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Long Term Survival and Limb Salvage in Patients With Non-Revascularisable Chronic Limb Threatening Ischaemia

Maarten C. Verwer [a], Joep G.J. Wijnand [a], Martin Teraa [a], Marianne C. Verhaar [b], Gert J. de Borst [a,*]

[a] Department of Vascular Surgery, University Medical Centre Utrecht, Utrecht, The Netherlands
[b] Department of Nephrology & Hypertension, University Medical Centre Utrecht, Utrecht, The Netherlands

WHAT THIS PAPER ADDS

Despite technological advances in the treatment of chronic limb threatening ischaemia (CLTI), a proportion of CLTI patients have no viable options for revascularisation. Current evidence on major clinical outcomes in this population is limited to one year mortality and amputation rates. Five year survival and amputation free survival were investigated in this unique and large randomised cohort of non-revascularisable CLTI patients ($n = 150$), and it was found that slightly fewer than half survived with preservation of the limb. The findings could benefit vascular specialists in terms of medical management and patient guidance when no viable vascular intervention can be performed.

Objective: The aim of this study was to provide long term survival and limb salvage rates for patients with non-revascularisable (NR) chronic limb threatening ischaemia (CLTI).

Methods: This was a retrospective review of prospectively collected data, derived from a randomised controlled trial (JUVENTAS) investigating the use of a regenerative cell therapy. Survival and limb salvage of the index limb in CLTI patients without viable options for revascularisation at inclusion were analysed retrospectively. The primary outcome was amputation free survival, a composite of survival and limb salvage, at five years after inclusion in the original trial.

Results: In 150 patients with NR-CLTI, amputation free survival was 43% five years after inclusion. This outcome was driven by an equal rate of all cause mortality (35%) and amputation (33%). Amputation occurred predominantly in the first year. Furthermore, 33% of those with amputation subsequently died within the investigated period, with a median interval of 291 days.

Conclusion: Five years after the initial need for revascularisation, about half of the CLTI patients who were deemed non-revascularisable survived with salvage of the index limb. Although the prospects for these high risk patients are still poor, under optimal medical care, amputation free survival seems comparable with that of revascularisable CLTI patients, while the major amputation rate within one year, especially among NR-CLTI patients with ischaemic tissue loss, is very high.

Keywords: Amputation free survival, Chronic limb-threatening ischaemia, Natural history, Non-revascularisable
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INTRODUCTION

Despite medical and technological treatment advances, patients with peripheral artery disease (PAD) still have a high morbidity and mortality risk compared with the general population.[1] This is particularly true for patients with chronic limb threatening ischaemia (CLTI), with reported five year all cause and cardiovascular mortality rates twice as high (57% and 29%) compared with patients with intermittent claudication (IC) (31% and 15%), respectively, according to a Dutch national registry study.[1] Furthermore, the amputation rate in CLTI patients of 15% — 20% at one year reflects a large impact on quality of life and healthcare costs.[2]

Alarmingly, the prevalence of PAD will probably grow as populations are ageing and prevalence of risk factors for PAD, such as diabetes mellitus (DM), increase. Between 2017 and 2045 the prevalence of DM is expected to rise from 451 to 693 million people worldwide.[3] Already, up to 30% of all patients with IC and 50% of all patients with CLTI are diagnosed with DM, which co-prevalence is associated with lower revascularisation success rates, decreased wound healing, and higher amputation and mortality rates compared with those without diabetes.[4—8] The increasing

* Corresponding author. University Medical Centre Utrecht, Heidelberglaan 100, HP G.04.232, 3584, CX Utrecht, The Netherlands.
E-mail address: G.J.deBorst-2@umcutrecht.nl (Gert J. de Borst).

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prevalence of patients with DM is expected to lead to a parallel increase in the number of patients with non-revascularisable or so called "no option" PAD, and specifically no option or non-revascularisable CLTI (NR-CLTI).

