Lower extremity arterial reconstruction for critical limb ischemia in diabetes

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Background: **The impact of diabetes mellitus on the technical and clinical outcomes of infrainguinal arterial reconstruction (IAR) for critical limb ischemia (CLI) remains controversial. This study analyzed the outcome of IAR in diabetic patients with CLI over a 17-year period.**

Methods: **Details on all consecutive patients undergoing primary IAR at our institution were stored prospectively in a vascular registry from 1995 to 2011. Demographics, risk factors, indications for surgery, inflow sources and outflow target vessels, types of conduit, and adverse outcomes were analyzed. Postoperative surveillance included clinical examination, duplex scans, and ankle-brachial index measurements in all patients at discharge, 1 and 6 months after surgery, and every 6 months thereafter. End points were patency, limb salvage, survival, and amputation-free survival rates, and were assessed using Kaplan-Meier life-table analysis. The χ^2 or Fisher exact, Student *t*, and log-rank tests were used to establish statistical significance.**

Results: **Overall, 1407 IARs were performed in 1310 patients with CLI by the same surgeon, 705 (50.2%) in 643 diabetic patients and 702 in 667 nondiabetic patients. Autogenous vein conduits were used in 87% of the IARs. There were no perioperative deaths. Diabetic patients had significantly more major (16.7% vs 11.8%; $P = .02$) and minor complications (9.7% vs 6.5%; $P = .02$) than nondiabetic patients. At 5 and 10 years, there were no significant differences between diabetic and nondiabetic patients in the rates of primary patency (65% and 46% vs 69.5% and 57%; log-rank test, $P = .09$), secondary patency (76% and 60% vs 80% and 68%; log-rank test, $P = .20$), limb salvage (88% and 76% vs 91% and 83%; log-rank test, $P = .12$) survival (51% and 34% vs 57% and 38%; log-rank test, $P = .41$), or amputation-free survival (45.5% and 27% vs 51% and 29%; log-rank test, $P = .19$). The type of conduit did not affect patency or limb salvage rates in either group.**

Conclusions: **Diabetic patients receiving IAR for CLI can have the same survival and amputation-free survival rates as nondiabetic patients. Their comparable technical and clinical outcomes strongly demonstrate that diabetics with CLI can expect the same quantity and quality of life as nondiabetics with CLI, and aggressive attempts at limb salvage in patients with diabetes mellitus, including distal and foot level bypass grafting, should not be discouraged. (J Vasc Surg 2014;59:708-19.)**

With its rising incidence (expected to increase by 200% between 2005 and 2050[1]), diabetes mellitus (DM) is one of major risk factors for peripheral arterial disease (PAD).[2] Its prevalence is very high among people with critical limb ischemia (CLI), defined as pain at rest and/or the presence of ischemic ulcer or gangrene, ranging between 35% and 80% of patients undergoing lower extremity bypass surgery to avoid limb loss (opposed to around 10% in the general population),[3] making the management of CLI in diabetic patients an important surgical challenge in clinical practice.[4] There have been reports of infrainguinal arterial reconstruction (IAR) for CLI in diabetics being associated with higher rates of revascularization failure, limb loss, morbidity,[5-8] and mortality,[6,8-12] and DM is reportedly an independent predictor of failure in percutaneous lower extremity procedures in patients with CLI, accounting for unacceptably frequent restenoses needing reinterventions.[13,14] Many studies involving aggressive revascularization efforts and exploiting technical advances in extreme distal arterial reconstruction and better postoperative care have challenged these results, however, reporting excellent technical outcomes after IAR for CLI, with no difference between diabetic and other patients.[9,10,15,16-23] There is no standard method for reporting the outcome of lower extremity vascular reconstructions. Most studies only measure the effectiveness and durability of IAR for CLI in technical terms as patency and limb salvage (defined as preservation of the affected limb with no need for major amputation),[3,5,7,9-12,15,16-23] neglecting such clinical parameters as amputation-free survival (defined as survival with a saved functional limb).[6,8,22] While the former are the most important objective of the surgery, the latter would be the main goal from the patient's point of view. Given the conflicting data on the technical outcomes and amputation and mortality risks after IAR

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for CLI, we wondered whether diabetic patients undergoing IAR for CLI fared worse than other patients.

METHODS

Patients. Details of all consecutive patients undergoing primary IAR for PAD at our tertiary referral center between 1995 and 2011 were stored prospectively in a vascular registry. For the purpose of the study, the registry was queried to identify diabetic and other patients treated up until December 2011. Type 1 and type 2 diabetic patients were considered as a single group because there were no differences in their demographic and clinical characteristics at presentation. The following data were considered: patient demographics, risk factors, indication for revascularization, inflow source and outflow target vessel, type of conduit, and adverse outcomes. An electrocardiogram (ECG) was obtained for each patient, and any past myocardial infarction (MI), congestive heart failure, and/or angina were recorded. Patients who had an uneventful clinical history and normal ECG results underwent no further work-up; for the other cases, our consultant cardiologist decided whether echocardiograms and/or dipyridamole thallium scans were warranted. All patients underwent preoperative standard biplanar arteriography, magnetic resonance angiography, or computed tomography angiography, or a combination thereof, to confirm the clinical and vascular laboratory diagnosis of PAD (based on arterial mapping with duplex ultrasonography and measuring the ankle-brachial index [ABI]) and plan surgery. All patients with foot lesions were treated on the basis of a standard protocol.[24]

Surgical technique. All revascularizations were completed using a single-team approach for arterial dissection and vein harvesting when an autologous vein was used. The preferred conduit was the great saphenous vein (SV), which was harvested whenever feasible—judging from venous mapping by duplex scan and confirmed to be appropriate when examined directly during surgery—and the reversed SV bypass was the surgeon's personally preferred procedure. If the ipsi- or contralateral great SV was unsuitable or not totally available, and spliced veins (great/small SV and arm vein) were unavailable, then the surgeon opted for a 7- or 8-mm polytetrafluoroethylene (PTFE) graft (thin-walled expanded PTFE [Gore-Tex; W. L. Gore, Flagstaff, Ariz]) instead. If the surgeon was able to confirm preoperative angiographic findings of the superficial femoral artery or the popliteal artery sufficing for inflow, then a short bypass revascularization was performed, exposing the chosen inflow artery in the usual way. All distal anastomotic sites below the knee underwent standard vein patch angioplasty no longer than 3 cm, as described elsewhere.[25] The vein for the patch was obtained from wherever one was available (eg, saphenous remnants, veins harvested from an arm under local anesthesia, or SV collaterals). Revascularization was always completed with patients under regional anesthesia (epidural or spinal) and administering intravenous unfractionated heparin (5000 U) before clamping; heparin was not reversed with protamine. Intraoperative contrast or duplex scan arteriography was not used. Heparin infusion is started 6 to 10 hours postoperatively, with oral warfarin administered on the first postoperative day, regardless of the conduit used. Warfarin treatment was then continued for 6 months, aiming to achieve a normalized ratio of two to three in most cases; aspirin (100 mg a day) was prescribed when warfarin was withdrawn. After 6 months, 100-mg aspirin was taken daily. Patients who are already taking statins, beta-blockers, or angiotensin-converting enzyme inhibitors, or on a diet rich in omega-3 fatty acids continued to take their treatment during the postoperative period.

