Cryoplasty Versus Conventional Balloon Angioplasty of the Femoropopliteal Artery in Diabetic Patients: Long-Term Results from a Prospective Randomized Single-Center Controlled Trial

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Abstract The purpose of this study was to investigate the immediate and long-term results of cryoplasty versus conventional balloon angioplasty in the femoropopliteal artery of diabetic patients. Fifty diabetic patients (41 men, mean age 68 years) were randomized to cryoplasty (group CRYO; 24 patients with 31 lesions) or conventional balloon angioplasty (group COBA; 26 patients with 34 lesions) of the femoropopliteal artery. Technical success was defined as <30% residual stenosis without any adjunctive stenting. Primary end points included technical success, primary patency, binary in-lesion restenosis (>50%), and freedom from target lesion recanalization. Cox proportional hazards regression analysis was performed to adjust for confounding factors of heterogeneity. In total, 61.3% (19 of 31) in group CRYO and 52.9% (18 of 34) in group COBA were de novo lesions. More than 70% of the lesions were Transatlantic Inter-Society Consensus (TASC) B and C in both groups, and 41.4% of the patients in group CRYO and 38.7% in group COBA suffered from critical limb ischemia. Immediate technical success rate was 58.0% in group CRYO versus 64.0% in group COBA ($p = 0.29$). According to 3-year Kaplan–Meier estimates, there were no significant differences with regard to patient survival (86.8% in group CRYO vs. 87.0% in group COBA, $p = 0.54$) and limb salvage (95.8 vs. 92.1% in groups CRYO and COBA, respectively,

$p = 0.60$). There was a nonsignificant trend of increased binary restenosis in group CRYO (hazard ratio [HR] 1.3; 95% CI 0.6–2.6, $p = 0.45$). Primary patency was significantly lower in group CRYO compared with group COBA (HR 2.2; 95% CI 1.1–4.3, $p = 0.02$). Significantly more repeat intervention events because of recurrent symptoms were required in group CRYO (HR 2.5; 95% CI 1.2–5.3, $p = 0.01$). Cryoplasty was associated with lower primary patency and more clinically driven repeat procedures after long-term follow-up compared with conventional balloon angioplasty.

Keywords Cryoplasty · Balloon angioplasty · Femoropopliteal artery · Diabetes

Introduction

Diabetes mellitus (DM) is developing into a worldwide epidemic with an estimated prevalence of 5.4%, and >300 million people will be affected by the year 2025 [1]. DM is a well-recognized independent risk factor of atherosclerosis and peripheral arterial disease, inducing multilevel, mainly small-vessel disease of the coronary and infrapopliteal arteries [1, 2]. Owing to a higher prevalence of diabetic foot ulcers and critical limb ischemia (CLI), diabetic patients demonstrate a 5 times higher risk of amputation and a 10 times higher risk of mortality after percutaneous treatment of peripheral arterial occlusive disease (PAOD) compared with normoglycemic patients [3]. Of note, almost half of all amputees suffer from DM [4]. Interestingly, DM has been identified as an independent risk factor of recurrent occlusive disease symptoms, and there is a trend toward decreased vascular patency and higher rates of repeat intervention procedures after percutaneous or surgical revascularization of the infrainguinal arteries [5–9].

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Despite their safety and versatility, current results of minimally invasive endovascular techniques for atherosclerotic lesions in the superficial femoral (SFA) and popliteal (PA) arteries remain mediocre, with reported 2-year patency rates between 40 and 60% [10, 11]. Low primary patency and increased repeat intervention rates, mainly due to vascular restenosis by means of intimal hyperplasia and negative vessel wall remodelling, has orientated modern cardiovascular research toward new alternative techniques, such as atherectomy, laser-assisted angioplasty, covered stent-grafts, brachytherapy, and cryoplasty [12–14]. Of note, there is no controlled evidence in the literature regarding percutaneous therapies of the femoropopliteal artery in the setting of DM apart from single-center patient cohorts [15]. Especially with regard to new minimally invasive technologies, such as cryoplasty, no properly designed, randomized controlled trials are available [16, 17]. We conducted a prospective, single-center, randomized, controlled trial comparing cryoplasty with conventional balloon angioplasty for the treatment of femoropopliteal arterial occlusive disease in the demanding population of DM patients. The investigators report their immediate and long-term clinical and angiographic results.

Materials and Methods

Study Design

Institutional Review Board approval was obtained by the Hospital's Ethical and Scientific Committee. The nature of the study was explained to all potential subjects, including the fact that there would be an equal possibility that a patient could be assigned to either study arm. Patients were further informed that this was designed to be a long-term study and signed the appropriate informed consent form. The randomization was performed with pooled 1:1 envelopes, which were opened only after lesions were successfully crossed.

