgeon is usually consulted and further investigations are conducted, upon which the revascularisation plan is then based. Specific target times for revascularisation are difficult to establish because of various referral patterns and very heterogeneous ulcers. The guideline for the timing of revascularisation according to previous studies can be encapsulated in the words: "the sooner, the better."

According to the Finnish guidelines, whenever a tissue lesion of suspected ischaemic origin is detected referral for

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vascular evaluation is made, thus commencing the treatment process at the vascular outpatient clinic in Helsinki University Hospital (HUH). The aim has been to organise the first visit within 1 week of the referral for all these patients, including all diabetic patients with an ulcer. After ankle brachial index (ABI) and toe pressure (TP) measurements in the vascular laboratory, vascular imaging, usually magnetic resonance angiography (MRA), is scheduled, after which the decision on treatment is made and revascularisation is scheduled. If ischaemia is detected, the presence of an ulcer is considered to be a sign of CLI and therefore revascularisation is scheduled within 2 weeks from the decision.

This retrospective study was launched in order to determine the success of elective treatment of ischaemic ulcers and to determine guidelines for the treatment process. The main focus was on wound healing, the number of emergency procedures while waiting for an elective procedure, and major amputations and deaths during follow-up. Owing to the growing incidence of diabetes, there was also focus on the treatment trajectories of diabetic foot ulcers.

MATERIALS AND METHODS

The study population for this retrospective study was collected from the 2187 consecutive patients visiting the senior vascular consultant's outpatient clinic between January 1 2010 and December 31 2011 (Fig. 1). The inclusion criterion was a foot ulcer of suspected ischaemic origin including all diabetic ulcers. The ABI was documented and toe pressure (TP) measurements were taken at the first evaluation, but no threshold values were set for inclusion in the study. In addition to the patients assigned for revascularisation, the patients assigned for conservative treatment were included, to gain a comprehensive perspective on the entire elective treatment process.

The whole treatment process was analysed starting from referral, with follow-up continuing until the end of 2013. The time spent on each step of the treatment process from referral to revascularisation was investigated. Cancellations of the intended treatment, and the number as well as the reasons for urgent diagnostics and treatments while waiting for elective treatment were noted. The outcome of the treatment process was analysed separately for endovascular treatment (ET), open surgery (OS), and for patients not receiving revascularisation. Wound healing was analysed during follow-up and healing was regarded as achieved when the wound had healed completely or was so close to being healed that no further follow-up was considered necessary. Limb salvage (LS) and amputation free survival (AFS) were assessed by intention-to-treat (ITT) analysis on the basis of the originally assigned treatment and per treatment (PT) analysis according to the final revascularisation, that is the one that was considered to be the first successful one. For example, when OS was performed after failed ET, the limb belonged to the OS group in the PT analysis, but if a bypass graft undergoing surveillance required ET due to stenosis or occlusion, the limb remained in the OS group. The main focus in this study was the diabetic foot; therefore, their treatment process and outcome during follow-up were analysed separately.

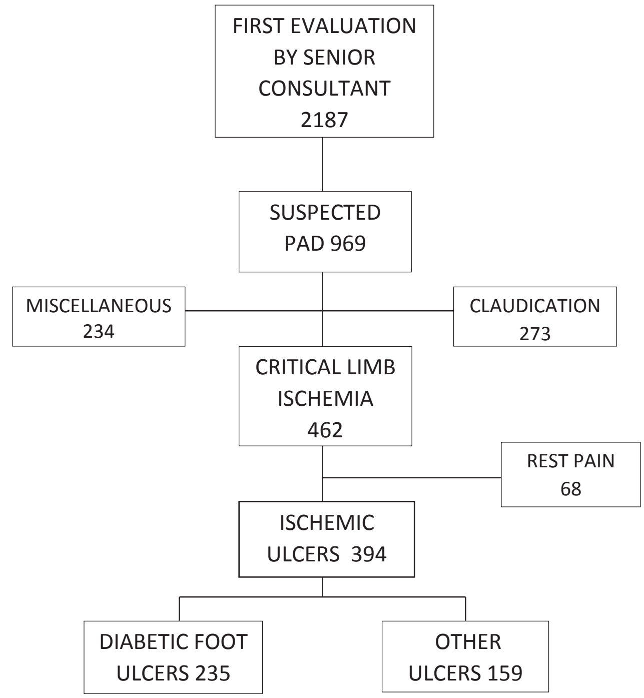

Figure 1. The patients visiting senior consultant at Helsinki University Hospital vascular outpatient clinic in 2010–2011.

