Diabetes Is Associated With Decreased Limb Survival in Patients With Critical Limb Ischemia: Pooled Data From Two Randomized Controlled Trials

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Diabetes Care 2016;39:2058–2064 | DOI: 10.2337/dc16-0850

OBJECTIVE

Although never assessed prospectively, diabetes mellitus (DM) is assumed to negatively affect the outcomes of critical limb ischemia (CLI). DM was highly prevalent in two recently conducted randomized controlled trials in CLI patients, the PADI (Percutaneous Transluminal Balloon Angioplasty [PTA] and Drug Eluting Stents for Infrapopliteal Lesions in Critical Limb Ischemia) and JUVENTAS (Rejuvenating Endothelial Progenitor Cells via Transcutaneous Intra-Arterial Supplementation) trials. To determine the implications of DM in a population of patients with infrapopliteal CLI, clinical outcomes were compared in patients with and without DM.

RESEARCH DESIGN AND METHODS

Individual data from patients with CLI (Rutherford category ≥4) were pooled. Patients were considered to have DM when this diagnosis was reported in the hospital electronic medical records. Rates of major amputation (above ankle level) and major events (major amputation or death) were compared between CLI patients with and without DM. Hazard ratios (HRs) were calculated.

RESULTS

Of a total of 281 patients, DM was present in 49.1%. The major amputation rate at 5 years of follow-up was higher in patients with DM than in patients without DM (34.1% vs. 20.4%, *P* = 0.015). The major event and death rate did not differ. The unadjusted HR of DM for the major amputation risk was 1.87 (95% CI 1.12–3.12). Model factors with significant HRs in the multivariate analysis were baseline Rutherford category (HR 1.95; 95% CI 1.24–3.06) and ankle-brachial index (ABI) >1.4 (HR 2.78; 95% CI 1.37–5.64).

CONCLUSIONS

CLI patients with DM are at a significantly higher risk of major amputation than CLI patients without DM. This increased risk is associated with a higher prevalence of baseline ABI >1.4 and more severe ischemia at initial presentation in patients with DM.

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Received 19 April 2016 and accepted 5 August 2016.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc16-0850/-/DC1.

**A complete list of members of the PADI and JUVENTAS Study Groups can be found in the APPENDIX.*

Critical limb ischemia (CLI) is the most severe form of peripheral artery disease (PAD) and imposes an increasing burden on health care. The current incidence is substantial, with 500–1,000 new cases per 1 million inhabitants every year in Western Europe and North America (1,2). Moreover, with a 6-month major amputation rate of 10 to 40% and a 1-year mortality rate of 25% in CLI patients who are not able to be revascularized, its poor prognosis is striking (1–3).

One of the main goals in the treatment of CLI is to prevent major amputation, because a lower leg amputation in these patients is a high-risk procedure with a 30-day mortality of ±10% and less than 30% of surviving patients are ambulatory outdoors at 17 months of follow-up (4). Identifying those patients who are at particularly high risk of major amputation is important to improve clinical decision making and to select the most appropriate therapy for each patient.

PAD progresses more rapidly in patients with diabetes mellitus (DM) (5). The risk of developing CLI is four-times higher in patients with DM than in patients without DM (1). PAD in patients with DM is often accompanied by peripheral neuropathy with sensory dysfunction, which is thought to contribute to the development of foot ulcers and progressive tissue loss in patients with CLI (6). Although CLI in patients with diabetes is often assumed to have a worse prognosis, this has not been proven prospectively in populations consisting exclusively of CLI patients. In studies that focus on CLI, patients with and without DM are usually reported as one group (7). Because CLI patients are typically elderly, vulnerable, and fragile patients who are at high risk for cardiovascular events (1), CLI study populations are often small, which limits subgroup analyses and separate reporting of results for patients with and without DM.

The PADI (Percutaneous Transluminal Balloon Angioplasty [PTA] and Drug Eluting Stents for Infrapopliteal Lesions in Critical Limb Ischemia) and JUVENTAS (Rejuvenating Endothelial Progenitor Cells via Transcutaneous Intra-Arterial Supplementation) trials investigated different treatment strategies in patients with CLI (8,9). DM was a common comorbidity in both studies. Our study pooled data from these two studies with the aim of determining whether the prognosis regarding major amputation and major events differs between CLI patients with and without DM.