Although the clinical prognosis of NR-CLTI patients has been reported, the evidence is limited to one year mortality and amputation rates in non-consecutive case series and randomised controlled trials that report these outcomes as an ancillary result. Available data combined in a meta-analysis investigating the natural history of NR-CLTI, reported a one year mortality and amputation rate of 22%.[9] Within this analysis, consisting of 11 studies, only two studies reported a follow up exceeding two years but both were published more than 30 years ago (study periods were 1979—1986 and 1971—1983, respectively).[10,11] Hence, the current long term prognosis of CLTI patients without revascularisation options remains unclear, while knowledge about the contemporary prognosis in this specific population is valuable for numerous of reasons, for example counselling patients and family, substantiating treatment decisions (not limited to PAD alone, as these patients often have multiple morbidities), the timing of palliative care, and optimal selection of patients for future (regenerative therapy) trials.

The aim of this study was to provide long term survival and limb salvage rates for NR-CLTI patients. Five year survival and amputation free survival were investigated in "no option CLTI patients" who participated in a randomised controlled trial (RCT).

METHODS

The details of the JUVENTAS trial design were published previously.[12] In short, in this single centre, double blind, placebo controlled RCT, the clinical effects of repetitive infusion of bone marrow mononuclear cells into the common femoral artery were investigated in 160 patients. Notable inclusion criteria were the ineligibility for surgical or endovascular revascularisation (thus deemed non-revascularisable [NR]), as defined by a multidisciplinary team of vascular surgeons and radiologists in the University Medical Centre of Utrecht, and severe PAD consisting of severe IC, persistent recurring rest pain or non-healing ulcers present for more than four weeks. Noteworthy exclusion criteria were a history of malignancy within the 10 years prior to inclusion and a life expectancy of less than one year.

The primary outcome of the initial study was major amputation of the index limb within six months after randomisation. All cause mortality was a secondary outcome. Inclusion was conducted between 2006 and 2012. No effect of the trial intervention was observed.[13]

For the current study, only the NR-CLTI population included in the JUVENTAS trial was analysed. For baseline, the original information was used, without any new retrospectively reconstructed data (such as the Society for Vascular Surgery Wound, Ischaemia, and foot Infection [WIfI] classification).[14] But in addition to the original protocol, information about major amputation and all cause mortality was successfully requested from the general practitioners, more than five years after inclusion ($n = 158$). The patient and the referring hospital were contacted when the follow up was unknown by the general practitioner ($n = 2$). The leg on which a patient was included in the original trial was defined as the index limb. Major amputation was defined as amputation through or above the ankle joint. The primary outcome of this study was ipsilateral amputation free survival (AFS), the inverse composite of ipsilateral major amputation and all cause mortality. The study was conducted according to the Declaration of Helsinki, the medical ethics board in the participating hospital approved the study, and all patients provided written informed consent.

Statistical analyses

Baseline characteristics, such as risk factors, medication use, wound characteristics, and the ankle brachial index (ABI), stratified for AFS, are provided. Categorical variables were reported as numbers with percentages, non-normally distributed data were reported as median with interquartile ranges (IQR) and normally distributed results were given as mean with standard deviation (SD). Normality of data was analysed using the Shapiro-Wilk test. Continuous variables were analysed using Student *t* test or Mann—Whitney *U* test as appropriate. Categorical variables were analysed using Fisher's exact test.

Additional analyses were performed to evaluate contributing factors for lower limb amputation and all cause mortality. Scaling (*z* transformation) was performed after log10 transformation of non-normally distributed continuous variables. Univariable Cox proportional hazard regression was performed on a selection of risk factors with a plausible relationship to the outcome. Multivariable analysis was performed including predictors with a p value $< .10$ in univariable analyses using a forward stepwise approach. The proportional hazard assumption was verified by examining the Schoenfeld residuals.

The statistical analyses were performed using SPSS for Windows version 25.0 (SPSS Inc., Chicago, IL, USA) and R version 4.0.0 (R Core Team, Auckland, New Zealand).

RESULTS

Patient characteristics

Of the original 160 included patients, eight patients had severe IC (Rutherford stage 3) and were excluded from analyses (none underwent amputation or died within five years). Of the remaining 152 CLTI patients, two were lost to follow up in an early phase. Hence five year follow up data were available for 150 patients, including 102 males (68%), with a median age of 67 (IQR 56, 76) years, of whom 56 (37%) patients had DM. At time of inclusion, 51 patients had rest pain (Rutherford stage 4), 90 patients had ischaemic ulceration not exceeding the digits of the foot

(Rutherford stage 5) while nine patients had severe ischaemic ulcers or gangrene (Rutherford stage 6).