The demographic characteristics are expressed as percentages, and the delays in the treatment process as median days with interquartile ranges (IQR). LS and AFS were assessed using the Kaplan–Meier method. To assess the independent risk factors for major amputation, univariate analysis was performed followed by the Cox proportional hazards model consisting of the factors reaching $p < .2$ in the univariate analysis. Using univariate analysis, all the comorbidities, wound location, and delay to treatment were tested. Multivariate analysis was performed for the overall series and separately for diabetic and non-diabetic patients. Statistical analysis was performed with the SPSS 19.0. statistical software (IBM SPSS Inc., Chicago, IL, USA).

RESULTS

Of the 969 first evaluations for suspected PAD at the senior consultant outpatient clinic during 2010–2011, 394 patients with a total of 449 affected limbs had ulcers. The typical patient in the study population lived at home, needed walking assistance, had hypertension and diabetes, and was on either antithrombotic or anticoagulant medication (Table 1). The suspected ischaemic ulcer had normally existed for more than 1 month, was located in the forefoot, and there had been no previous revascularisations (Table 2).

Treatment strategies

Revascularisation was scheduled for 233 patients with a total of 248 affected limbs. The initial treatment strategy, which was ET for 201 and OS for 47 limbs, changed for

Table 1. The characteristics of the 394 patients.

	All (n = 394)	Diabetics (n = 242)	Non-diabetics (n = 152)	p
Age (years)	77.23	75.49	79.98	.001
Male (%)	52.0	58.3	42.1	.002
Living conditions (%)				
Home	77.9	83.5	69.1	<.001
Assisted living	11.9	8.3	17.8	.005
Institution	10.4	8.3	13.2	.079
Mobility (%)				
Unassisted	28.1	29.3	26.3	.023
Cane/walking aid	47.4	48.8	46.1	.515
Wheelchair	18.8	18.6	19.1	.905
Bedridden	5.5	3.3	8.6	.013
Comorbidities (%)				
Hypertension	74.1	82.6	60.5	<.001
Coronary disease	42.1	47.5	32.9	.004
Lung disease	22.1	21.1	23.7	.055
Diabetes I and II	4.8 and 56.6	7.9 and 92.1	.0	
Renal insufficiency	29.7	38.8	15.1	<.001
Rheumatoid disease	12.9	9.1	18.4	.007
Dementia	19.7	16.1	24.3	.044
Antithrombotic medication (%)				
Aspirin	56.1	59.1	51.3	.208
Warfarin	24.6	27.3	20.4	.215
Clopidogrel	5.6	6.6	3.9	.586
Statin medication (%)	41.9	50.4	28.3	<.001
Smoking status (%)				
Smoker	24.9	21.9	29.6	.085
Ex-smoker >5 years	20.8	24,4	14.5	.018
Non-smoker	20.6	23.6	16.4	.091
Not known	33.8	30.2	39.5	.057

17.7% (n = 44) limbs during the treatment process resulting in 223 endovascular and 44 open procedures, as illustrated in Fig. 2. After the first endovascular treatment, 40.0% (n = 89) required additional revascularisations at the same lesion site: 17.0% (n = 38) underwent OS because of once or twice failed ET, and 26.5% (n = 59) underwent one to nine (median 1) additional endovascular procedures during follow-up because of failed or only partly successful ET. After OS, 19.5% (n = 16) received additional ET during surveillance because of graft (n = 15) and outflow stenosis (n = 1), and 15.9% (n = 7) patients underwent re-operation: one additional bypass after femoral endarterectomy, three thrombectomies, and three bypasses because of graft occlusion.

A decision on treatment was not reached for six patients: three of them died within 3 weeks of the first visit and three did not attend either the scheduled imaging or the follow-up for reasons unknown. For 195 patients no revascularisation was planned, most commonly because of anticipated spontaneous healing (n = 95), after minor amputation (n = 21), or wound revision (n = 4) (Table 3).