RESEARCH DESIGN AND METHODS

PADI Trial

Study Design, Population, and Procedures

Between October 2007 and February 2013, 137 patients with 144 limbs were enrolled in the PADI trial, an investigator-initiated, multicenter, randomized controlled, nonblinded, double-arm study. Adult patients with CLI (defined as Rutherford category ≥4) (10) caused by infrapopliteal lesions were eligible for enrolment. Major exclusion criteria were (sub)acute limb ischemia, increased risk of bleeding, and estimated glomerular filtration rate (eGFR) <20 mL/min/1.73 m^2. Treatment with paclitaxel-eluting coronary stents (TAXUS Liberté; Boston Scientific, Natick, MA) was compared with percutaneous transluminal angioplasty with optional bail-out bare-metal stents. The rationale of this study, detailed inclusion and exclusion criteria, and study procedures have been reported previously (11).

Follow-up and End Points

Patient assessments were planned before intervention, at discharge, after 3, 6, and 12 months, and annually until 5 years or until a major end point (major amputation or death) was reached. No patients were lost to follow-up until 12 months after inclusion. Long-term follow-up until 5 years is still ongoing. Follow-up of patients who underwent a major amputation was obtained by phone assessments or using data from patient medical records.

The primary end point of the PADI trial was the 6-month primary binary patency of treated lesions, defined as ≤50% stenosis on computed tomography angiography. Secondary end points were Rutherford classification (10), minor (below ankle level) and major amputation (above ankle level) of the trial leg, and periprocedural (within 30 days) complications, serious adverse events, and death. Short-term results have been published previously (12). The trial was registered at ClinicalTrials.gov with the identifier NCT00471289.

JUVENTAS Trial

Study Design, Population, and Procedures

The JUVENTAS trial is a single-center, double-blind placebo-controlled randomized controlled trial that investigated the effects of repetitive infusion of bone marrow mononuclear cells into the common femoral artery (9). The cohort included 160 patients (160 limbs). Inclusion criteria consisted of severe infrapopliteal PAD, defined as class IIB to IV in the Fontaine classification (1), that was not amenable for conventional revascularization. Major exclusion criteria were factors that diminished life expectancy and/or precluded follow-up. The intervention consisted of three intraarterial infusions of autologous bone marrow mononuclear cells. Patients in the placebo group received an autologous peripheral blood infusion designed to mimic the cell therapy product.

Follow-up and End Points

Primary outcome was major amputation (amputation through or above the ankle joint) or death at 6 months. Secondary outcomes were amputation at 2 months and during the entire observation period, as well as changes in Fontaine/Rutherford classification, minor amputations, ulcer size, ankle-brachial index (ABI), and quality of life (8). Results have been published elsewhere (8). No patients were lost to follow-up in the primary trial period of 6 months. Follow-up was extended until a maximum 5 years for this additional analysis, using patient medical records or by contacting patients by phone. The trial was registered at ClinicalTrials.gov under number NCT00371371.

Patient Selection

Data of the PADI and JUVENTAS trials were pooled on a patient level. We selected patients with CLI (i.e., Rutherford category 4/Fontaine stage III, or Rutherford category 5 or 6/Fontaine IV). Four patients were included in both trials; they were included in the analysis only once, with the longest available follow-up period.

Selected PADI and JUVENTAS patients were analyzed according to the presence of DM. Subjects were classified as having DM when this diagnosis was reported in the hospital electronic medical records. All subjects in this study with DM were treated with blood glucose–lowering medication (oral hypoglycemic medications, insulin, and/or other noninjectable therapies); none were on diet or lifestyle modification alone.

Outcomes

Baseline characteristics, presence of ulcers at baseline and after 6 months of follow-up, major amputation, and major event rates until 5 years after treatment

were compared between patients with and without DM. Major amputation was defined as amputation above the ankle level. A major event was defined as a major amputation or death. In addition, survival rates were analyzed separately for patients with and without a major amputation.

Statistical Analysis

Categorical variables were compared with the use of the two-sided χ^2 test, ordinal variables with the Mann-Whitney test, and continuous variables with the two-sided Student *t* test. A two-sided *P* value $\leq$0.05 was considered to indicate statistical significance. Missing data at inclusion were $<$5% for any parameter. In case of missing data, data points were imputed by multiple regression.