Outcomes

After five years, 64 of the 150 patients (43%) survived without major amputation of the index limb. Of the other 86 patients, 53 (35% of total) died and 49 (33% of total) underwent a major amputation. In 16 patients, amputation was performed prior to their death within the five year interval. The median time between amputation and death was 291 days (IQR 35, 583).

The Kaplan—Meier curves for AFS, amputation, and death, are shown in Fig. 1. As seen, all cause mortality is evenly distributed along the five year interval while amputation occurs predominantly within the first year. The one year AFS was 70% (95% CI 63 — 78), attributed to 24% (95% CI 17 — 31) major amputation and 11% (95% CI 6 — 16) mortality.

Determinants of outcomes

Table 1 summarises the baseline characteristics of the 150 included patients, stratified by the five year composite outcome. Male gender ($p = .033$), higher age ($p < .001$), higher Rutherford stage ($p = .004$), history of a cerebrovascular event ($p < .001$) and cardiogenic chest pain ($p = .001$), use of diuretics ($p = .031$), lower glomerular filtration rate ($p = .013$), HDL cholesterol ($p = .005$), and haemoglobin ($p = .004$) were statistically significantly more common in the group with the composite of amputation and mortality.

The results of univariable and multivariable Cox proportional hazard regression analyses are detailed in Table 2 for the composite outcome and Table 3 for individual outcomes. Age (HR 1.77, 95% CI 1.35 — 2.32; $p < .001$), Rutherford 5 (HR 1.79, 95% CI 1.07 — 2.99; $p = .027$), Rutherford 6 (HR 3.48, 95% CI 1.46 — 8.27; $p = .005$), and HDL cholesterol (HR 0.68, 95% CI 0.53 — 0.88; $p = .003$) were independent predictors for the composite of amputation and death. Fig. 2 presents AFS for these predictors, in which the continuous variables age and HDL cholesterol are categorised based on their median value. Similarly, history of a cerebrovascular event (HR 2.49, 95% CI 1.19 — 5.20; $p = .015$), history of contralateral amputation (HR 3.3, 95% CI 1.44 — 7.60; $p = .005$), higher leucocytes (HR 1.48, 95% CI 1.12—1.95; $p = .006$), and lower haemoglobin (HR 0.72, 95% CI 0.56 — 0.92; $p = .010$) were predictors for amputation, whereas age (HR 2.26, 95% CI 1.49 — 3.44; $p < .001$), lower glomerular filtration rate (HR 0.64, 95% CI 0.47 — 0.87; $p = .004$), and HDL cholesterol (HR 0.54, 95% CI 0.39 — 0.76); $p < .001$) were independent predictors of death. For all of these, the proportional hazard assumption holds and thus these predictors were not time dependent.

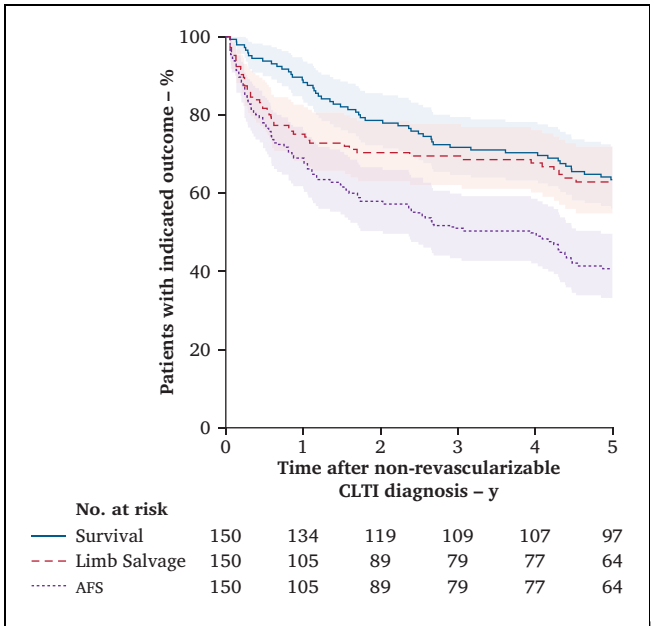

Figure 1. Cumulative Kaplan—Meier estimate of amputation free survival (AFS), survival and limb salvage during a five year period, with 95% confidence intervals, in patients with non-revascularisable chronic limb threatening ischaemia (CLTI).