Perioperative cardiac complications were classified by the consultant cardiologist and included (1) MI with a diagnosis based on creatine kinase levels and ECG findings; (2) pulmonary edema confirmed by chest radiography; (3) documented ventricular fibrillation or primary cardiac arrest; and (4) new congestive heart failure requiring a pacemaker. A postoperative ECG was routinely obtained in all patients with a history of coronary artery disease, congestive heart failure, or arrhythmia (rhythm other than sinus), and cardiac isoenzymes were obtained in all patients who had new findings at postoperative ECG.

Postoperative surveillance. All patients had a clinical examination with duplex scans and their ABI measured at the time of discharge, then at 1 and 6 months after surgery, and every 6 months afterward. A color duplex scan of the inflow artery, the entire conduit, both anastomoses, and the initial portion of the outflow artery was always performed as part of their follow-up. A palpable distal pulse, the ABI, or a patent graft on duplex scan was used to judge the patency of the graft. When any stenoses were discovered on duplex scanning, arteriography or computed tomography angiography were used to confirm the finding, and they were repaired electively when imaging indicated a more than 50% reduction in diameter.

After surgery, patients were examined as often as necessary until their wounds had healed completely, and this process was recorded in terms of any wound-related complications that prompted readmission to hospital, redo surgery, or extra treatments (antibiotics or a nurse's visiting at home), as well as the time taken for surgical incisions and ischemic wounds requiring arterial reconstruction to heal. Secondary procedures needed to treat ischemic ulcers or gangrene (eg, debridement or toe amputation) were also included in calculating the total time taken for ischemic wounds to heal. If the complete treatment of the original ischemic lesions also involved minor toe or foot amputations or debridement after the arterial reconstruction, they were seen as forming part of the primary procedure, not as redo surgery. The criteria adopted in our analysis were chosen so as to comply with the standards of the Ad Hoc Committee of the Joint Council of Vascular Societies for Reports Dealing with Lower Extremity Ischemia.[26]

Statistical analysis. Continuous data were compared with Student *t*-test, frequencies and categorical data with the χ^2 or Fisher exact test, as appropriate. Primary patency

Table I. Demographics, risk factors, comorbidities, and clinical presentation

	Total	*DM*	*nDM*	P *value*
Lower extremity revascularizations	1407 (100)	705 (50.2)	702 (49.8)	
Patients	1310 (100)	643 (49.0)	667 (51.0)	
Male	833 (63.6)	418 (65.0)	415 (62.2)	.29
Age, years		72.9 ± 9.8	75.7 ± 6.9	<.001
Hyperlipemia[a]	794 (60.6)	411 (63.9)	383 (57.4)	.01
Hypertension[b]	858 (65.5)	439 (68.3)	419 (62.8)	.03
Smoking history[c]	709 (54.1)	358 (55.7)	351 (52.6)	.27
CKD (creatinine >2.0 mg/dL)	146 (11.1)	85 (13.2)	61 (9.1)	.02
Cardiac disease	677 (51.6)	354 (55.0)	323 (48.4)	.01
Prior MI	365 (27.9)	180 (28.0)	185 (27.7)	.91
Prior PTA stenting/CABG	255 (19.5)	129 (20.0)	126 (18.9)	.59
Prior inflow procedures	208 (15.8)	103 (16.0)	105 (15.7)	.89
History				
Pulmonary disease	219 (16.7)	111 (17.2)	108 (16.2)	.60
Stroke	143 (10.9)	76 (11.8)	67 (10.0)	.30
Clinical presentation				
Rest pain	359 (25.5)	138 (19.6)	221 (31.5)	<.001
Nonhealing ulcer	535 (38.0)	289 (41.0)	246 (35.0)	.02
Gangrene	513 (36.5)	278 (39.4)	235 (33.5)	.02
ABI measurement		0.51 ± 0.36 (0.32-0.55)	0.43 ± 0.24 (0.36-0.46)	<.001

ABI, Ankle-brachial index; *CABG,* coronary artery bypass grafting; *CKD,* chronic kidney disease; *DM,* diabetes mellitus; *MI,* myocardial infarction; *nDM,* no diabetes mellitus; *PTA,* percutaneous transluminal angioplasty; *SD,* standard deviation.
Continuous data are presented as mean ± standard deviation (range) and categoric data as number (%).
[a]Arterial pressure >160/90 mm Hg or blood pressure treated with medication.
[b]Serum concentration of cholesterol >6.5 mmol/L or triglycerides >2.0 mmol/L.
[c]Current use or cessation within the last 5 years.

(uninterrupted patency of the original graft with no further intervention); assisted primary patency (patency supported by simple measures, primarily percutaneous transluminal angioplasty [PTA], or patch angioplasty); secondary patency (patency of the thrombosed original graft kept patent by thrombectomy, thrombolytic therapy, PTA, patch angioplasty, and proximal/distal graft extension); limb salvage; amputation-free survival; and survival rates were calculated using the actuarial life-table method (Kaplan-Meier analysis), and curves were compared using the Mantel-Cox log-rank test. Cox proportional hazard analysis was used to see which statistically or marginally significant factors at univariate analysis could influence outcomes, calculating the odds ratio with 95% confidence intervals. All tests were two-tailed and statistical significance was inferred at a *P* value of less than .05. Since each perioperative and late outcome was correlated with the surgical procedure, and patients undergoing bilateral IAR were exposed to twice the risk of graft failure or limb loss, several items of data were analyzed vis-à-vis surgical procedures instead of patients.