The observed amputation and major event rates were estimated with the Kaplan-Meier method. Patients were censored at end of follow-up.

Hazard ratios (HRs) of DM for the risk of major amputation were calculated with Cox proportional hazards regression models. A full model adjusted for age, smoking, history of stroke, history of coronary artery disease, previous treatment for PAD, impaired renal function (eGFR $<$30 mL/min/1.73 m^2), Rutherford category at baseline, and categorized ABI at baseline of $<$0.7, 0.7–1.4, and $>$1.4 (including immeasurable ABI owing to incompressible vessels) was created for the multivariate analysis. Missing ABIs as a covariate for this model were imputed. We also performed backward reduction of model factors. The best performing model was based on the lowest Akaike information criterion. Potential interactions between variables were analyzed. The proportional hazards assumptions for all presented Cox models were evaluated by plotting Schoenfeld residuals. Stratification according to randomization was used to correct for the effects of treatment in the Kaplan-Meier analyses and Cox proportional hazards regression analyses. Analyses were performed in SPSS 22 software and R 3.1.0 software.

RESULTS

Patient Characteristics

Of the PADI trial, 133 patients (97.1%) fulfilled all inclusion criteria and were selected for this pooled analysis (12); of whom 84 patients (63.2%) had DM. Of the JUVENTAS cohort, 152 patients (95.0%) were selected, of whom 57 patients (37.5%) had DM. Four patients were included in both trials; thus, 281 subjects were selected.

Table 1 reports the baseline characteristics. Overall, 138 patients (49.1%) had DM. Significantly more patients with DM than those without DM had a history of stroke or transient ischemic attack and coronary artery disease. Significantly more patients without DM were current smokers or had smoked in the past.

Patients with DM showed a significantly higher Rutherford category at baseline. More patients without DM had an ABI $<$0.7, whereas a larger proportion of patients with DM showed an ABI between 0.7 and 1.4, or an ABI $>$1.4 ($P < 0.001$).

Supplementary Table 1 reports the baseline characteristics separately for patients with and without diabetes in the PADI and JUVENTAS cohorts.

End Points

Patients were monitored for a median duration of 142.5 weeks, equivalent to 767 patient-years of observation. The mean follow-up time of surviving patients with DM was 184.5 (SD 92.8) weeks and of surviving patients without DM was 197.6 (SD 112.6) weeks.

Table 2 reports the significantly higher rate of major amputations in patients with DM compared with patients without DM, with an estimated rate of 34.1% of the former undergoing a major amputation during 5 years of follow-up versus 20.4% of the latter (*P* = 0.015). This is also graphically shown by the Kaplan-Meier curves of the estimated cumulative incidence rates of major amputation (Fig. 1*A*). Most of the major amputations in both groups were performed in the first 6 months after randomization.

The major event rate (major amputation or death) and death rate did not differ significantly between patients with or without DM (Table 2 and Fig. 1*B*). Figure 1*C* shows that survival is significantly decreased in patients after amputation (*P* = 0.006). This poor survival after major amputation is comparable in patients with and without DM (*P* = 0.63) (Supplementary Fig. 1). The survival of patients without a major amputation did not differ between patients with and without DM (*P* = 0.99) (Supplementary Fig. 2).

Both at baseline and at 6 months of follow-up, ulcers were present in a significantly larger percentage of patients