DISCUSSION

The long term prognosis in this well defined and granulated CLTI population without options for revascularisation (NR-CLTI) was revealed to be poor, with 43% of the patients completing five years survival without limb loss. This result was driven by an equal rate of all cause mortality and amputation: one third of the patients died (35%) and one third underwent amputation of the index limb (33%). Furthermore, a third of those with limb loss after inclusion died within the five year time interval (33%).

The present data correspond with the findings of a small, long term retrospective observational study ($n = 30$), the only published equivalent, reporting a five year mortality of 30% for this NR-CLTI subgroup.[15] No registry studies have been performed and thus prognostic information for NR-CLTI patients is very limited. As such, the present data provide the best available insight into today's perspective for these patients in terms of mortality and limb salvage.

Two registry studies concerning the "real world" CLTI population reported higher all cause mortality rates of 54% and 57% for four and five years, respectively. This may relate to the fact that the present study population was younger and had lower prevalences of history of coronary artery disease and DM.[1,16] In trial selected patients treated for severe limb ischaemia, the BASIL trial reported an AFS of 38% within the completed follow up (3 — 7 years), which was mainly driven by mortality (56%), possibly as a result of an older study population.[17] Although the overall amputation rate was not given, only 7% of the patients that were alive at the final follow up underwent amputation, compared with 22% in the present study. This seems particularly high, but four year amputation rates of CLI patients in a retrospective cohort and according to Rutherford stages 4, 5, and 6 (12%, 35%, and 67%, respectively) were more comparable with the present cohort (20%, 38%, and 56%, respectively).[18] In the present cohort, 33% of

Table 1. Characteristics of 150 patients with non-revascularisable chronic limb threatening ischaemia stratified by endpoint

	Amputation free survival (n = 64)	Amputation or mortality (n = 86)	p value*
Female gender	27 (42.2)	21 (24.4)	.033
Age − y	60.50 (51.50, 70.00)	71.00 (62.25, 79.00)	<.001
BMI − kg/m^2	26.56 (24.53, 29.17)	25.15 (22.72, 27.77)	.055
Peripheral artery disease			
Rutherford classification			.004
Rutherford 4	31 (48.4)	20 (23.3)	
Rutherford 5	31 (48.4)	59 (68.6)	
Rutherford 6	2 (3.1)	7 (8.1)	
History of			
Cerebrovascular event	2 (3.1)	20 (23.3)	.001
Cardiogenic chest pain	15 (23.4)	44 (51.2)	.001
Coronary intervention	13 (20.3)	32 (37.2)	.040
Contralateral major amputation	2 (3.1)	8 (9.3)	.24
Contralateral minor amputation	3 (4.7)	5 (5.8)	1.0
Ipsilateral minor amputation	5 (7.8)	10 (11.6)	.62
Contralateral bypass	9 (14.1)	16 (18.6)	.61
Contralateral PTA or stent	13 (20.3)	21 (24.4)	.69
Ipsilateral bypass	34 (53.1)	41 (47.7)	.62
Ipsilateral PTA or stent	37 (57.8)	53 (61.6)	.76
Dialysis	2 (3.1)	3 (3.5)	1.0
Hypertension	37 (59.7)	53 (63.1)	.80
Diabetes mellitus	19 (29.7)	37 (43.0)	.13
Smoking			.12
Never	6 (9.4)	15 (17.9)	
History of smoking	36 (56.2)	51 (60.7)	
Currently	22 (34.4)	18 (21.4)	
Use of medication			
Antiplatelets			.008
None	20 (31.2)	25 (29.1)	
Aspirin	41 (64.1)	39 (45.3)	
Clopidogrel	1 (1.6)	6 (7.0)	
Aspirin and clopidogrel	1 (1.6)	13 (15.1)	
Dipyridamole	1 (1.6)	3 (3.5)	
Anticoagulants			.74
None	42 (65.6)	51 (59.3)	
Acenocoumarol	19 (29.7)	29 (33.7)	
Fenprocoumon	3 (4.7)	6 (7.0)	
Lipid lowering drugs			.97
None	10 (15.6)	15 (17.4)	
Statin	51 (79.7)	66 (76.7)	
Ezetimibe	0 (0.0)	1 (1.2)	
Statin and ezetimibe	3 (4.7)	4 (4.7)	
ACE inhibitors	20 (31.2)	38 (44.2)	.15
Angiotensin 2 receptor blockers	13 (20.3)	18 (20.9)	1.0
Diuretics	22 (34.4)	46 (53.5)	.031
Beta blockers	24 (37.5)	42 (48.8)	.22
Laboratory results			
GFR − mL/min/1.73m^2	78.36 (64.12, 86.76)	62.04 (44.34, 86.83)	.013
Total cholesterol − mmol/L	4.40 (3.50, 5.17)	4.20 (3.32, 4.80)	.15
Triglycerides − mmol/L	1.40 (0.90, 1.92)	1.45 (1.00, 2.05)	.44
HDL cholesterol − mmol/L	1.32 (0.96, 1.55)	1.06 (0.84, 1.30)	.005
Haemoglobin − mmol/L	8.40 (7.88, 8.95)	7.80 (7.12, 8.50)	.004
Thrombocytes − $\times 10^3$/mm^3	283 (223, 330)	279.50 (234, 343)	.92
Leucocytes − $\times 10^3$/mm^3	7.90 (6.83, 9.72)	8.55 (7.03, 10.15)	.17
Outcomes			
Death	0	53	
Amputation	0	49	