RESULTS

During the study period, 1407 IARs were performed for CLI in 1310 patients by the same surgeon at our center; 643 patients (48%; 705 IARs) were diabetic and 667 (702 IARs) were not. Staged bilateral IARs were performed in 97 patients (62 of them diabetic). Another 181 patients underwent 215 IARs (34 bilateral) for claudication and were not considered for this analysis. Arterial reconstructive surgery was not considered for 54 other patients who were mentally impaired (n = 37) or had a life expectancy of less than 1 year (n = 17) and who were bedridden or nonambulatory, and 87 (68 of them diabetic) with extensive ischemic soft tissue breakdown between the calcaneus and metatarsal heads (plantar region). All the 54 former patients had necrotic ulcers or gangrene; primary amputations were needed to treat their disease in 33 cases, whereas the other 21 had major amputations, which were usually performed no more than a month after percutaneous procedures had proven ineffectual. Among the latter 87 patients with extensive tissue loss in the plantar region, 48 underwent early major amputation (within 30 days), whereas in 39, it was delayed after a primary percutaneous intervention had failed. The patients referred for primary amputation at our institution formed a different cohort with no scope revascularization or ultimate ambulation, and they were transferred to general surgery or orthopedic units. Table I summarizes the demographics, risk factors, comorbidities, and other variables for the diabetic and nondiabetic patients considered here; the former were significantly younger at presentation (72.9 ± 9.8 vs 75.7 ± 6.9; $P < .001$) and more likely to have arterial hypertension (68.3% vs 62.8%; $P = .03$), cardiac disease (55.0% vs 48.4%; $P = .01$), hyperlipidemia (63.9% vs 57.4%; $P = .01$), and chronic kidney disease (CKD; 13.2% vs 9.1%; $P = .02$). Patients who had previously undergone more proximal endovascular procedures (PTA alone or PTA and stenting of the iliac artery) to improve inflow in the ipsilateral limb were comparable in the two groups. The two groups did not differ in any of the other variables considered (Table I). The indications for surgery

Table II. Inflow sources, outflow target vessel, type of conduit, and preoperative foot care procedures

Variable	*Total, No. (%)*	*DM, No. (%)*	*nDM, No. (%)*	P *value*
Inflow sources				
Iliac/graft	195 (13.8)	90 (12.8)	105 (14.9)	.23
CFA	714 (50.7)	367 (52.0)	347 (49.4)	.32
DFA	75 (5.3)	32 (4.5)	43 (6.1)	.18
Distal SFA/AK popliteal	260 (18.5)	139 (19.7)	121 (17.2)	.24
BK popliteal	111 (7.9)	57 (8.0)	54 (7.7)	.78
TPT/tibial	52 (3.7)	20 (2.8)	32 (4.5)	.09
Outflow vessel target				
AK popliteal	364 (25.9)	161 (22.8)	203 (28.9)	.009
BK popliteal/TPT	358 (25.4)	167 (23.7)	191 (27.2)	.13
Tibial	515 (36.6)	279 (39.6)	236 (33.6)	.02
Proximal third	196 (13.9)	102 (14.5)	94 (13.4)	.56
Mid-third	88 (6.2)	48 (6.8)	40 (5.7)	.39
Distal third	231 (16.4)	129 (18.2)	102 (14.5)	.06
Inframalleolar artery	170 (12.1)	98 (13.9)	72 (10.2)	.03
Bypass procedure conduit				
Reversed autogenous GSV	1118 (79.4)	569 (80.7)	549 (78.2)	.24
In situ	27 (1.9)	12 (1.7)	15 (2.1)	.55
Spliced vein (GSV, SSV, arm)	40 (2.8)	17 (2.4)	23(3.2)	.32
Composite (vein/PTFE)	48 (3.4)	26 (3.7)	22 (3.1)	.56
PTFE	174 (12.4)	81 (11.5)	93 (13.2)	.31
Preoperative foot care procedures				
Drainage	170 (12.1)	99 (14.0)	71 (10.1)	.02
Debridement	215 (15.3)	124 (17.6)	91 (12.9)	.01

AK, Above-the-knee; *BK,* below-the-knee; *CFA,* common femoral artery; *DFA,* deep femoral artery; *DM,* diabetes mellitus; *GSV,* great saphenous vein; *nDM,* no diabetes mellitus; *PTFE,* polytetrafluoroethylene; *SFA,* superficial femoral artery; *SSV,* small saphenous vein; *TPT,* tibial-peroneal trunk.

are shown in Table I. Tissue loss was significantly more common among the diabetics in the subset of nonhealing ulcer (41% vs 35%; $P = .02$) or gangrene (39.4% vs 33.5%; $P = .02$), whereas rest pain was significantly more common in nondiabetics (31.5% vs 19.6%; $P < .001$). In both groups, the most frequent inflow sources were the common femoral artery and the superficial femoral artery or above-the-knee popliteal artery (52% and 19.7% in diabetics, 49.4% and 17.2% in nondiabetics, respectively), whereas tibial and inframalleolar arteries were used as target outflow vessels in more than one-half of the diabetic group, reflecting the different patterns of disease in both groups (Table II). The reversed autogenous great SV was used for most revascularizations (81% in the diabetic group and 78% in the other group); there was no difference between the groups in the use of in situ or spliced veins or composite or prosthetic conduits (Table II). Preoperative foot care procedures (ie, drainage or debridement) were needed in significantly more diabetic patients (14% vs 10%; $P = .02$; and 17.6% vs 12.9%; $P = .01$, respectively).

Perioperative mortality and morbidity data. Table III details the perioperative outcomes. There were no perioperative deaths. Diabetic patients had a significantly higher incidence of major (16.7% vs 11.8%; $P = .02$) and minor complications (9.7% vs 6.5%; $P = .02$), but the differences failed to reach significance when each systemic or local complication was considered separately. Fifty-seven grafts failed and/or required revision within the first 30 days following the initial operation (32 in the diabetic group and 25 in the nondiabetic group) because of graft thrombosis. Eight of the thrombosed grafts were not revised owing to a poor target vessel (n = 6) or patients' refusal (n = 2), and 17 of the revised grafts thrombosed again in the perioperative period, resulting in 25 major amputations (Table III). Flow was restored and maintained in 32 grafts. An additional 33 grafts (14 in the diabetic group and 19 in the nondiabetic group) were identified as being at high risk for failure using duplex ultrasonography in the immediate postoperative period; operative revision was performed for 19 grafts, PTA was used in 9, and 5 were treated with a combination of PTA and operative revision. The diabetic group had more additional local procedures (26.5% vs 12.9%; $P < .001$) and minor amputations (27.5% vs 22.5%; $P = .03$), whereas no differences emerged between the two groups in terms of the improvement in postoperative ABI measurements.