Study inclusion and exclusion criteria are listed in Table 1. The primary patient inclusion criteria were non-insulin (NIDDM)- or insulin-dependent DM (IDDM) and atherosclerotic peripheral arterial disease with symptoms of severe claudication or CLI (Rutherford stages 3 to 6). Hemodynamically significant stenosis ($\geq 70\%$ by visual estimation) or occlusion of the SFA and/or the PA, as documented by either digital subtraction angiography (DSA) or computed tomography angiography, was a mandatory angiographic inclusion criterion. Both de novo and in-stent restenotic (ISR) lesions were enrolled. Patients with diet-controlled diabetes, a history of severe contrast allergy or hypersensitivity, intolerance to aspirin and/or clopidogrel, systemic coagulopathy or hypercoagulation disorders, acute limb ischemia, Buerger disease, deep vein

Table 1 Inclusion and exclusion criteria

Inclusion criteria

NIDDM or IDDM

Severe claudication or CLI (Rutherford stage 3 to 6)

Stenosis $\geq 70\%$ or occlusion of the SFA and/or the PA

De novo and ISR lesions

Exclusion criteria

Diet-controlled diabetes

History of severe contrast allergy or hypersensitivity

Intolerance to aspirin and/or clopidogrel

Systemic coagulopathy or hypercoagulation disorders

Acute limb ischemia

Buerger disease

Deep vein thrombosis

Infected tissue loss

Absent pedal arch runoff

SFA superficial femoral artery, *PA* popliteal artery

thrombosis, infected tissue loss, and absent pedal arch runoff were excluded from the trial.

Procedure

All patients were premedicated with aspirin (100 mg/d) and clopidogrel (75 mg/d) for at least 3 days before the procedure. Patients who were receiving metformin for their diabetes were adequately hydrated and properly advised to temporarily modify their therapy as determined by European Society of Urogenital Radiology (ESUR) guidelines [18].

An antegrade or retrograde femoral artery access using an appropriate-size sheath (6F to 7F) was performed. A bolus dose of unfractionated heparin (3000 to 5000 IU) was administered immediately after sheath placement, and an infusion rate of 1000 U/h was maintained during the rest of the procedure. Routine endovascular maneuvers using standard guidewires and catheters were used to cross the SFA and/or the PA lesion as needed. Lesion treatment was then randomized either to (1) cryoplasty with the PolarCath balloon (PolarCath Peripheral Dilatation System; Boston Scientific, Natick, MA) or (2) conventional balloon angioplasty with commercially available semicompliant or noncompliant balloon catheters (inflation period 60 to 120 s). In all cases, balloon size was chosen according to reference vessel diameter per visual estimate. Balloon length was chosen to match lesion length, and if that was not possible, to slightly exceed it, according to routine clinical practice. Stenting was reserved for bail-out in case of elastic recoil, postdilatation residual stenosis $>30\%$, or severe flow-limiting dissection (type C). Outflow obstructive lesions of the infrapopliteal arteries were treated as

necessary to improve runoff. At the end of the procedure, hemostasis was achieved with manual compression or a closure device. Patients were routinely hospitalized overnight and discharged the next day with a prescription for dual antiplatelet therapy (75 mg/d clopidogrel and 100 mg/d aspirin) for 6 weeks and solely clopidogrel or aspirin indefinitely thereafter.

Cryoplasty Treatment

Cryoplasty therapy was performed with the use of the PolarCath Peripheral Dilatation System, which includes an over-the-wire, double-lumen dilatation balloon catheter manufactured of Pebax® (Atochem Inc, PA, USA) and an inflation system consisting of a microprocessor unit and a nitrous oxide cartridge. The cryoplasty catheter is formed by three layers (inner, middle, and outer), and its fluoroscopic visibility is attained by radiopaque markers placed in the middle layer.

Balloon inflation is achieved by a specially designed apparatus that releases liquid nitrous oxide from the specially designed high-pressure cartridge through the catheter lumen and into the lower-pressure balloon chamber, where it changes state from liquid to gas and expands its volume. The whole phenomenon is based on the Thomson-Joule effect ($\mu = \Delta T / \Delta P$). The rapid expansion of the gas volume inflates the balloon and produces a rapid decrease in temperature, thus effectively cooling the balloon surface and the adjacent vessel wall to 10°C while the inflation pressure gradually reaches 8 Atm, the pressure of which is tightly regulated by a valve mechanism attached to the double-balloon catheter. The inflation-active cooling/deflation-passive thawing time period ranges from 26 to 30 s. The technique theoretically aims at both better immediate and long-term results because cooling of the atherosclerotic plaque and its elastic components is believed to achieve a more uniform and less traumatic angioplasty, resulting in better plaque remodelling with less flow-limiting dissections and vessel wall recoiling. Several in vitro studies have shown that the specific circle of −10°C active cooling/passive thawing creates a dehydration/rehydration effect in the adjacent cells through the a change in the osmotic forces acting in the vessel area around the catheter. The whole cryoplasty procedure is believed to induce cell apoptosis (programmed cell death enhancement) rather than necrosis of the remaining endothelium and of the smooth muscle cells of the middle vessel layer and may therefore result in less inflammation, less neointimal hyperplasia, and consequently decreased vascular restenosis [19–21]. Because the time span and pressure limit of the cryoplasty catheter cannot be adjusted by the operator, a second inflation session with the same PolarCath balloon, as deemed necessary, was performed in