Delay

The median time from referral to revascularisation for the whole study population was 45 (IQR 27—62) days. The delay from referral to revascularisation was 44 (3—664) days for ET alone and 51 (4—455) days for OS alone. For patients undergoing OS after failed ET, the delay was 69 (19—780) days ($p < .04$). The structure of the treatment process and the delay at each step is presented in Fig. 3. There were 54 (20.3%) urgent procedures, most of which (n = 29) were scheduled at the first outpatient clinic visit. The remaining 25 patients arrived at the emergency room because of a worsened condition while waiting for elective treatment. The reasons for urgent procedures were infection (n = 24), gangrene (n = 18), and increased pain (n = 12). Of the 24 patients with wound infection, eight had elevated C-reactive protein above 100 mg/L and one had a septic infection with fever.

Limb salvage and amputation free survival

The 1 year LS for the different treatment strategies were according to ITT analysis 81.6% (n = 164) for ET, 89.4% (n = 42) for OS, and 85.6% (n = 167) for conservative treatment (p = .201), and according to PT analysis 81.1% (n = 150) for ET, 92.7% (n = 76) for OS, and 83.5% (n = 147) for conservative treatment (p = .015). The 1 year AFS according to ITT analysis was 57.2% (n = 115) for ET, 55.3% (n = 26) for OS, and 59.5% (n = 116) for conservative treatment (p = .348), and according to PT analysis 57.3% (n = 106) for ET, 63.4% (n = 52) for OS, and 59.7% (n = 105) for conservative treatment.

The overall LS across the whole follow-up period, in a median of 25.9 (0.1—49.2) months, was, according to ITT analysis, 77.1% (n = 155) for ET, 89.4% (n = 42) for OS, and

Table 2. Characteristics of the 449 affected limbs.

	All (n = 449)	Diabetic feet (n = 273)	Non-diabetic feet (n = 176)	p
Amputation status (%)				
Minor amputation[a]	10.5	13.2	6.3	.019
Major amputation[b]	3.8	5.1	1.7	.064
Previous revascularisation (%)				
Angioplasty/stenting	8.9	10.6	6.3	.112
Bypass/Femoral endarterectomy	7.3	8.4	5.8	.277
Wound status (%)				
Ulcer	82.9	79.9	87.5	.036
Gangrene	15.6	18.3	11.4	.047
Already healed	1.6	1.8	1.1	.561
Wound location (%)				
Forefoot	55.9	59.3	50.0	.052
Heel	15.8	16.8	14.2	.453
Leg	20.0	16.2	26.1	.010
Forefoot + heel	4.5	4.4	4.5	.940
Forefoot + leg	2.7	1.8	4.0	.169
Heel + leg	1.1	1.5	.6	.377
Forefoot, heel + leg	0.2	0.0	.6	.212
Wound duration (%)				
<1 month	25.2	27.8	21.0	.104
2 months	23.2	24.2	21.6	.526
3 months	10.7	11.0	10.2	.241
>3 months	26.5	24.5	29.5	.799
Not known	14.5	12.5	17.6	.129
Vascular laboratory[c]				
Ankle brachial index	0.85	0.95	0.65	.009
Toe pressure	36	41	31	<.001

[a] Ipsi-, contra-, or bilateral.
[b] Contralateral above the ankle amputation.
[c] Median values.