Long-term outcomes. Of the 1310 patients alive 30 days after IAR, 42 (3.2%, 42 IARs) were lost to follow-up, so 1268 patients (96.8%, 1365 IARs) completed the follow-up, and 625 of them (687 IARs) were diabetic. The median follow-up was 6.3 years in the diabetic group (mean, 7 ± 2.2; range, 0.1-17 years) and 7.1 years in the other group (mean, 7.8 ± 2.6; range, 0.1-17 years). The two groups were stratified by vein or prosthetic graft to establish whether this might influence the technical outcome. Figs 1-6 show details of Kaplan-Meier life-table analyses on primary patency, assisted primary patency, secondary patency, limb salvage, survival, and amputation-free survival rates for the diabetic and nondiabetic groups, before and after stratifying patients by type of conduit.

Table III. Perioperative (30-day) outcomes

	Total	*DM*	*nDM*	P *value*
Death	0			
Systemic complications	205 (14.6)	118 (16.7)	87 (11.6)	.02
Nonfatal MI	39 (2.8)	24 (3.4)	15 (2.1)	.14
Renal failure	29 (2.0)	17 (2.4)	12 (1.7)	.35
Pneumonia	53 (3.8)	30 (4.2)	23 (3.2)	.33
Arrhythmia	84 (6.0)	47 (6.7)	37 (5.2)	.27
Graft thrombosis	57 (4.0)	25 (3.5)	32 (4.5)	.33
Vein	21 (1.5)	9 (1.3)	12 (1.7)	.50
PTFE	36 (2.5)	16 (2.2)	20 (2.8)	.49
Major amputation	25 (1.8)	17 (2.5)	8 (1.3)	.07
Minor complications	115 (8.1)	69 (9.7)	46 (6.5)	.02
Wound hematoma/dehiscence	45 (3.2)	27 (3.8)	18 (2.5)	.17
Inguinal lymphocele	62 (4.4)	36 (5.1)	26 (3.7)	.20
Wound infection	8 (0.5)	6 (0.8)	2 (0.2)	.28
Additional local procedures	278 (19.7)	187 (26.5)	91 (12.9)	<.001
Drainage	60 (4.2)	36 (5.1)	24 (3.4)	.11
Debridement	218 (15.5)	151 (21.4)	67 (9.5)	<.001
Minor amputations	352 (25.0)	194 (27.5)	158 (22.5)	.03
Toe(s), ray(s)	254 (18.0)	140 (19.8)	114 (16.2)	.08
Transmetatarsal	98 (7.0)	54 (7.7)	44 (6.3)	.30
ABI measurement		0.84 ± 0.17 (0.75-0.90)	0.83 ± 0.13 (0.77-0.89)	.21

ABI, Ankle-brachial index; *DM,* diabetes mellitus; *MI,* myocardial infarction; *nDM,* no diabetes mellitus; *PTFE,* polytetrafluoroethylene; *SD,* standard deviation.

Continuous data are presented as mean ± standard deviation (range) and categoric data as number (%).

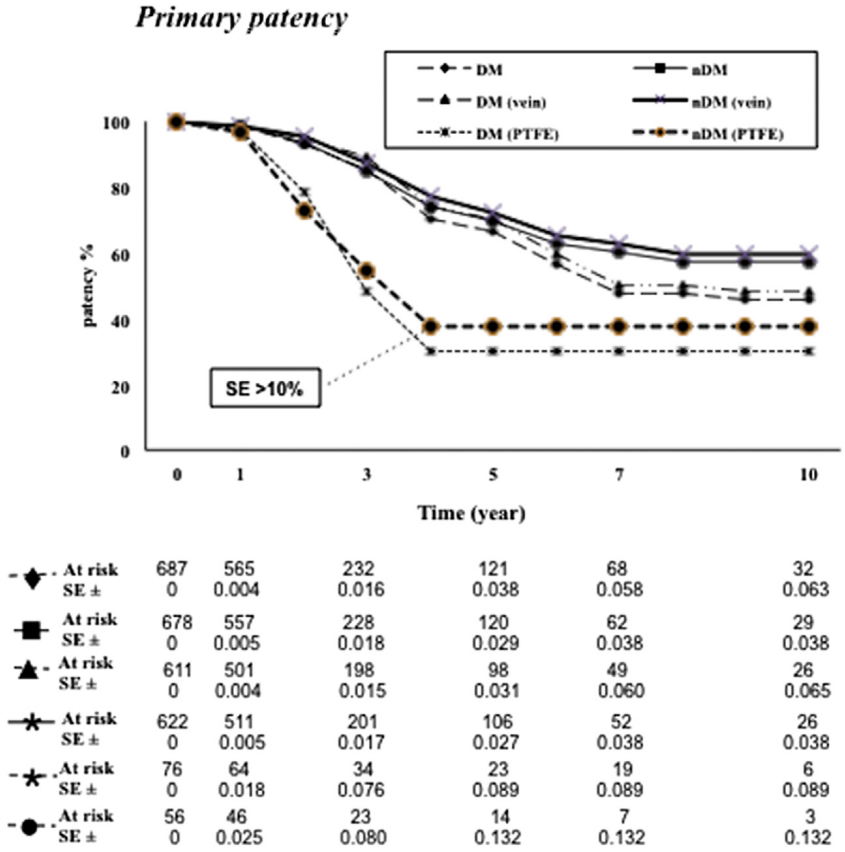

Fig 1. Kaplan-Meier life-table analysis of primary patency rates for diabetes mellitus (*DM*) and no diabetes mellitus (*nDM*) patients (odds ratio [OR], 1.20; 95% confidence interval [CI], 0.97-1.52; log-rank test, $P = .09$), for DM and nDM patients using vein graft (OR, 1.19; 95% CI, 0.94-1.54; log-rank test, $P = .13$) or polytetrafluoroethylene (*PTFE*) graft (OR, 1.03; 95% CI, 0.60-1.77; log-rank test, $P = .89$). Raw number of the limbs at risk and the standard error (*SE*) analyzed for each interval are shown for each subgroup. The SE exceeds 10% after 4 years only in the nDM group using PTFE graft.