cases of tight resistant lesions to achieve a satisfactory final result.

Follow-Up, End Points, and Definitions

Patients were prospectively scheduled for regular clinical and angiographic follow-up visits at 6 months, 1 year, and annually thereafter unless clinical deterioration indicated differently. Patient mobility status was interrogated, and all angiographic end points were evaluated with intra-arterial DSA.

Primary end points included technical success, primary patency, binary in-lesion restenosis, and freedom from target lesion recanalization (TLR). Secondary clinical end points included 30-day complications, patient mortality, limb salvage, and minor amputation of the treated limbs. Technical success for group CRYO was defined as a successful angioplasty result with residual lesion stenosis <30% on visual estimate and without adjunctive use of an additional high-pressure balloon or bail-out stent. In group COBA, technical success was defined as a successful angioplasty result with residual lesion stenosis <30% on visual estimate and without bail-out stenting. Lesions requiring additional angioplasty with a conventional balloon because of a suboptimal postangioplasty result, even after a maximum of two cryoplasty sessions, were classified as cryoplasty technical failures.

Primary patency was defined as angiographic visualization of a nonoccluded lesion and no need for any additional repeat interventional procedure within the previously treated lesion. Absent or thread-like blood flow were classified as vascular occlusions. Binary in-lesion restenosis was defined as vascular restenosis of the treated lesion >50% threshold according to reference vessel diameter. TLR included any additional recanalization procedure within the area of the treated femoropopliteal lesion because of clinical deterioration and relapse of symptoms (i.e., clinically driven repeat procedures). The rest of the secondary clinical end points were defined according to published international guidelines and reporting standards [22].

SFA lesions were initially classified according to Transatlantic Inter-Society Consensus (TASC) guidelines. However, during data analysis of the study they were retrospectively modified according to the more recent TASC II guidelines [23]. Infrapopliteal runoff arteries were counted and graded with a simplified scoring system (0 to 2) as described elsewhere [24]. Baseline and follow-up angiographic images were reviewed by two independent expert vascular interventional radiologists using the dedicated computerized vessel analysis software of the angiography unit. A consensus was reached in case of borderline differences.

Statistical Analysis

Discrete variables were expressed as counts and percentages, and continuous variables were given as medians and interquartile ranges (IQR: i.e., between the 25th and 75th percentiles) in parentheses or as means $\pm$ SE if they passed the normality test as stated later in the text. Kolmogorov–Smirnov goodness-of-fit test was used to determine whether continuous data should be treated as originating from normal distributions. Unpaired Student *t* test was used to test the significance of difference of variables that passed the normality test. Mann–Whitney test was used for qualitative variables and for nonparametric testing of continuous variables that did not pass the normality test. Comparison of two proportions was done by testing the null hypothesis that the proportions were equal, with an appropriate quantity as a standardized normal deviate test. Life-table analysis with the Kaplan–Meier method was employed for calculation of the cumulative proportion outcomes up to 36-month angiographic and 42-month clinical follow-up time-points. Kaplan–Meier curves were compared with the log-rank test.

Results were stratified according to type of treatment (cryoplasty vs. COBA). To identify independent risk factors affecting the analyzed end points, stepwise regression analysis was performed using the Cox proportional-hazards regression model during the total follow-up period. Dependent variables were IDDM, increased serum creatinine level (>1.5 mg/dL), nicotine use (≤ 12 months), hyperlipidemia (more than mild increase) controlled with diet or drugs), initial lesion grade (stenosis or occlusion), TASC II lesion classification, lesion type (de novo or ISR), runoff score (0 to 3), heavy calcifications of the lesion, and treatment modality (cryoplasty vs. COBA). The covariates included primary patency, binary in-lesion restenosis, and TLR-free survival. The results were expressed as HRs with 95% confidence intervals (CIs) and the associated level of statistical significance. In cases of significant results, the adjusted curve plots of the identified covariate are presented. Statistical analysis was performed using the SPSS/PASW statistical software package (version 17.0; SPSS/PASW, Chicago, IL). The threshold of statistical significance was set at $p = 0.05$.