Table 1—Baseline characteristics, according to diabetes state

	Patients without DM (*n* = 143)	Patients with DM (*n* = 138)	*P* value*
Age, mean (SD), years	67.9 (15.0)	70.9 (11.3)	NS†
Male sex	94 (65.7)	99 (71.7)	NS
Smoking status			$<$0.001
Former smoker	62 (43.4)	54 (39.1)	
Current smoker	48 (33.6)	24 (17.4)	
Previous stroke or TIA	14 (9.8)	33 (23.9)	0.002
Coronary disease	47 (32.9)	62 (44.9)	0.038
Impaired renal function§	15 (10.5)	19 (13.8)	NS
Renal disease requiring dialysis	8 (5.6)	9 (6.5)	NS
On anticoagulation medication	136 (95.1)	129 (93.5)	NS
History of PAD	107 (74.8)	102 (73.9)	NS
Rutherford category			
Mean (SD)	4.8 (0.6)	5.0 (0.6)	0.002‡
Median (min–max)	5 (4–6)	5 (4–6)	
ABI, mean (SD)	0.57 (0.30)	0.70 (0.35)	0.003†
ABI			
$<$0.7	97 (67.8)	55 (39.9)	$<$0.001
0.7–0.9	18 (12.6)	31 (22.5)	
0.9–1.2	15 (10.5)	27 (19.6)	
1.2–1.4	3 (2.1)	2 (1.4)	
$>$1.4/immeasurable	10 (7.0)	23 (16.7)	

Data are *n* (%), unless stated otherwise. Missing ABIs were imputed. TIA, transient ischemic attack. *By χ^2 test, unless stated otherwise. †By *t* test. ‡By Mann-Whitney test. §Determined by eGFR $<$30 mL/min/1.73 m^2.

Table 2—Cumulative proportion experiencing amputation/death categorized by diabetes

	Patients without DM (*n* = 143)		Patients with DM (*n* = 138)		
	n	% (95% CI)	*n*	% (95% CI)	*P* value*
Major amputation					
0–6 months	16	11.4 (6.1–16.7)	26	19.7 (12.8–26.6)	
0–12 months	22	16.0 (9.9–22.1)	31	23.8 (16.5–31.1)	
0–24 months	24	17.8 (11.3–24.3)	36	28.3 (20.5–36.1)	
0–36 months	25	18.7 (12.0–25.4)	37	29.2 (21.2–37.2)	
0–48 months	26	20.4 (13.1–27.7)	38	30.8 (22.4–39.2)	
0–60 months	26	20.4 (13.1–27.7)	39	34.1 (23.9–44.3)	0.015
Death					
0–6 months	11	8.0 (3.5–12.5)	17	12.8 (7.1–18.5)	
0–12 months	24	17.9 (11.4–24.4)	25	19.2 (12.3–26.1)	
0–24 months	34	25.6 (18.2–33.0)	41	32.0 (24.0–40.0)	
0–36 months	41	31.3 (23.3–39.3)	48	38.1 (29.5–46.7)	
0–48 months	45	36.1 (27.3–44.9)	52	43.0 (33.8–52.2)	
0–60 months	53	48.0 (37.6–58.4)	59	55.7 (44.7–66.7)	0.78
Amputation/death					
0–6 months	25	17.5 (11.2–23.8)	38	27.5 (20.1–34.9)	
0–12 months	42	29.4 (22.0–36.8)	47	34.1 (26.3–41.9)	
0–24 months	51	35.7 (27.9–43.5)	62	45.0 (36.8–53.2)	
0–36 months	59	41.7 (33.5–49.9)	70	51.2 (42.8–59.6)	
0–48 months	63	46.3 (37.7–54.9)	74	55.6 (47.0–64.2)	
0–60 months	69	54.4 (44.8–64.0)	82	68.7 (58.7–78.7)	0.19

*Overall log-rank test, stratified by randomization.

with DM (*P* = 0.043 and *P* = 0.002, respectively) (Supplementary Table 2).

The unadjusted HR of DM for the risk of major amputation was 1.87 (95% CI 1.12–3.12; *P* = 0.017) (Table 3). The multivariate analysis with all factors included and with stratification by randomization showed a HR of DM of 1.59 (95% CI 0.91–2.78; *P* = 0.11). The model factors with significant HRs in the multivariate analysis were Rutherford category at baseline (HR 2.03; 95% CI 1.28–3.21; *P* = 0.003) and a baseline ABI >1.4 (HR 2.62; 95% CI 1.23–5.57; *P* = 0.012).

Multivariate analysis with the inclusion of DM, baseline Rutherford category, and baseline ABI category yielded the best performing model with the lowest Akaike information criterion. In this model, the HR of DM was 1.56 (95% CI 0.92–2.65; *P* = 0.10), of baseline Rutherford category was 1.95 (95% CI 1.24–3.06; *P* = 0.004), and of baseline ABI>1.4 was 2.78 (95% CI 1.37–5.64; *P* = 0.005).