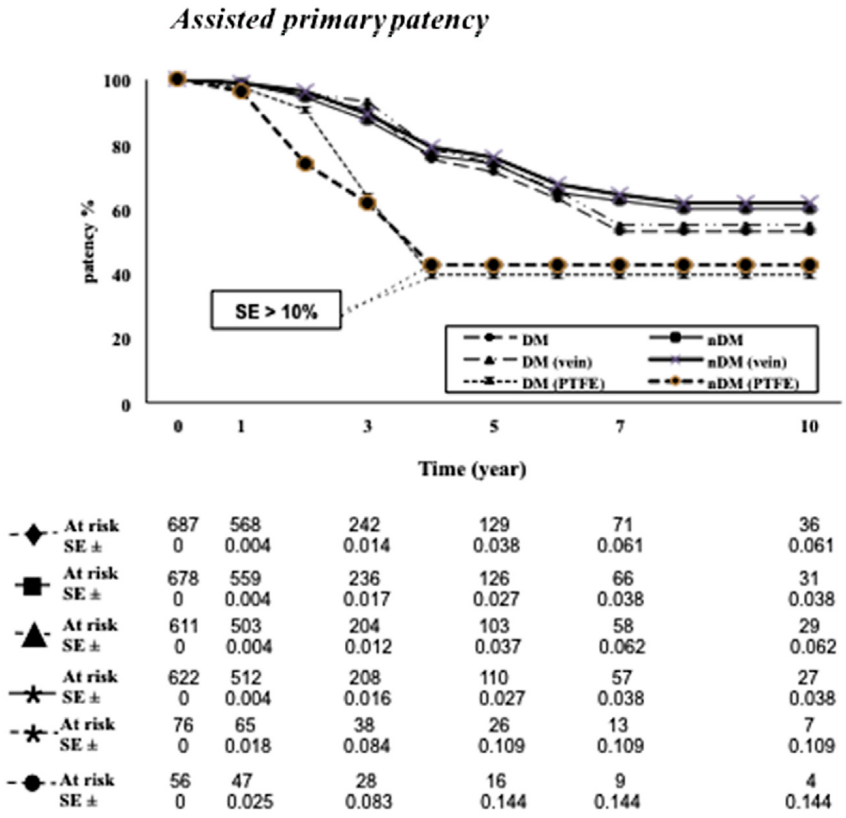

Fig 2. Kaplan-Meier life-table analysis of assisted primary patency rates for diabetes mellitus (*DM*) and no diabetes mellitus (*nDM*) patients (odds ratio [OR], 1.06, 95% confidence interval [CI], 0.83-1.36; log-rank test, $P = .60$), for DM and nDM patients using vein graft (OR, 1.07; 95% CI, 0.82-1.40; log-rank test, $P = .57$) or polytetrafluoroethylene (*PTFE*) graft (OR, 0.83, 95% CI, 0.44-1.54; log-rank test, $P = .56$). Raw number of the limbs at risk and the standard error (*SE*) analyzed for each interval are shown for each subgroup. The SE exceeds 10% after 4 years in the DM and nDM groups using PTFE graft.

At 5 and 10 years, the primary patency rates were similar for the diabetic and nondiabetic patients (65% and 46% vs 69.5% and 57%; log-rank test, $P = .09$), whatever the type of conduit used (Fig 1). The 5- and 10-year assisted primary patency rates were 72% and 53% for the diabetics and 74% and 60% for the nondiabetics (log-rank test, $P = .60$), with no significant difference between the groups even after stratifying patients by conduit (Fig 2). All the lesions involved were detected on duplex imaging and were usually intrinsic defects distributed along the length of the failing but still patent graft. Graft revisions mainly involved thrombectomy and/or lysis, percutaneous vein graft dilation, and patch angioplasty. At 5 and 10 years, the secondary patency rates were comparable (76% and 60% in the diabetics vs 80% and 68% in the others; log-rank test, $P = .20$), regardless of the type of conduit (Fig 3). In most of the failed grafts, the failure was due to outflow or inflow disease secondary to myointimal proliferation and hyperplasia or the progression of atherosclerotic lesions. Graft patency was restored with thrombectomy/lysis, until a satisfactory runoff was observed, and a distal extension of the revascularization with a "jump" vein graft in cases of outflow disease, or revision (proximal graft extension) in the cases of inflow disease. Some failed IARs required operative revision only (thrombectomy) or thrombolytic therapy with urokinase, providing there was no underlying anatomic defect or no atherosclerotic disease adjacent to the graft responsible for graft failure, which was presumably related to a decrease in blood flow in a poor runoff bed. Overall, 109 major amputations were performed (23% of them during the perioperative period) with no significant differences between the diabetic and nondiabetic groups (8.4% vs 7.5%; $P = .53$) and the use of vein (8.3% vs 7.4%; $P = .60$) or PTFE conduits (9.2% vs 8.9%; $P = .95$). No major amputation was necessary during the follow-up of above-the-knee IARs. Twenty-one (19.2%) major amputations (18 in diabetic patients and 3 in nondiabetic patients; $P = .003$) were needed because of persistent foot infections and/or osteomyelitis despite a patent graft and occurred between 8 and 18 months after surgery. At 5 and 10 years, the limb salvage rates were 88% and 76%, respectively, in the diabetic patients, 91% and 83% in nondiabetic patients (log-rank test, $P = .12$), and no significant difference emerged after stratifying patients by type of conduit (Fig 4). The 5- and 10-year survival rates were 51% and