Results

Between January 2005 and October 2007, a total of 50 patients (41 men and 9 women) with a mean age of 68 ± 9.5 years (range 47 to 82), who were scheduled for percutaneous recanalization of the SFA or the PA due to PAOD, gave informed consent and were randomly assigned to one of the two groups. Twenty-four patients

(29 limbs with 31 lesions) were treated with cryoplasty (group CRYO), whereas the remaining 26 patients (31 limbs with 34 lesions) underwent conventional balloon angioplasty (group COBA) and served as the control group. The follow-up completion date was May 2009. Various balloon types commercially available in our department, including semi-compliant and noncompliant high-pressure balloons, were applied in the COBA control group as follows: (1) Ultra-Thin Diamond and Blue Max PTA; Boston Scientific, Natick, MA; (2) Profiler; Angiodynamics, Latham, NY; and (3) Cronus; Medispe WS AG, Zug, Switzerland.

Baseline demographics, anatomic lesion characteristics, and procedural variables of both groups are listed in Tables 2 and 3. The majority of the patients treated had severe intermittent claudication classified as Rutherford stage 3 (58.6% in group CRYO vs. 61.3% in group COBA, $p = 0.42$). There was an almost equal distribution of de novo and ISR lesions in both groups, but there were no

Table 2 Baseline patient demographics and clinical status

Demographics	Cryoplasty	COBA	<i>p</i>
Patients (<i>n</i>)	24	26	–
Limbs (<i>n</i>)	29	31	–
Male sex	21 (87.5)	22 (84.6)	0.38
Age (y)	65.3 ± 10.4	70.3 ± 7.8	0.12
Smoking habit	12 (50)	11 (42.3)	0.29
IDDM	10 (41.7)	9 (34.6)	0.30
Hyperlipidemia	17 (71.0)	15 (58.0)	0.16
Arterial hypertension	23 (95.8)	23 (88.5)	0.16
Carotid disease ^a	9 (37.5)	5 (19.2)	0.07
Cardiac disease ^b	7 (29.2)	10 (38.5)	0.35
Renal disease	8 (33.3)	4 (15.4)	0.06
Physical health status ^c			
ASA 1 to 2	18 (75.0)	20 (77.0)	0.43
ASA 3	6 (25.0)	6 (23.0)	0.43
Rutherford category of PAD			
Stage 3	17 (58.6)	19 (61.3)	0.42
Stage 4	10 (34.5)	6 (19.4)	0.09
Stage 5	1 (3.4)	4 (12.9)	0.09
Stage 6	1 (3.4)	2 (6.5)	0.29
CLI	12 (41.4)	12 (38.7)	0.41

Continuous data are presented as mean $\pm$ SE; categorical data are given as counts and percentages in the *parentheses*

ASA American Society of Anesthesiologists

^a Transient ischemic attack or stroke

^b History of myocardial infarction (MI) or occult MI by electrocardiogram, stable or unstable angina, controlled arrhythmia, drug-compensated congestive heart failure (CHF), poorly controlled arrhythmia, and poorly compensated CHF

^c ASA class 1 denotes a healthy individual; class 2 denotes mild systemic disease; and class 3 denotes severe but not incapacitating disease

Table 3 Procedural variables

Variables	Cryoplasty	COBA	<i>p</i>
Lesions treated (<i>n</i>)	31	34	–
TASC A	4 (13.8)	6 (19.4)	0.2
TASC B	17 (58.6)	12 (38.7)	0.06
TASC C	8 (27.6)	11 (35.5)	0.02
TASC D	0 (0.0)	2 (6.5)	0.08
De novo lesions	19 (61.3)	18 (52.9)	0.2
ISR lesions	12 (38.7)	16 (47.1)	0.2
Heavy calcifications	9 (29.0)	10 (29.4)	0.4
Initial occlusions	7 (22.6)	5 (14.7)	0.2
Mean treated lesion length (cm) ^a	11.9 ± 5.1	12 ± 6.0	0.91
Mean stented lesion length (cm) ^a	50 ± 18.5	68.3 ± 34.3	0.28
Mean balloon diameter (mm)	5.7 ± 0.65	5.7 ± 0.57	0.5
Subintimal approach	2 (6.5)	2 (5.9)	0.4
Popliteal artery	4 (12.9)	2 (5.9)	0.16

Categoric data are given as counts and percentages in *parentheses*

^a Data are presented as mean ± SD

significant differences (Table 3). Most of the lesions treated were characterized as TASC B and C lesions according to the revised classification system (86.2% in group CRYO vs. 74.2% in group COBA, $p = 0.21$). The average lesion length was 11.9 ± 5 cm in group CRYO and 12.0 ± 6 cm in group COBA ($p > 0.05$). Almost 29% of the lesions in both groups were characterized as heavily calcified, whereas a similar number of initial occlusions were treated (22.6 vs. 14.7% in groups CRYO and COBA, respectively, $p = 0.22$). Only 4 lesions were treated using the subintimal technique (6.5% in group A and 5.9% in group B, $p = 0.46$). The minority of the lesions (4 of 31 lesions [12.8% in group A] and 2 of 34 lesions [5.9% in group B], $p = 0.16$) were located in the PA. At the end of the procedure all treated limbs had at least one runoff vessel to the distal foot.