CONCLUSIONS

Our data show that a significantly larger percentage of CLI patients with DM require a major amputation within 5 years compared with CLI patients without DM. Patients in our cohorts with CLI and DM had an almost 20% risk to undergo major amputation in the first 6 months after inclusion versus 10% in patients without DM. Within 5 years, the estimated major amputation rate is one of three in patients with DM versus one of five in patients without DM. Survival is poor after major amputation, both for patients with and without DM.

Higher baseline Rutherford category and ABI >1.4 were significant predictors of major amputation, which may suggest that merely these manifestations of DM are more important for the outcome of CLI than the disease itself. Both factors are more common in patients with DM.

In addition, compared with patients without DM, significantly more patients with DM had a history of stroke, transient ischemic attack, and coronary artery disease, indicating more extensive vascular disease.

The association between DM and the development of PAD has been described previously but is not well known (1). The course of PAD in patients with DM is more aggressive compared with patients without DM, with the former group being at higher risk of developing CLI (1,13). The fate of a patient's ischemic leg related to the presence or absence of concomitant DM is less well studied (7). To our knowledge, this study is the first that has prospectively proven in a true CLI population that DM is associated with lower limb survival in patients with CLI, by comparing 138 CLI patients with DM and 143 CLI patients without DM from two prospective randomized trials. Our results are supported by a previous retrospective population-based cohort study showing a lower amputation-free survival after leg bypass surgery in CLI patients with DM than in CLI patients without DM (14).

The higher mean Rutherford category at baseline in the subgroup with DM in the current study may relate to the high prevalence of concomitant peripheral neuropathy in these patients. Because pain perception is blunted in case of neuropathy, patients are not aware of the development of an ischemic ulcer or gangrene. Consequently, the presentation of CLI in patients with DM is usually at a later stage with more severe lesions (6). This is supported by our finding that ulcers are more prevalent at baseline and at 6 months of follow-up in patients with DM.

An ABI >1.4 is probably related to medial artery calcification (MAC), leading to poorly compressible, stiffened arteries. MAC is more often seen in patients with DM and end-stage renal disease (15–18). Several studies have reported an association between an elevated ABI and amputation (18–20). Our data confirm that an ABI >1.4 is strongly associated with a higher risk of amputation in patients with DM. Arterial wall stiffness caused by MAC is associated with reduced arterial flow volume in the lower extremities of patients with DM (21). In these patients, besides recanalization, treatment should be considered for the stiff and calcified vessel wall, although options in this field thus far are limited. It has been suggested that nitrogen-containing bisphosphonates might limit cardiovascular calcification (22). An association of high dietary menaquinone (vitamin K_2) intake with reduced coronary calcification has been reported (23). Chelation therapy with disodium EDTA has also been proposed to treat vascular calcifications, but proof of efficacy thus far is insufficient (24).

It is recommended that in case of a high or immeasurable ABI, additional noninvasive diagnostic testing, such as