Data are presented as n (%) or median (interquartile range). PTA = percutaneous transluminal angiography; ACE = angiotensin converting enzyme; GFR = glomerular filtration rate; HDL = high density lipoprotein; BMI = Body Mass Index.

* Parametric continuous data tested with the Student t test, non-parametric continuous data with the Mann−Whitney U test, categorical data with Fisher's exact test.

those who underwent amputation subsequently died within the investigated period. This rate is relatively low as amputation is an established risk factor for death, and five year mortality rates of up to 85% have been reported in elderly CLI amputees, and seven year rates after below and above the knee amputations in a veteran cohort (published in 2003) were 72% and 80%, respectively.[19–21] However, subjects were much older in both studies, which troubles comparison.

More published evidence is available on the short term outcomes of this subgroup. At one year, NR-CLTI patients in JUVENTAS were at an especially high risk of amputation (24% of total), but mortality was lower (11%). In comparison, two meta-analyses reported one year amputation rates of 22% and 34%, and mortality rates of 22% and 20%.[9,22] This is perhaps the result of similar design of some of the included studies in these meta-analyses: most recent short term prognostic data are derived from small RCTs investigating gene or cell therapy in no option patients.[23–25] Other (older) case series included in these meta-analyses do not provide up to date information for the current CLTI population, especially as recent studies show gradual reduction of amputation and mortality rates.[1,9–11,26,27]

Short and long term results considered, the present results indicate that NR status is associated with an increased early risk of major amputation, although this risk tails off off in subsequent years. In contrast, mortality is fairly evenly distributed throughout follow up. This is important for both patients and physicians and might imply that NR status is not the primary cause of death, but rather a gradation of a common denominator: progressive systemic atherosclerotic disease. Direct comparison between CLTI and NR-CLTI is difficult, but outcomes are generally in the same order of magnitude. In contrast, a more benign (PAD) population with means of intervention recently revealed considerably better outcomes, as all cause mortality and amputation rates of just 9.1% and 3.5% at three years in the placebo arm of the recent VOYAGER-trial demonstrate.[28] As the difference in outcomes for CLTI and NR-CLTI patients is less pronounced than that of CLTI and IC patients, NR status is

Table 2. Results of Cox proportional hazard regression analysing the predictors for the composite endpoint of amputation and death in 86 patients with non-revascularisable chronic limb threatening ischaemia