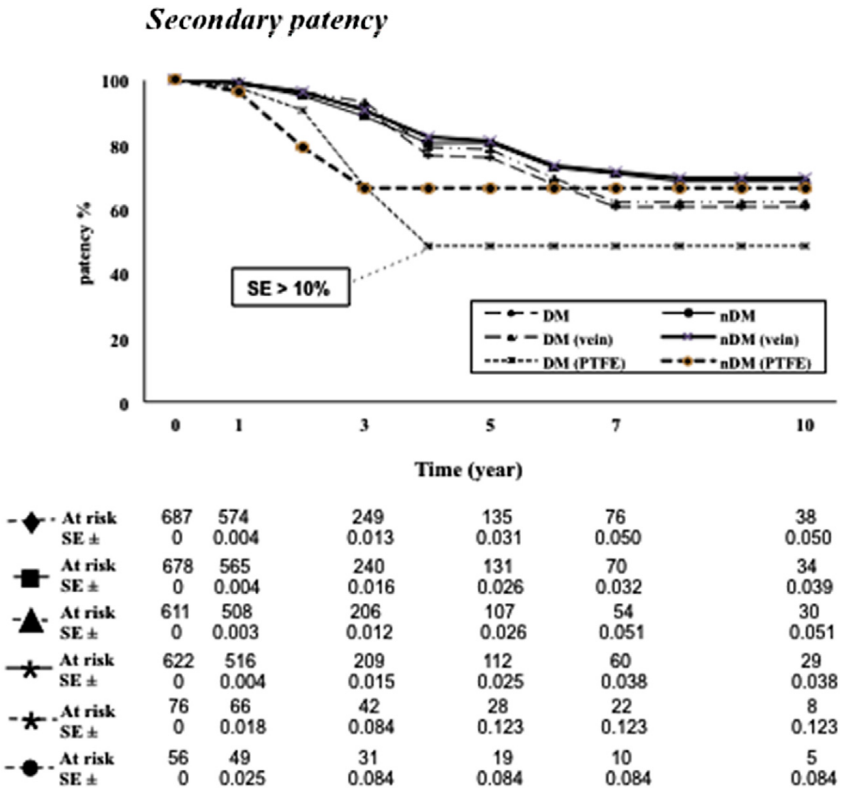

Fig 3. Kaplan-Meier life-table analysis of secondary patency rates for diabetes mellitus (*DM*) and no diabetes mellitus (*nDM*) patients (odds ratio [OR], 1.18; 95% confidence interval [CI], 0.91-1.56; log-rank test, $P = .20$), for DM and nDM patients using vein graft (OR, 1.19; 95% CI, 0.89-1.60; log-rank test, $P = .23$) or polytetrafluoroethylene (*PTFE*) graft (OR, 0.96; 95% CI, 0.47-1.95; log-rank test, $P = .91$). Raw number of the limbs at risk and the standard error (*SE*) analyzed for each interval are shown for each subgroup. The SE exceeds 10% after 4 years only in the DM group using PTFE graft.

34%, respectively, in the diabetic group and 57% and 38% in the nondiabetic group (log-rank test, $P = .41$; Fig 5). The main known cause of death in both groups was cardiac disease.

At 5 and 10 years, the amputation-free survival rates were 45.5% and 27%, respectively, for the diabetics, and 51% and 29% for the nondiabetics (log-rank test, $P = .19$; Fig. 6). On univariate analysis, considering all prognostic variables—age, sex, smoking, hypertension, hyperlipidemia, cardiac disease, CKD, prior MI or cardiac surgery, prior stroke or inflow procedures, inflow source and target outflow vessel, and type of conduit—as potential predictors of revascularization failure or limb loss, none of these variables influenced the outcome in either group.

DISCUSSION

Clinical and epidemiologic studies have found DM an important risk factor for PAD,[2] and patients with PAD often have cerebrovascular or coronary artery diseases that account for their poor prognosis and lower life expectancy compared with the general population.[27,28] PAD also carries a strong risk of major lower extremity amputation in diabetic people.[29] CLI is the most severe stage of overt PAD, and diabetic patients with CLI might be expected to have a worse long-term prognosis than their nondiabetic counterparts.

Our present findings indicate that diabetics can undergo IAR for CLI with technical and clinical outcomes statistically no different from those seen in nondiabetic patients, despite a significantly higher risk of nonfatal perioperative complications. Our diabetic patients were significantly younger at the time of surgery and had a higher incidence of cardiac disease, hypertension, hyperlipidemia, and CKD than our nondiabetic patients, which is hardly surprising given that hypertension and hyperlipidemia are risk factors for metabolic syndrome, and CKD is often a complication of DM.

Although cardiac disease was present in more than 50% of our patients, with high rates of prior MI and PTA/stenting or coronary artery bypass grafting, the overall incidence of perioperative nonfatal MI was only 2.8%, and its higher prevalence among diabetic patients was statistically insignificant (3.4% vs 2.1%; $P = .14$). The diabetic and nondiabetic patients' comparable rate of cardiac complications confirms other reports[10,19,22] but contrasts with the higher perioperative cardiac morbidity often encountered in diabetics[5,11] and attributed to a higher incidence of subclinical coronary artery disease that is sometimes clinically silent.[11]

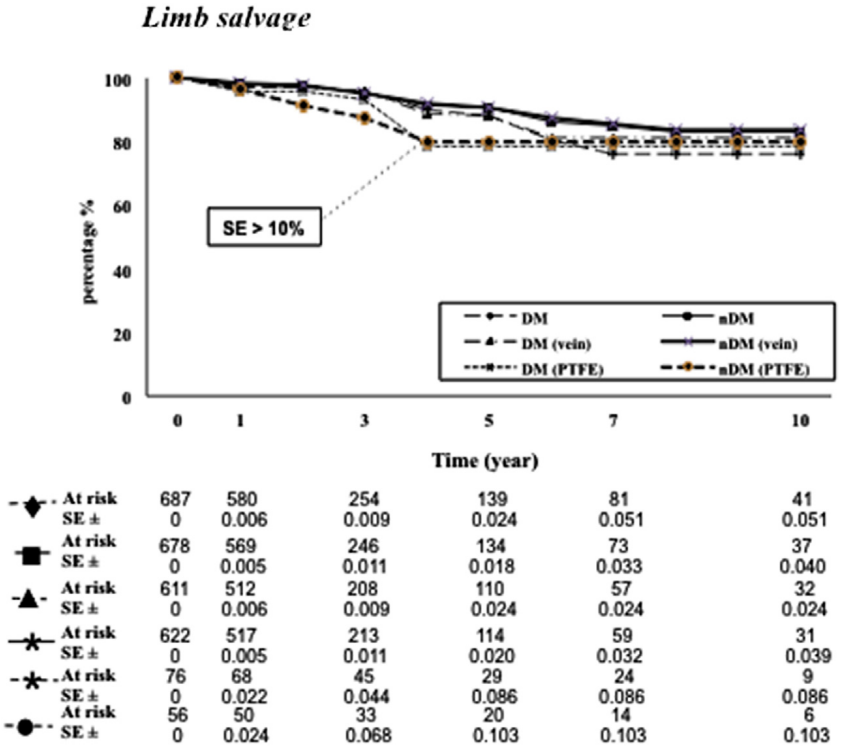

Fig 4. Kaplan-Meier life-table analysis of limb salvage rates for diabetes mellitus (*DM*) and no diabetes mellitus (*nDM*) patients (odds ratio [OR], 1.32; 95% confidence interval [CI], 0.91-1.96; log-rank test, $P = .12$), for DM and nDM patients using vein graft (OR, 1.38; 95% CI, 0.93-2.10; log-rank test, $P = .10$) or polytetrafluoroethylene (*PTFE*) graft (OR, 0.81; 95% CI, 0.26-2.48; log-rank test, $P = .71$). Raw number of the limbs at risk and the standard error (*SE*) analyzed for each interval are shown for each subgroup. The SE exceeds 10% after 4 years only in the nDM group using PTFE graft.