Technical success rate was similar between the two groups (58.0% in group CRYO vs. 64.0% in group COBA, $p = 0.29$). Our protocol included a balloon-inflation time of 60 to 120 seconds in group COBA, and the duration of an eventual second inflation was 120 seconds (mean time 82.9 ± 29.5). In group CRYO, more than half of the lesions (64.5%) required a second cryoplasty application due to suboptimal angioplasty result or flow-limiting dissection. In nine cases (29.0%), the additional aid of a conventional angioplasty balloon was required to achieve immediate technical success. The incidence of flow-limiting (type C) dissections was analogous in both arms (16.1% in group CRYO vs. 17.6% in group COBA, $p = 0.435$). Regarding the overall need for stenting, there was a trend toward less stent use for cases in which cryoplasty treatment was used as initial treatment (25.8 vs. 35.3% in group COBA,

$p = 0.2$). In addition, overall stent length was less in the cryoplasty group, but this was not statistically significant (mean stent length 50 mm in group CRYO vs. 68 mm in group COBA, $p = 0.28$). No immediate procedure-related complications (thromboembolic events, hemorrhage, or death) occurred. The final semiquantitative runoff score was significantly higher in group CRYO (runoff score 2 [2] vs. 1 [1, 2] in group COBA, $p = 0.002$). Immediate procedural outcomes are listed in Table 4.

Angiographic and clinical follow-up periods were similar in both patient arms: The mean angiographic follow-up period was 23.5 ± 1.9 months in group CRYO vs. 25.3 ± 2.0 months in group COBA ($p = 0.6$), whereas the mean clinical follow-up period was 32 ± 9 months in group CRYO vs. 32 ± 2 months in group COBA, respectively ($p = 0.7$), without any significant differences in patient compliance between the two groups. Only one patient (1 of 24; 4.16%) assigned to group CRYO was lost from angiographic but not from clinical follow-up after 6 months due to an ischemic stroke. After 3 years, there were no significant differences with regard to patient survival (86.8% in group CRYO vs. 87.0% in group COBA; $p = 0.54$ by log-rank test) and limb salvage (95.8 vs. 92.1% in groups CRYO and COBA, respectively; $p = 0.60$ by log-rank test), according to life-table survival analysis (Fig. 1). None of the deaths were related to the procedure. Minor amputation rates were similar in the two study arms (6.9% in group CRYO vs. 9.7% in group COBA, $p = 0.3$).

According to Kaplan–Meier estimates from bivariable survival analysis, angiographic primary patency ≤ 36 months was not significantly different between the two groups (66.6 vs. 67.6%, 59.2 vs. 54.6%, and 59.2 vs. 54.6% in

Table 4 Procedural outcomes

Outcomes	Cryoplasty	COBA	<i>p</i>
Technical success	18 (58.0)	22 (64.7)	0.4
Flow-limiting dissection (type C)	5 (16.1)	6 (17.6)	0.2
Adjunctive stent use ^a	8 (25.8)	12 (35.3)	0.2
Final runoff score ^b	2 (2–2)	1 (1–2)	0.002
Puncture-site related complications			
Major	0 (0.0)	0 (0.0)	–
Minor	1 (3.5)	1 (3.2)	0.4
Procedure related adverse events	0 (0.0)	0 (0.0)	–
Minor amputations	2(6.9)	3(9.7)	0.3
Double application of cryoplasty	20 (64.5)	–	–
COBA mean inflation time (s) ^c	–	82.9 ± 29.5	–

Categoric data are given as counts with percentages in parentheses

^a Number of cases in which stents were placed due to flow limiting dissection and/or elastic recoil