	Univariable analysis		Multivariable analysis*	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Female gender	0.63 (0.38 − 1)	.062		
Age†	1.73 (1.3 − 2.3)	<.001	1.77 (1.35 − 2.32)	<.001
BMI†	0.97 (0.92 − 1)	.21		
Rutherford 5‡	2.08 (1.25 − 3.46)	.005	1.79 (1.07 − 2.99)	.027
Rutherford 6‡	4.05 (1.71 − 9.61)	.001	3.48 (1.46 − 8.27)	.005
Cerebrovascular event	2.93 (1.8 − 4.9)	<.001		
Cardiogenic chest pain	2.07 (1.4 − 3.2)	<.001		
Coronary intervention	1.65 (1.1 − 2.6)	.026		
Contralateral major amputation	1.99 (0.96 − 4.1)	.063		
Contralateral minor amputation	1.19 (0.48 − 2.9)	.70		
Ipsilateral minor amputation	1.15 (0.59 − 2.2)	.68		
Contralateral bypass	1.29 (0.75 − 2.2)	.35		
Contralateral PTA or stent	1.13 (0.69 − 1.8)	.63		
Ipsilateral bypass	0.88 (0.58 − 1.3)	.56		
Ipsilateral PTA or stent	1.19 (0.77 − 1.8)	.44		
Dialysis	0.87 (0.27 − 2.7)	.81		
Diabetes mellitus	1.45 (0.94 − 2.2)	.090		
ACE inhibitors	1.39 (0.91 − 2.1)	.13		
Angiotensin-2 receptor blockers	1.05 (0.62 − 1.8)	.87		
Diuretics	1.64 (1.1 − 2.5)	.023		
Beta blockers	1.37 (0.9 − 2.1)	.14		
Glomerular filtration rate †	0.81 (0.65 − 1)	.064		
Total cholesterol †	0.85 (0.69 − 1)	.12		
Triglycerides †	1.06 (0.86 − 1.3)	.57		
HDL cholesterol †	0.74 (0.59 − 0.92)	.008	0.68 (0.53 − 0.88)	.003
Haemoglobin †	0.73 (0.61 − 0.88)	< .001		
Thrombocytes †	1.07 (0.86 − 1.3)	.56		
Leucocytes †	1.15 (0.94 − 1.4)	.17		

PTA = percutaneous transluminal angiography; ACE = angiotensin converting enzyme; HDL = high density lipoprotein; HR = hazard ratio; CI = confidence interval. Empty fields are not entered into the final model; BMI = Body Mass Index.

* Multivariable HRs were calculated with the Cox proportional hazard analysis using a forward stepwise approach (derived from factors with $p <$ .10 in univariable analysis).

† Non-parametric continuous data were log transformed and scaled to provide an HR per standard deviation increase.

‡ Rutherford 5 and 6 are compared with Rutherford 4 stage.

Table 3. Results of Cox proportional hazard regression analysing the predictors for amputation and death in 150 patients with non-revascularisable chronic limb threatening ischaemia