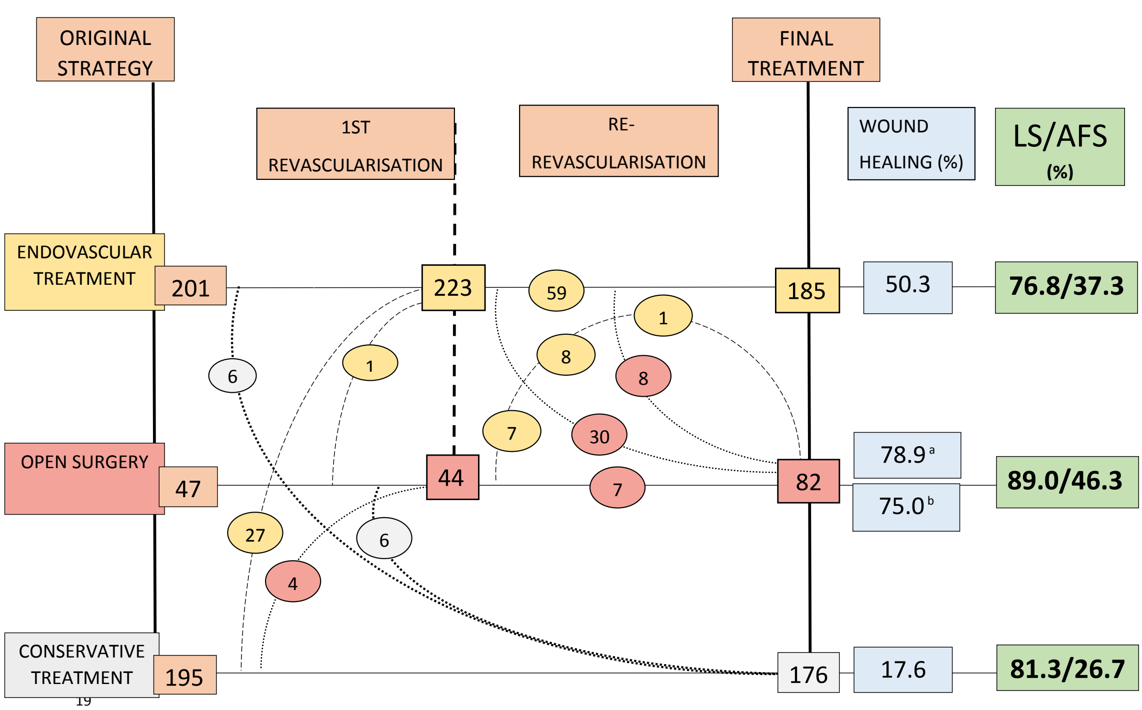

Figure 2. Outcome of the different treatment strategies. Overall limb salvage (LS) and amputation free survival (AFS) after the final treatment. [a] Wound healing for patients undergoing secondary open surgery. [b] Wound healing for patients undergoing primary open surgery.

Table 3. The reasons for no revascularisation for 195 limbs, and their outcome.

	All ($n = 195$)	DM ($n = 120$)	Non DM ($n = 75$)	p
Reasons (%)				
Wound likely to heal…				
spontaneously	48.7	59.2	32.0	<.001
after minor amputation/revision	12.8	11.7	14.7	.477
Major amputation needed	6.2	7.5	4.0	.322
Poor overall condition	26.2	13.3	46.7	<.001
Revascularisation not considered possible	5.1	6.7	2.7	.218
Patient refuses treatment	1.0	1.7	0	.261
Outcome (%)				
Later revascularisation	15.9	17.5	13.3	.439
Major amputation	17.4	17.5	17.3	.976
Death	64.1	60.0	70.7	.131
Amputation free survival	29.7	34.2	22.7	.962

73.3% ($n = 143$) for conservative treatment. According to PT analysis, LS was 76.8% for ET, 89.0% for OS ($p = .020$), and 81.3% ($n = 143$) for conservative treatment. The overall AFS according to ITT analysis was 38.8% ($n = 78$) for ET and 38.3% ($n = 18$) for OS, and according to PT analysis 37.3% ($n = 69$) for ET and 46.3% ($n = 38$) for OS (Fig. 2). No statistically significant difference was found in overall AFS between patients undergoing OS first and patients undergoing OS after failed ET (45.5% vs. 47.4%, $p =$ NS), but LS was better in the OS-first group (95.5%) than in those receiving OS after failed ET (81.6%) ($p = .045$). Also, no significant difference was found for patients undergoing emergency revascularisation (LS 79.2%, AFS 37.7%) compared with those who underwent elective surgery (LS 80.0%, AFS 40.4%).

After univariate analysis the following factors were included in the multivariate analysis: diabetes, coronary disease, wound location, dementia, and delay from the referral to the intervention (<2 weeks, ≥2 weeks). Independent risk factors for major amputation in the overall series were diabetes (OR 2.8, 95% CI 1.3—5.8), dementia (OR 2.5, 95% CI 1.22—5.22), and a wound located in the heel (OR 1.3, 95% CI 1.1—1.5).