^b Median with IQR in *parentheses*

^c Data presented as mean ± SE

Fig. 1 **A** Patient survival and **B** limb salvage Kaplan–Meier analysis for groups CRYO and COBA

group CRYO vs. group COBA at 12, 24, and 36 months respectively, $p = 0.894$ by log-rank test). Numbers of lesions at risk in group CRYO were 12, 7, and 2 and in group COBA were 22, 12, and 4 at 12, 24 and 36 months, respectively. However, after adjustment for confounding factors of heterogeneity with multivariable Cox model, cryoplasty was identified as a strong independent predictor for decreased primary patency (HR 2.2, 95% CI 1.1–4.3, $p = 0.02$; Table 5 and Fig. 2). De novo atheromatous lesions were also identified as a strong independent predictor of decreased in-lesion primary patency compared with ISR lesions (HR 2.0; 95% CI 1.0–4.0; $p = 0.002$; Table 6). In-lesion angiographic binary restenosis was significantly higher in group CRYO (58.5% vs. 22.7%, 74.1% vs. 47.0%, and 100.0% vs. 78.9% [$p < 0.006$ by log-rank test] at 12, 24, and 36 months for groups CRYO and COBA, respectively) (HR 1.3, 95% CI 0.6–2.6 [$p = 0.4$ by Cox model]; Table 5 and Fig. 3A). Binary in-lesion restenosis was also adversely affected by impaired renal function (HR 2.5, 95% CI 1.4–4.6, $p = 0.002$; Table 6; Fig. 3B). Subgroup bivariable Kaplan–Meier analysis evaluating outcomes of ISR lesions failed to identify any statistically significant difference between the two groups with regard to primary patency (62.5% in group CRYO vs. 53.8% in group COBA, $p = 0.97$), restenosis (100% in group CRYO vs. 92.3% in group COBA, $p = 0.71$), and TLR-free survival (41.6 vs. 45% in groups CRYO and COBA, respectively, $p = 0.2$) at ≤ 36 months.

In addition, significantly more TLR events due to recurrent symptoms were noted in group CRYO at

≤ 36 months (48.4 vs. 26.5%, 66.5 vs. 40.4%, and 66.5 vs. 52.3% [$p < 0.04$ by log-rank test] at 12, 24, and 36 months, respectively). Cryoplasty also proved to be a highly significant predictor of increased TLR events (HR 2.5, 95% CI 1.2–5.3, $p = 0.01$ by Cox model; Table 5; Fig. 4). Smoking, renal disease, IDDM, and hyperlipidemia were also calculated as predictive factors of increased clinically driven repeat procedures (Table 6).

Discussion

More than 200 million people worldwide have DM, 90% of which is insulin-resistant type II DM [25]. It is also well known that diabetic patients demonstrate a higher prevalence of PAOD. A large pool of cardiological studies have reported a significantly higher prevalence of coronary artery disease in diabetic compared with nondiabetic patients [26]. Notably, small-vessel coronary artery disease in diabetic patients is characterized by a more diffuse distribution and calcified pattern, numerous repeat procedures of revascularization owing to increased vascular restenosis, increased rates of major adverse cardiac events, and decreased survival [26–28]. With regard to the lower extremities, diabetic patients with intermittent claudication symptoms have an increased risk of acute limb ischemia, which also entails a higher major amputation risk, 35 and 21%, respectively, according to one observational study, compared with 19 and 3% in nondiabetic patients, correspondingly [23].

Table 5 Bivariable and multivariable Cox proportional hazards regression analysis of primary end points stratified for CRYO versus COBA

Variable	CRYO (%)	COBA (%)	p^*	HR [†]	95% CI	Adjusted $p^{\dagger}$
Lesion primary patency	59.2	54.6	0.894	2.2	1.1–4.3	0.02
Lesion binary restenosis	100.0	78.9	0.006	1.3	0.6–2.6	0.4
TLR-free survival	33.5	47.7	0.04	2.5	1.2–5.3	0.01

* Calculated by log-rank bivariable analysis

[†] Cox model adjusted for IDDM, renal disease, smoking, hyperlipidemia, lesion grade, lesion type (de novo or ISR), heavy calcifications, TASC classification, and type of treatment (cryoplasty or COBA)

Fig. 2 Primary patency stratified for cryoplasty and COBA. **A** Kaplan–Meier analysis plots and **B** Cox-adjusted plots stratified for the type of treatment modality used (CRYO vs. COBA)

Table 6 Significant predictors of outcomes other than type of treatment as identified by the Cox model

Variable	Independent variable	Regression coefficient β	SE	HR	95% CI	Adjusted <i>p</i>
Lesion primary patency	<i>De novo</i> lesions	0.695	0.352	2.0	1.0–4.0	0.04
Lesion binary restenosis	Renal disease	0.923	0.303	2.5	1.4–4.6	0.002
TLR-free survival	Smoking	0.879	0.435	2.4	1.0–5.7	0.04
TLR-free survival	IDDM	−0.835	0.400	0.4	0.2–0.8	0.03
TLR-free survival	Renal disease	0.984	0.407	2.7	1.2–5.9	0.01
TLR-free survival	Hyperlipidemia	−0.908	0.379	0.4	0.2–0.8	0.01

Cox model adjusted for IDDM, renal disease, smoking, hyperlipidemia, lesion grade, lesion type (de novo or ISR), heavy calcifications, and TASC and Rutherford classifications