	Amputation (n = 49)				Mortality (n = 53)			
	Univariable analysis		Multivariable analysis*		Univariable analysis		Multivariable analysis*	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Female gender	0.8 (0.43–1.5)	.48			0.51 (0.26–1)	.049		
Age †	1.27 (0.93–1.7)	.14			2.27 (1.5–3.5)	<.001	2.26 (1.49–3.44)	<.001
BMI †	0.93 (0.87–1)	.061			0.97 (0.91–1)	.40		
Rutherford 5‡	2.24 (1.11–4.55)	.025			2.26 (1.15–4.42)	.018		
Rutherford 6‡	5.20 (1.77–15.3)	.003			2.69 (0.86–8.46)	.09		
Cerebrovascular event	2.06 (1.02–4.2)	.044	2.49 (1.19–5.20)	.015	2.28 (1.2–4.3)	.012		
Cardiogenic chest pain	1.47 (0.84–2.6)	.18			2.54 (1.5–4.4)	<.001		
Coronary intervention	1.49 (0.83–2.7)	.18			1.58 (0.91–2.8)	.11		
Contralateral major amputation	3.16 (1.4–7)	.010	3.3 (1.44–7.60)	.005	0.75 (0.23–2.4)	.62		
Contralateral minor amputation	1.26 (0.39–4.1)	.70			1.61 (0.58–4.5)	.36		
Ipsilateral minor amputation	0.76 (0.27–2.1)	.60			1.63 (0.77–3.5)	.20		
Contralateral bypass	1.56 (0.79–3)	.20			0.89 (0.42–1.9)	.75		
Contralateral PTA or stent	1.27 (0.67–2.4)	.46			0.85 (0.44–1.7)	.64		
Ipsilateral bypass	1.02 (0.58–1.8)	.95			0.66 (0.38–1.1)	.13		
Ipsilateral PTA or stent	1.37 (0.76–2.5)	.30			0.85 (0.5–1.5)	.57		
Dialysis	1.03 (0.25–4.2)	.97			1.04 (0.25–4.3)	.96		
Diabetes mellitus	1.78 (1–3.1)	.043			0.94 (0.54–1.7)	.84		
ACE inhibitors	1.41 (0.8–2.5)	.24			1.3 (0.76–2.2)	.34		
Angiotensin 2 receptor blockers	0.89 (0.43–1.8)	.76			0.78 (0.38–1.6)	.49		
Diuretics	1.3 (0.74–2.3)	.36			1.94 (1.1–3.3)	.017		
Beta blockers	0.95 (0.53–1.7)	.85			1.96 (1.1–3.4)	.016		
Glomerular filtration rate †	1.08 (0.81–1.5)	.59			0.56 (0.43–0.73)	<.001	0.64 (0.47–0.87)	.004
Total cholesterol †	0.72 (0.55–0.95)	.020			0.87 (0.67–1.1)	.29		
Triglycerides †	0.93 (0.7–1.2)	.59			1.12 (0.85–1.5)	.41		
HDL cholesterol †	0.76 (0.57–1)	.057			0.62 (0.47–0.83)	.001	0.54 (0.39–0.76)	<.001
Haemoglobin †	0.69 (0.54–0.88)	.002	0.72 (0.56–0.92)	.010	0.71 (0.55–0.9)	.005		
Thrombocytes †	1.39 (1.1–1.8)	.019			0.83 (0.63–1.1)	.20		
Leucocytes †	1.3 (1–1.7)	.052	1.48 (1.12–1.95)	.006	1.05 (0.81–1.4)	.72		

PTA = percutaneous transluminal angiography; ACE = angiotensin converting enzyme; HDL = high density lipoprotein; HR = hazard ratio; CI = confidence interval. Empty fields are not entered into the final model; BMI = Body Mass Index.

* Multivariable HRs were calculated with the Cox proportional hazard analysis using a forward stepwise approach (derived from factors with $p <$ .10 in univariable analysis).

† Non-parametric continuous data were log transformed and scaled to provide an HR per standard deviation increase.

‡ Rutherford 5 and 6 are compared with Rutherford 4 stage.

perhaps not a major risk factor. With regard to this concept, although long term prognosis is poor, the present authors believe that NR status in CLTI does not drive towards immediate amputation *per se* if best medical/wound treatment can be applied, contrary to what perhaps seems the general belief of vascular specialists, and neither does this amputation always lead to premature death (compared with CLTI patients with revascularisation options). The emphasis for management of these high risk patients should therefore lie on strategies to decrease the amputation risk in the short term and enable optimal management of comorbidities in the long term. This approach could facilitate vascular specialists in medical management and patient counselling and is otherwise crucial in the design of future regenerative trials, and their selection of patients.

Putting the study outcomes into perspective is difficult because of a paucity of prognostic data for NR-CLTI, and heterogeneity of study design and populations. The disparity between the present results and some of the current literature could be attributed to a trial effect, selection bias, definition, and time. The so called "trial effect", has been suggested to influence outcome, although little evidence is available on this topic.[29,30] However, extensive care and strict surveillance, as implemented in these trials, are thought to reduce adverse outcomes in cardiovascular disease and thus hypothetically support this claim.[31–33] If these assumptions are valid, the present relatively benign results compared with the CLTI registry studies suggest that extensive care could improve the prognosis of the no option patient significantly, even for a relatively short amount of time (as in this study), and thus more effort is warranted to enable optimal management.