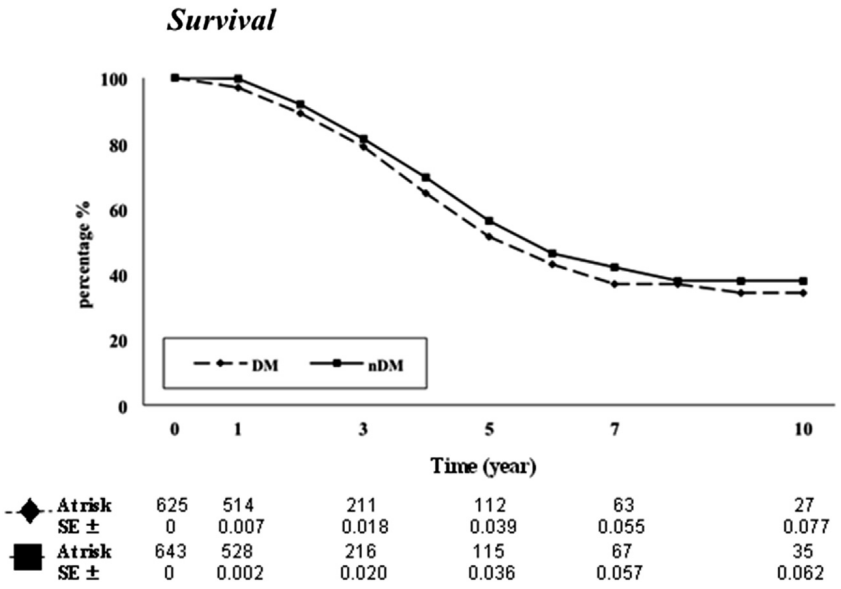

Fig 5. Kaplan-Meier life-table analysis of survival rates for diabetes mellitus (*DM*) and no diabetes mellitus (*nDM*) patients (odds ratio [OR], 1.08; 95% confidence interval [CI], 0.88-1.33; log-rank test, $P = .41$). Raw number of the patients at risk and the standard error (*SE*) analyzed for each interval are shown for each subgroup.

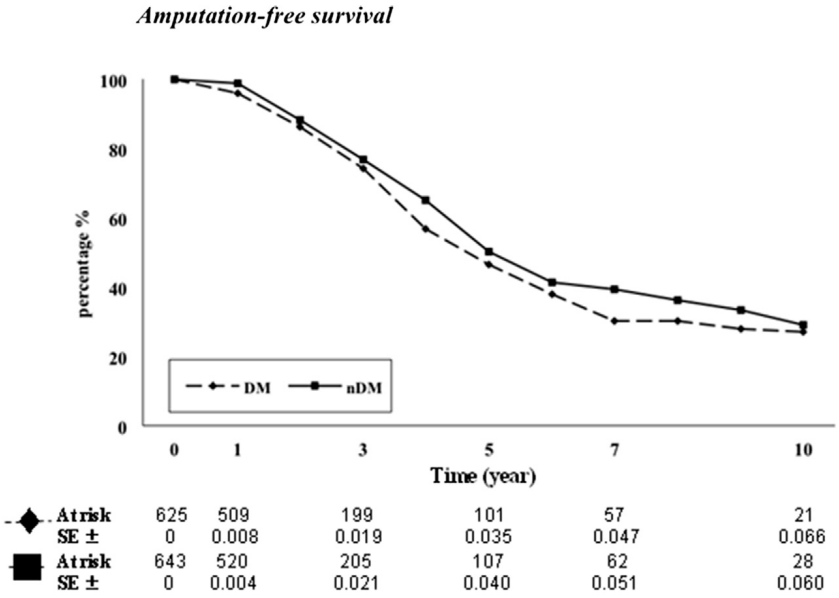

Fig 6. Kaplan-Meier life-table analysis of amputation-free survival rates for diabetes mellitus (*DM*) and no diabetes mellitus (*nDM*) patients (odds ratio [OR], 1.12, 95% confidence interval [CI], 0.94-1.35; log-rank test, $P = .19$). Raw number of the patients at risk and the standard error (*SE*) analyzed for each interval are shown for each subgroup.

There were no perioperative deaths in our series (as already reported in our recently published study in which severe claudication and CLI were indications for IAR[30]), whereas others have reported perioperative mortality rates of 0.9% to 7%, usually with no difference between diabetic and nondiabetic groups[3,15,19-22] (Table IV). We have no objective data to explain our remarkable results in terms of a low perioperative cardiac morbidity and no deaths; they may be due to our recognition of the patterns of cardiac disease in diabetic patients and particularly the higher incidence of silent coronary ischemia[31] and higher likelihood of congestive heart failure in such patients,[32] prompting the use of lower cardiac stress testing thresholds and an aggressive approach to invasive perioperative cardiac monitoring.[33] Our nil perioperative mortality is comparable with the 0.9% 30-day mortality rate reported in a consecutive series of 795 infrapopliteal revascularizations performed for CLI in diabetic patients,[20] and other authors reported the same 0.9% in their series of 228 pedal bypass reconstructions for CLI in diabetic (n = 170) and nondiabetic patients (n = 58).[19]

Although diabetic patients' significantly more advanced disease at presentation might be expected to coincide with worse technical outcomes, this was not true of our sample. The diabetics fared just as well in IAR patency and limb salvage rates as their nondiabetic counterparts, even after stratifying by type of conduit. These findings correlate well with other reports on the impact of DM on conventional technical outcome measures[9,10,15,17-23] but contrast with worse patency rates and higher limb loss rates recorded in diabetic patients[5-8,11] attributable to a poor infrageniculate runoff (a marker of more severe disease), late surgery, and often broad tissue loss (especially with deep infection), leading to major amputation despite a patent revascularization.

Our intensive postoperative graft surveillance protocol prompted many successful prophylactic lesion revisions, explaining the marked improvement in patency rates for failing and failed revascularizations at any time points in both groups.

The incidence of limb loss was comparable in our diabetic and nondiabetic patients and is consistent with the findings in most published series.[9,10,15,17-23] The type of conduit did not influence this outcome, probably because prosthetic grafts were only used in about 10% of our IARs. Considering that 80% of diabetic and 70% of nondiabetic patients had surgery for soft tissue loss, the two groups' comparable 5- and 10-year limb salvage rates (88% and 76% in the diabetic group, 91% and 83% in the nondiabetic group) clearly demonstrate the surgical procedure's efficacy.