TLR target lesion revascularization, HR hazard ratio, IDDM insulin-dependent diabetes mellitus

Fig. 3 Angiographic binary restenosis plots. **A** Kaplan–Meier curves of cryoplasty and COBA and **B** Cox adjusted plots stratified for renal disease (initial serum creatinine level >1.5 mg/dl)

The aggressive nature of peripheral arterial disease in the setting of diabetes, by means of faster progression and wider lesion dissemination of the disease afflicting both the macrovasculature and microvasculature of the lower limbs, coupled with the rapidly increasing size of the affected population, has turned the interest of the research community toward novel therapies of revascularization [9, 11, 29]. Atherosclerosis in diabetes exhibits a phenotypically different and more aggressive behavior than in

normoglycemic patients. Diabetic vessels develop cylindrical calcifications of the media tunica, progressive intimal restenosis, and amplified rates of proliferation, adhesion, and migration of vascular smooth-muscle cells [2, 27, 28]. Patients with PAOD and diabetes experience walking difficulties and nonhealing foot ulcers not only because of inadequate blood supply to the limb and coexisting diabetic neuropathy but also due to alterations in normal muscle metabolism and glucose use [30–32]. The

Fig. 4 TLR-free survival. **A** Kaplan–Meier analysis plots and **B** Cox-adjusted plots stratified CRYO versus COBA

significant financial and social healthcare burden of diabetic vascular disease has prompted interventional specialists to apply aggressive risk-factor modification and extensive percutaneous recanalization procedures to prevent limb loss, increase vascular patency with less repeat procedures, and ultimately augment overall survival in this demanding patient group [9, 30].

The intense restenotic response due to neointimal hyperplasia and negative remodeling, which results in poor vascular patency after angioplasty and/or stenting of the SFA and/or PA of arteries in case of diabetes, has motivated us to study the potential therapeutic benefit of cryoplasty in these lesions. We conducted a prospective, single-center, randomized, controlled study comparing cryoplasty with standard balloon angioplasty. The initial hypothesis was that the presumed more uniform and less traumatic immediate performance of cryoplasty, in synergy with the induction of the apoptotic effect, would result in less neointimal hyperplasia and, as a consequence, better immediate and long-term angiographic and clinical results. Apart from a few uncontrolled cohort studies or case series, scientific data about the actual value of cryoplasty in terms of immediate technical success and late outcomes are scarce [16, 17]. To our knowledge, this is the first prospective randomized trial investigating the merits of this relatively new procedure in the demanding setting of diabetic femoropopliteal occlusive disease.

According to our results, cryoplasty was a safe procedure when applied in the femoropopliteal artery of diabetic patients and performed equally well compared with conventional balloon angioplasty with regard to immediate technical success (58.0 vs. 64.7%, $p = 0.4$) and long-term limb salvage (95.8 vs. 92.1%, $p = 0.54$). However, the tested hypothesis, i.e., that cryoplasty would result in superior immediate technical success rates with less stent use due to flow-limiting dissection and/or elastic recoil, was not verified. In our study, application of cryoplasty showed only a nonsignificant trend toward less bail-out stenting (25.8% in group CRYO vs. 35.3% in group COBA). Of note,

nonetheless, despite the almost equivalent length of treated lesions and the number of stents used, there was a nonsignificant trend toward less overall stent length in group CRYO compared with control group COBA. Hence, one could argue that the notion of cryoplasty achieving more uniform plaque remodeling with less vessel wall barotrauma was neither confirmed nor actually rejected in this controlled trial. Literature reports about adjunctive bail-out stenting after cryoplasty are variable and range from 8.9% up to 33.3% in case of treatment of occluded lesions [16].

In a significant number of lesions that were particularly difficult to treat (20 of 31 [64.5%]), probably because of the heavily calcified vessel wall, two consecutive cryoplasty applications were needed. This underscores the increased difficulty that heavily calcified diabetic lesions present to cryoplasty treatment. We speculate that the lower pressure (≤ 8 Atm) and the compliant nature of the cryoplasty catheter, which can be attributed to the compressible gas used for the inflation, compared with the uniformly liquid-inflated noncompliant or semicompliant conventional balloons, may result in more immediate technical failures, especially in the setting of resistant, eccentric, fibrotic, or fibrocalcific lesions. It should be stressed that although many operators may anecdotally perform multiple repeated cryoplasty sessions in the same lesion, i.e., during the same procedure, because of an initial suboptimal angioplasty result or in case of tandem lesions, there are no published data about the actual biomechanical effects as well as the induction of apoptosis after consecutive applications of freezing–thawing to the vessel wall [33, 34].