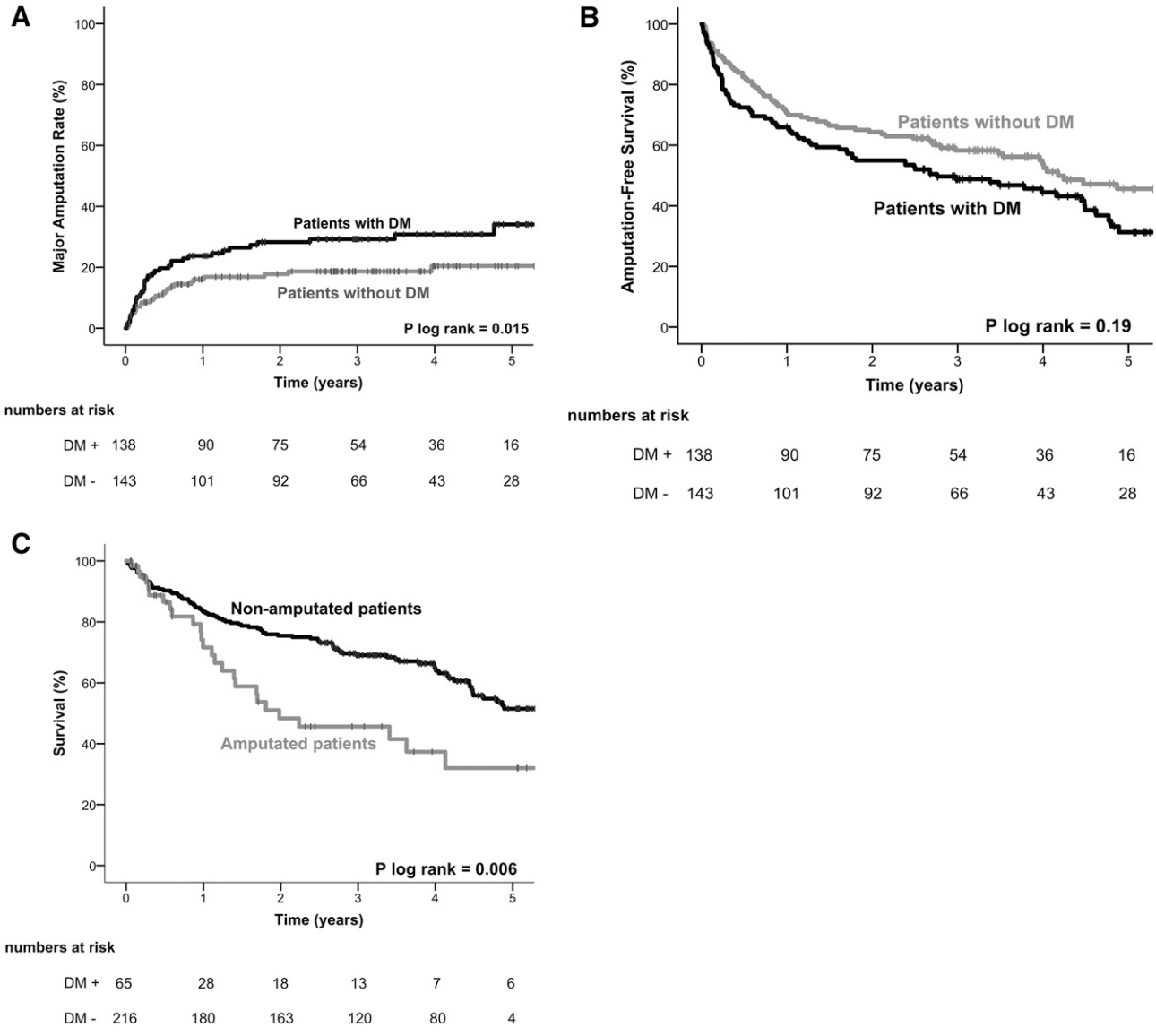

Figure 1—Kaplan-Meier curves representing the estimated cumulative incidence rates of major amputation (*A*) and amputation-free survival (*B*) per patient for patients with and without DM, and survival in amputated and nonamputated patients (*C*).

toe systolic pressures, pulse volume recordings, transcutaneous oxygen measurements, or vascular imaging (e.g., duplex ultrasound), should be performed to detect coexisting stenotic or occlusive arterial disease (1,15). A high or immeasurable ABI in a population with DM with a clinical suspicion of CLI requires a careful diagnostic process and treatment strategy to avoid amputation. Our study underscores the limited value of the ABI in the assessment of PAD in DM, because almost half of our patients with DM and CLI had baseline ABI values between 0.7 and 1.4 (25).

Amputation-free survival was lower in patients with DM than in patients without DM at all times at follow-up, but this difference did not reach statistical significance. The difference in the amputation-free survival rate is mostly attributable to the higher amputation rate in patients with DM, because the death rate in patients with DM is comparable with that in patients without DM.

Survival was significantly lower in patients after a major amputation during follow-up. This is analogous to a previously conducted study that reported a survival rate after major amputation of only 55% at 3 years of follow-up (4) and illustrates the poor prognosis of patients after major amputation. The diminished survival after major amputation did not differ between patients with and without DM, but these subgroups were considered too small for further subanalysis. Two retrospective cohort studies did find significantly lower survival rates in patients with DM than in patients without DM during follow-up after minor and major lower extremity amputations (26,27). Because neither of these studies analyzed the indications for amputation, whether these patients are comparable with the current study population with severe CLI cannot be determined.