Contrasting with several reports[6,8-11] but consistently with others,[20] we failed to confirm any worse survival for diabetic than for nondiabetic patients with CLI. In addition, the limited use of amputation-free survival as an outcome measure in most recently published case series or trials, makes it very hard to compare the rates of diabetic and nondiabetic patients alive at 5 and 10 years with a functional limb (46% and 27% vs 50% and 29%, respectively) in the various experiences. Comparable amputation-free survival rates between diabetic and nondiabetic patients were reported in one prospective study on 44 diabetics and 69 nondiabetics, although these patients underwent combined arterial reconstruction and peripheral PTA, and they were only followed for 12 months.[22] Conversely, a population-based cohort study comparing 742 diabetic

Table IV. Results of infrainguinal arterial reconstructions (IARs) in diabetic and nondiabetic patients in the recent literature

Author	*BPG*	*VG, %*	*CLI, %*	*30-day death, %*	*% PP, years*	*% SP, years*	*% LS, years*	*% S, years*	*% AFS, years*
Karacagil[9]									
DM	120	61	91	5	46 (3)	NA	70 (3)	62 (3)	NA
nDM	212	55	68	1.4	52 (3)	NA	62 (3)	86 (3)	NA
Wolfle[10]									
DM	94	62	100	2	66 (1)	72 (1)	85 (1)	78 (1)	NA
nDM	117	67	100	1	56 (1)	63 (1)	83 (1)	95 (1)	NA
AhChong[12]									
DM	176	66	100	4	46 (4)	57 (4)	78 (5)	33 (5)	NA
nDM	89	63	100	1	34 (4)	47 (4)	81 (5)	43 (5)	NA
Rutherford[17]									
DM	104	56	85	NA	60 (3)	NA	NA	NA	NA
nDM	142	43	85	NA	42 (3)	NA	NA	NA	NA
Shah[18]									
DM	387	100	74	NA	74 (5)	NA	86 (5)	NA	NA
nDM	294	100	49	NA	76 (5)	NA	94 (5)	NA	NA
Panneton[19]									
DM	170	96	100	1.3	62 (5)	71 (5)	78 (5)	65 (5)	NA
nDM	58	97	100	1.8	50 (5)	58 (5)	78 (5)	52 (5)	NA
Akbari[20]									
DM	795	91.6	93.7	0.9	75.6 (5)	77 (5)	87.3 (5)	58.1 (5)	NA
nDM	167	88.6	82	4.2	71.9 (5)	73.6 (5)	85.4 (5)	58.0 (5)	NA
Dorweiler[21]									
DM	49	100	100	2	89 (4)	NA	87 (4)	NA	NA
nDM	0								
Awad[22],[a]									
DM	44	42	100	6.8	NA	NA	78 (1)	93 (1)	71 (1)
nDM	69	42	100	7.2	NA	NA	90 (1)	89 (1)	73 (1)
Present series									
DM	705	88.5	100	0	46 (10)	60 (10)	76 (10)	34 (10)	27 (10)
nDM	702	86.8	100	0	57 (10)	68 (10)	83 (10)	38 (10)	29 (10)

AFS, Amputation-free survival; *BPG,* bypass grafting; *CLI,* critical limb ischemia; *DM,* diabetes mellitus; *LS,* limb salvage; *NA,* not available; *nDM,* no diabetes mellitus; *PP,* primary patency; *S,* survival; *SP,* secondary patency; *VG,* vein graft.
[a]In this study, peripheral revascularizations include arterial reconstructions and endovascular procedures.

and 1098 nondiabetic patients who underwent leg bypass surgery for CLI found the diabetic patients' amputation-free survival period was significantly shorter than in nondiabetic patients (2.3 vs 3.4 years),[8] a finding consistent with the overall amputation-free survival of the Bypass vs Angioplasty in Severe Ischaemia of the Leg (BASIL) trial (55% at 3 years)[34] and of the Veterans Affairs National Surgical Quality Improvement Program (57% at 3 years).[6]

Percutaneous treatments in the peripheral circulation, especially for patients with CLI, have evolved in the last 5 years, and the outcomes have varied in the meantime. A percutaneous approach may be less traumatic than traditional bypass surgery, but periprocedural complications and 1-year mortality rates continue to be high in many series, particularly in the elderly population with distal arterial involvement. We reserve an aggressive approach in such patients, making an effort to the arterial reconstruction in any CLI patients showing an inclination to walk again, whenever their leg can be saved and the patient's general conditions allow for surgery. Endovascular procedures should always be attempted before any primary amputation (even though it is likely to be unsuccessful) in patients with multiple comorbidities whose life expectancy is poor, given there is nothing to lose by trying.

Limitations of the study. This study has several limitations to mention. First, our analysis is naturally limited by the fact that it was retrospective, even though our data were collected prospectively. Second, some say that analyzing results from only one institution is not very useful because it can only represent the experience of the authors reporting them. Our findings reflect a single surgeon's experience and, while this ensures a uniformity of surgical technique, it does not mean that it is reproducible. Third, for obvious reasons, this series did not include bedridden or nonambulatory cases, the mentally impaired, or patients whose life expectancy was less than a year. Patients with ample soft tissue loss in the plantar region were also ruled out because, judging from our experience, many such patients ultimately have major amputation after distal revascularization (usually despite a patent graft and regardless of the type of conduit) because they repeatedly develop deep infections that prevent the wound from healing completely for months, or because minor surgical revisions on more proximal parts of their feet make it difficult for them to walk. This selection bias may skew our results because, if we had considered such patients in our analysis, clinical events not associated with the arterial reconstruction per se would probably have influenced our data and our

consequent conclusions. Finally, we are well aware that our study may have considered a relatively selected patient cohort rather than a sample of the general population of CLI patients (with or without DM) also because the physicians who refer cases to our institution (a tertiary care center with a scientific interest and expertise in CLI management) for revascularization, probably already choose patients with a longer life expectancy, offering a conservative management instead (that ultimately leads to a major amputation) to patients with numerous comorbidities and poor general health. Other aspects that may have contributed to our patients' favorable outcome include the use of regional anesthesia (epidural or spinal anesthesia were used in all cases, limiting the risk of adverse postoperative events) and a relatively quick surgical procedure.

CONCLUSIONS

Judging from the results of the present study, diabetic patients undergoing IAR for CLI can have the same 5- and 10-year survival and amputation-free survival rates as their nondiabetic counterparts. The comparable technical and clinical outcomes reported here strongly demonstrate that diabetic patients with CLI can expect the same quantity and quality of life as other patients with CLI, and aggressive attempts at limb salvage in patients with DM, including distal and foot level bypass grafting, should not be discouraged.

AUTHOR CONTRIBUTIONS

Conception and design: EB, AT, GDG
Analysis and interpretation: EB, AT, GDG
Data collection: GP
Writing the article: EB, AT
Critical revision of the article: EB, AT, GDG
Final approval of the article: EB, AT, GP, FM, GDG
Statistical analysis: FM
Obtained funding: Not applicable
Overall responsibility: EB

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