On the other hand, differences in the present outcomes, caused by a discrepancy of real world and trial patients, are possibly the result of selection bias. Participation in a time consuming study with potential adverse events could potentially favour a compliant patient with ultimately, a lower *a priori* risk of mortality, because of better adherence

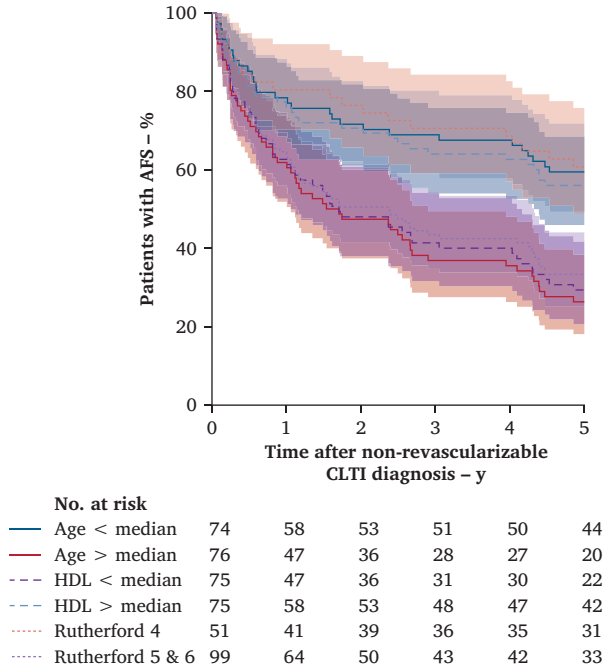

Figure 2. Cumulative Kaplan–Meier estimate of amputation free survival (AFS) during a five year period, with 95% confidence intervals, stratified by independent risk factors: Rutherford classification, median age, and median high density lipoprotein (HDL) in patients with non-revascularisable chronic limb threatening ischaemia (CLTI).

and disease awareness. Undoubtedly, the exclusion criteria in JUVENTAS in combination with an average to good ambulatory state (a non-ambulatory state can be a disincentive to participation because of the frequency of follow ups) influences both short and long term outcomes.[34–36] Furthermore, there is a lack of a standard definition of "no option", which could comprise patients without feasible intervention, and patients whose medical condition is too frail to justify the exposure to additional intra- and postoperative risks. Patients included in JUVENTAS match the first category, as established by a multidisciplinary team of vascular surgeons and radiologists in an academic hospital. However, other mentioned studies combined these categories, which subsequently influences these outcomes.[25–27]

Whether the no option patient of today is comparable with no option patients of 10 or 20 years ago in terms of AFS is arguable as secondary and tertiary prevention have improved and innovations have led to improved revascularisation alternatives.[1,37] Furthermore, a time dependent shift in aetiology (macro- to microvascular) could lead to different patient characteristics. However, the main principle of the present no option definition remains the same: all patients are subject to inadequate perfusion, resulting in high grade ischaemia, without any means of treatment in the foreseeable future. A uniform description should be considered for general use and research, in which it is proposed that there is emphasis on the "no option anatomy" category, as mentioned in the Global Vascular Guidelines on the management of CLTI.[38]

A limitation of the present analysis is the extension of original follow up without additional contacts or visits within this interval. However, the endpoints remained the same and almost no loss to follow up occurred. The two patients lost to follow up were removed from analysis because there was a significant gap between their last confirmed medical status and five year follow up. Both treatment and placebo arms were included in the present analyses. The JUVENTAS trial did not find a treatment related effect on AFS. At five years the present study reaffirmed no difference in AFS (46 *vs.* 40, $p = .53$), amputation (27 *vs.* 22, $p = .56$), or mortality (29 *vs.* 24, $p = .58$) for treatment *vs.* placebo, respectively.[13] Thus, including patients from both trial arms is justified.

In conclusion, the present study provides the necessary contemporary long term follow up data for NR-CLTI patients. The poor amputation free survival and general survival underscore the poor prospects for these patients. In comparison with other studies, the present analysis suggests that AFS and survival in NR-CLTI are no worse than in CLTI patients with revascularisation options.

CONFLICT OF INTEREST

None.

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