Wound healing

Of the revascularised limbs, 81.6% ($n = 218$) underwent surveillance for wound healing whereas 27.3% ($n = 48$) of the conservatively treated limbs were followed in the vascular department. Wound healing was achieved in a median of 68 (0—1148) days. After revascularisation, wound healing was achieved in 60.7% ($n = 162$) of the limbs. Wound healing was more likely after OS (76.8%) than after ET (50.8%) ($p < .001$). The wound healing rate was the same in patients undergoing OS as the first line treatment as in patients receiving OS after failed ET (NS).

Diabetic foot

Diabetic patients formed the majority of this patient population ($n = 235$, 67.3%), and of the 273 affected diabetic feet 159 (58.2%) underwent revascularisation. Patients with diabetes had more hypertension and coronary disease but

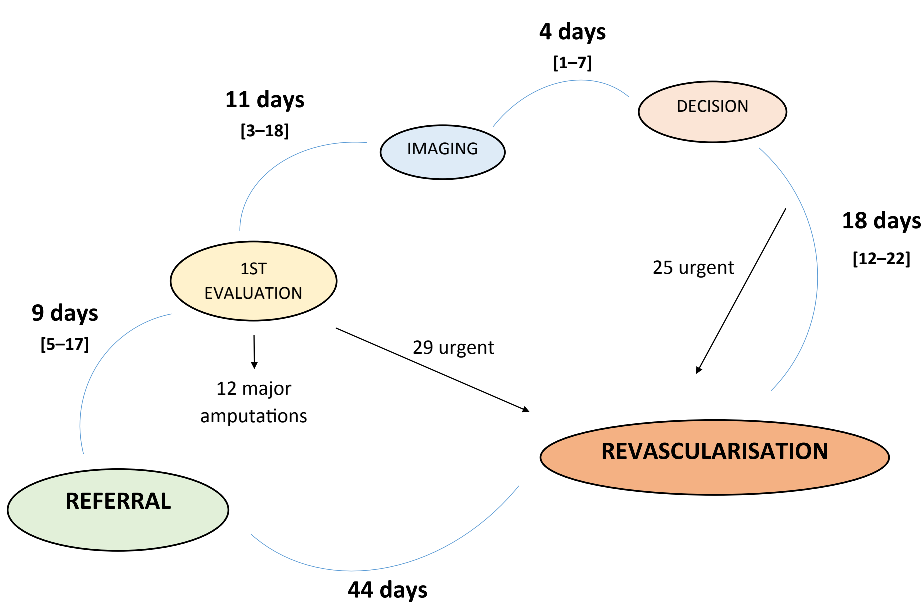

Figure 3. Delay on each step of the treatment process presented in median days with interquartile ranges.

were more often ambulatory and living at home than non-diabetic patients (Table 1). The primary treatment was ET in 85.5% ($n = 136$) of the diabetic feet and OS in 14.5% ($n = 23$). An additional 28 OS procedures after failed ET took place resulting in 67.9% ($n = 108$) diabetic feet undergoing ET and 32.1% ($n = 51$) OS.

Of the diabetic patients undergoing revascularisation, 84.3% ($n = 134$) participated in follow-up, and wound healing was achieved in a median of 78 (16—877) days for a total of 61.6% ($n = 98$) limbs, in 53.7% ($n = 58$) feet after ET, and in 78.4% ($n = 40$) after OS ($p = 0.003$). There was no significant difference in wound healing compared with non-diabetic patients (51.9%) after revascularisation ($p = .1$). The wound healing rate for those treated conservatively was 19.8% ($n = 21$).

In patients with diabetes, the median delay from referral to revascularisation (45 [IQR 29—66] days) and the median follow-up (25.9 months [22—146 days]) were similar to those without diabetes. In multivariate analysis diabetes was associated with inferior leg salvage ($p = .02$), but no difference was seen in overall survival ($p = .1$). When revascularisation was performed within 2 weeks, there was no difference in leg salvage between patients with and without diabetes with 100% versus 92.9% at 30 days and 86.5% versus 85.1% at 12 months respectively. When the delay from referral to revascularisation exceeded 2 weeks, leg salvage was significantly poorer in patients with diabetes ($p < .001$) (Fig. 4). When the multivariate analysis was performed separately for diabetic and non-diabetic patients, a delay of more than 2 weeks from the referral to revascularisation appeared to be an independent predictor for major amputation in diabetic patients (OR 3.1, 95% CI 1.4—6.9), but not in non-diabetic patients.