The Cox model identified a highly significant 2.2-fold increased hazard for reocclusion when cryoplasty was applied. Likewise, cryoplasty was a strong independent predictive factor associated with 2.5 times more events of repeat procedures of revascularization (TLR) in both bivariable and multivariable analysis. Moreover, the binary angiographic restenosis rate was significantly higher in the cryoplasty group, but this result was not confirmed by the adjusted p value of the Cox model, which indicated

impaired renal function as the only independent factor affecting restenosis. Arguably, however, the results reported herein are only applicable to the specific long, heavily calcified lesions of diabetic patients. In vivo experimental studies have also reported that cryoplasty induces probably more necrosis and inflammation, rather than apoptosis of smooth muscle cells, which are followed by a late aggressive neointimal hyperplastic response and vasoconstrictive wall remodeling [21, 35]. Of further interest, in vitro evaluation of cryoplasty in a calcified arterial wall with finite-element heat and mass-transfer computational models showed that temperatures as low as -110°C may be necessary for effective cryothermal plaque ablation, which obviously is not feasible in the setting of a real clinical scenario [36].

Long-term primary patency probability rates of almost 60% in both groups (59% in group CRYO vs. 55% in group COBA at 3 years) are similar to previously published data of endovascular SFA treatment [10, 11, 13, 14, 29]. We believe that these results are in line with the fact that the majority of the included patients suffered from severe intermittent claudication as well as high TASC grade and increased calcification of the treated lesions [10, 11, 37]. Furthermore, multivariable analysis with the Cox model isolated de novo atheromatous lesions, with almost two times higher risk of reocclusion, as a strong independent predictor of decreased vascular primary patency. Because the performance of cryoplasty was superior for ISR than for de novo lesions, this could encourage further investigations for the use of this technology in this particular group of revascularization procedures.

Recently published mid-term results from another prospective, single-center, randomized, controlled trial evaluating cryoplasty in the PA were similar to those reported herein. The investigators randomized 86 patients with atherosclerotic stenoses or occlusions of the PA between cryoplasty and conventional angioplasty treatment. Despite a nonsignificant trend toward higher 9-month primary patency (79% after CRYO vs. 67% after COBA), cryoplasty posed comparable initial grade C dissections and adjunctive stent placement with significantly inferior immediate technical success (35 vs. 54% for conventional angioplasty) [38]. In line with the previously mentioned data, the pioneering investigators of cryoplasty critically reappraised their initial results in the femoropopliteal arteries because of poor long-term freedom of restenosis, which decreased to $<50\%$ at 24 months. In a recent report, they explicitly stated that considering its additional costs, they had abandoned use of cryoplasty in their everyday practice [39, 40].

In contrast, 12-month follow-up results from the BTK Chill Trial, which evaluated cryoplasty in the infrapopliteal arteries of CLI patients, reported high rates of acute

technical success and major amputation-free interval (97.3% and 78.5%, respectively) followed by a low percentage of clinically driven repeat procedures (21% at 12 months) [41]. Almost 70% of the patients had diabetes. The above-mentioned differences in anatomic success and TLR-free interval rates between femoropopliteal and infrapopliteal cryoplasty trials could be accredited to smaller vessel diameter and different biomechanics of the below-the-knee anatomic region compared with the femoropopliteal artery.

Study limitations include the relatively small number of patients assigned to each group (thus underpowering the study for the extraction of more statistically significant results and better stratification of risk factors between the two groups) as well as the inherent bias of the single-center nature of the study. We should also underscore the off-label use of cryoplasty in heavily calcified lesions (approximately 30% of the total lesions treated in both groups). Of note, only 41.4% of patients in group CRYO and 38.7% in group COBA had CLI, and only a small percentage of the lesions in both groups were chronic total occlusions. As a result, patients included in the study might not be the most representative cases of a diabetic population. However, the study's main intention was to compare the efficacy of cryoplasty and COBA as an SFA recanalization tool with regard to primary patency, restenosis, and TLR-free survival rates. Nonetheless, according to our results and until further scientific evidence becomes available, the use of cryoplasty should be limited to selected angioplasty cases within properly designed clinical studies. We have shown that cryoplasty, in this particular group of diabetic patients, is a safe but not more efficient method of endovascular treatment than COBA. No substantial benefit was shown in terms of immediate technical success, stent use, and long-term primary patency. Furthermore, the restenosis and target lesion revascularization rates were higher, additionally compromising the cost-effectiveness of the procedure taking into account the higher cost of the PolarCath balloon and the comparable rates of adjunctive stent use. To conclude, cryoplasty of the femoropopliteal artery in diabetic patients was associated with lower primary patency and more clinically driven repeat procedures after long-term follow-up compared with conventional balloon angioplasty.

Conflict of interest statement The authors declare that they have no conflict of interest.

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