Some limitations of this study need to be considered. Subjects were classified as having DM based on the hospital electronic medical records. All of these subjects were using blood glucose–lowering medication (oral hypoglycemic medications, insulin, and/or other noninjectable therapies). It is possible that some

Table 3—Results of Cox proportional hazards regression analysis of variables for prediction of major amputation

Variables at baseline	HR	95% CI	*P* value*
Univariate analysis			
DM	1.87	1.12–3.12	0.017
Multivariate analysis			
Age	1.01	0.99–1.03	0.29
DM	1.59	0.91–2.78	0.11
Stroke	0.88	0.45–1.70	0.70
Coronary disease	1.02	0.59–1.75	0.95
PAD	1.47	0.73–2.95	0.28
Former smoker	0.91	0.45–1.81	0.78
Current smoker	1.39	0.65–2.98	0.40
eGFR <30 mL/min/1.73 m^2	1.59	0.81–3.13	0.18
Rutherford category	2.03	1.28–3.21	0.003
ABI <0.7	1.26	0.68–2.32	0.46
ABI >1.4	2.62	1.23–5.57	0.012
Multivariate analysis, best performing model			
DM	1.56	0.92–2.65	0.10
Rutherford category	1.95	1.24–3.06	0.004
ABI <0.7	1.32	0.73–2.41	0.36
ABI >1.4	2.78	1.37–5.64	0.005

*Stratified by randomization.

subjects in the group without DM might actually have had early, undiagnosed DM, which could have increased the chance of a false-negative but not of a false-positive observation. Our findings are therefore only applicable to patients with DM that requires blood glucose–lowering medication.

Because the study population consisted of two patient cohorts from randomized controlled trials designed to test interventions in CLI, potential heterogeneity exists because of treatment effects. To forestall this limitation, we have stratified by randomization in the Kaplan-Meier survival and Cox regression analyses to correct for effects of different treatment strategies. We also ascertained that there were no statistical interactions between the treatment arm and the presence of DM. We corrected for differences in baseline characteristics, by apply multivariate Cox regression analyses.

Some exclusion criteria were applied in the PADI and JUVENTAS trials, and therefore, our findings may not be extrapolated to every CLI patient. The PADI trial excluded patients with nontreatable iliac or femoropopliteal lesions, which may have resulted in a lower risk of major amputation in the study subjects. The same may be applied to the exclusion criterion of the PADI trial of a diminished renal function (eGFR <20 mL/min/1.73 m^2).

Patients included in the JUVENTAS trial had CLI caused by severe PAD that could not be revascularized. The risk of major amputation in these patients is supposedly higher than in patients with CLI who can be treated with surgical or endovascular recanalization. However, we stress that this study focuses on CLI, and because of the inclusion and exclusion criteria, a study population could be selected with comparable infrapopliteal CLI, which is the unique and major strength of our study.

Finally, infection is known to increase the risk of major amputation (1,28); however, data regarding the presence of concomitant infection in some patients with ulcers and necrosis are lacking.

In conclusion, CLI patients with DM have significantly more prevalent cardiovascular comorbidity and are at a substantially higher risk of major amputation compared with patients with CLI without DM. The higher amputation risk is associated with a higher proportion of patients with DM with ABI >1.4 at baseline and a more advanced clinical stage at presentation. Future research should indicate whether treatment strategies aimed at these factors could reduce the amputation rate in patients with DM.

Acknowledgments. The authors greatly appreciate the thoughtful comments to this manuscript of N.C. Schaper, MD, PhD, Department of Internal Medicine/Endocrinology, University Hospital Maastricht, the Netherlands.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. M.I.S. participated in data collection, researched data, wrote the manuscript, and takes overall responsibility. H.G. participated in data collection, researched data, and wrote the manuscript. M.T. and M.C.V. reviewed and edited the manuscript. R.W.S. participated in data collection and researched data. R.G.S.v.E. participated in data collection. J.-P.P.M.d.V. participated in data collection and reviewed and edited the manuscript. W.P.Th.M.M. participated in data analysis, wrote and edited the manuscript, and takes overall responsibility. H.v.O. participated in data collection and data analysis, wrote and edited the manuscript, and takes overall responsibility. M.I.S., W.P.Th.M.M., and H.v.O. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Appendix

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