DISCUSSION

The treatment process of ischaemic ulcers can be described as very complex even though the goal is very simple: adequate blood flow to the ischaemic wound area should be restored. Ideally, the patient undergoes timely revascularisation, the wound heals completely, and amputation is avoided. In this study, delaying revascularisation past 2 weeks meant greater limb loss for diabetic than for non-diabetic patients, a notable finding on a subject rarely investigated.[6] No significant difference was found in overall LS or AFS after revascularisation between patients with and without diabetes. The overall wound healing rate and time were also similar during follow-up and wound healing was significantly worse after ET for both groups ($p < .001$).

This study has some major limitations, the most important one being its retrospective nature. Categorising the ulcers and their progression rates retrospectively is extremely difficult, which is why all types of tissue loss have been included in the study. They were divided into ulcers and gangrene, but this division still does not describe the healing potential sufficiently, as superficial gangrene can heal spontaneously, and, on the other hand, an extensive ulcer might call for immediate amputation. Also, the data on wound healing are inevitably crude regarding healing times, since after the check at approximately 1 month, the follow-up visits were assigned individually, and the data were not available at all for many, especially for the patients treated conservatively. The extent of the arterial disease was disregarded in the analysis, which might also weaken the reliability of the wound healing results, but does not affect the treatment delays, for revascularisation is scheduled according to the clinical condition rather than the arterial lesion.

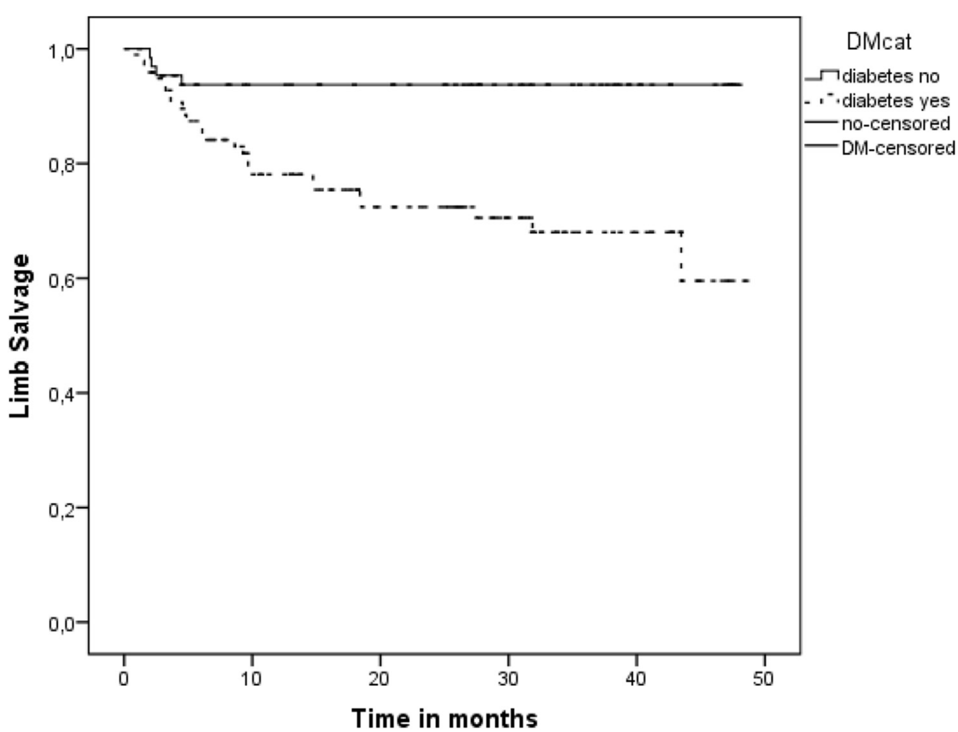

Figure 4. Limb salvage for diabetic patients and for patients with no diabetes after a delay >2 weeks from referral to revascularisation.

Including all the patients with tissue loss visiting the outpatient clinic resulted in a very heterogeneous study population with varying treatment patterns and times. This diversity may influence the results, but it also provides a comprehensive and a realistic perspective on the treatment process.

For revascularisation to take place, ischaemia needs to be detected first. Diabetic ulcers are often detected late because of neuropathy.[11] When analyzing the treatment process, the delay occurring before the referral either due to the referring physician or for patient related reasons should always be taken into account. In this study, 12 patients were considered to need a major amputation at the first visit to the vascular outpatient clinic, and 29 patients needed urgent revascularisation (Fig. 3). These patients reflect the delay occurring prior to referral. On the other hand, at first assessment a wound may appear non-ischaemic and ABI measurements may also be misleading,[12,13] so the wound's potential to heal can be overestimated. In this series, 15.9% ($n = 31$) of the feet first assigned to conservative treatment eventually required revascularisation because of poor healing or a deterioration of the tissue lesion. To further evaluate the healing potential, transcutaneous oxygen pressure measurement has been shown to be effective especially among diabetic patients,[14] a method also routinely used in Helsinki when wound healing seems uncertain.

The overall delay from referral to revascularisation of 45 (IQR 27—62) days can be considered prolonged even if the individual steps in the process were not that long (Fig. 3). The 25 (9.4%) urgent procedures reflect a delay in the treatment process: while waiting for revascularisation, the patient visits the emergency room due to a worsened ulcer situation. This has also been noticed in everyday practice; the number of patients with PAD visiting the emergency room has risen in the recent years from 502 patients in 2010 to 699 in 2014.

When deciding on revascularisation, the first decision is often not the final one. The possibility of changing the initial plan is what makes vascular surgery versatile and interesting, but it also makes the evaluation of the treatment processes very challenging. A considerable amount of crossover from ET to OS, 17.0% ($n = 38$) occurred during the study period, almost doubling the number ($n = 82$) of open procedures. The treatment philosophy is for the majority of the patients to have "endo first," even though OS has been and is still today highly regarded in this clinic. In addition, 15.9% ($n = 31$) of the patients primarily treated conservatively were later assigned to revascularisation. Reoperations and additional treatments are also typical in vascular surgery, in this study 38.6% ($n = 103$) underwent at least one re-revascularisation, more commonly after ET than after OS with 40.0% ($n = 89$) versus 31.8% ($n = 14$) of the cases respectively (Fig. 2).

The "endo first" philosophy has been shown to be effective in previous studies from this institution[15,16] and is also established elsewhere[17]; it now gains some further confirmation since there was no significant difference in the wound healing or AFS between patients who underwent OS after failed ET and those undergoing OS as the first line treatment. However, LS was inferior among these patients undergoing OS as a second or third revascularisation as was the LS in patients undergoing solely ET, results both possibly affected by the longer delay from referral to successful revascularisation. Nevertheless it would seem that instead of "endo first," some patients would have benefitted from an "open only" approach.

Another probable underlying factor for the inferior LS after ET is that when faced with the threat of major amputation, the tendency is to optimistically perform ET even when succeeding in revascularisation by any method seems highly unlikely. The approach to treatment is also well illustrated by the patient who underwent the most, a total of 12, revascularisations, starting with two endovascular treatments, then bypass surgery followed by seven more ETs and two graft interpositions. The perseverance was rewarded, for at the final follow-up the graft was patent and the wound had healed 305 days later.

At the end of follow-up, the AFS was also inferior after ET (37.3% vs. 46.3%), but with no statistical significance and overall, as low as was expected based on previous publications.[18,19]

In all, 59.2% ($n = 266$) of the limbs were followed for wound healing, but only 26.0% of the patients treated conservatively attended the surveillance. Needless to say, their wound healing remains unclear and little emphasis can be placed on the low percentage (17.6%) of healing achieved, especially when wound healing for those who attended the surveillance was 64.6% ($n = 31$) and 73.4% died during the follow-up. On the other hand, 81.6% of the revascularised limbs were surveyed, yielding fairly reliable information on their wound healing, which was significantly better after OS than ET.

CONCLUSIONS

According to this retrospective study, wound healing was significantly better after OS than after ET in the overall study population and in patients with diabetes. Diabetic patients achieved wound healing rates and times equal to patients with no diabetes. However, diabetes was associated with inferior leg salvage if the delay before revascularisation exceeded 2 weeks; therefore, timely revascularisation is crucial, especially in diabetic patients.

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