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Research Article

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Clinical Trial Review to Compare Cryoplasty versus Conventional Angioplasty in the Popliteal Artery: Midterm Results of the COLD Study

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Abstract

Background: Clinical review is applied to review safety and efficacy of cryoplasty versus conventional angioplasty for focal popliteal arterial occlusive disease, the review was done for PTA Balloon Catheter which is intended for Percutaneous Transluminal Angioplasty (PTA) in the peripheral vasculature, iliac, femoral, ilio-femoral, popliteal, infra popliteal, and renal arteries as well as the treatment of obstructive lesions of native and synthetic arteriovenous dialysis fistulae.

Purpose: To evaluate safety and efficacy of cryoplasty versus conventional angioplasty for focal popliteal arterial occlusive disease. Full clinical review has been done by **Zhejiang Zylox Medical Device Co., Ltd**. in order to document clinical safety, clinical performance and clinical benefits of PTA Balloon Catheter; the review has been applied according to New Medical Device Regulation MDR (2017/745/EC), MDD 93/42/EEC and BS EN ISO 14155:2020.

Materials and methods: Patients with focal atherosclerotic stenoses and occlusions of the popliteal artery were randomized to cryoplasty or conventional angioplasty as the initial treatment strategy. The primary objective was target lesion patency. The secondary endpoint was treatment success without the need for stents. Duplex ultrasonography was performed at 3, 6, 9, and 15 months.

Results: Eighty-six patients (mean age, 72 years; age range, 50 –94 years) were enrolled in this study. Forty patients were randomized to cryoplasty and 46 to conventional angioplasty. Demographics, risk factors, clinical stage of disease, and lesion details were comparable. On intention-to -treat basis, initial success was 35% for cryoplasty versus 54% for conventional angioplasty (P = .02). The rate of grade C dissection was 35% after cryoplasty and 26% after conventional angioplasty (P = .4). Optional long-term percutaneous transluminal angioplasty (PTA) was performed in 58% of cryoplasty patients. The rate of stent placement for dissection and/or residual stenosis was 30% after cryoplasty (including long-term dilation) and 39% after conventional angioplasty (P = .34) . The mean (±standard

deviation) target lesion patency at 9 months was 79.3% ± 7.5 for cryoplasty and 66.7% ±8.1 for conventional angioplasty; however, the results are not significant (P = .14).
Conclusions: Cryoplasty of the popliteal artery alone showed a lower anatomic success when compared with conventional angioplasty. Combined with optional long-term PTA, however, stent placement was not needed more often. There was a trend toward higher patency after cryoplasty, but differences were not statistically significant and results of long-term follow-up have to be awaited. Full clinical review has been done according to New Medical Device Regulation MDR (2017/745/EC), MDD 93/42/EEC and BS EN ISO 14155:2020

Keywords: cryoplasty versus conventional angioplasty, popliteal arterial, COLD Study

Introduction

FOR patients with symptomatic femoropopliteal arterial disease, percutaneous transluminal angioplasty (PTA) has been established as the first-line treatment for most atherosclerotic lesions. A substantial drawback of the procedure is the high rate of recurrent stenosis, which usually develops during the first 12 months after treatment (1). Initial failure of PTA caused by elastic recoil or hemodynamically relevant dissection can be managed with the implantation of stents, but clinical and experimental studies have shown that angioplasty triggers multiple cellular and molecular mechanisms that lead to a cascade of events and eventually results in in-creased vascular smooth muscle cell proliferation, synthesis of extracellular matrix, and consecutive formation of neointimal hyperplasia with luminal narrowing. In case of angioplasty failure, stents dramatically improve the im-mediate technical outcome; however, there are still major issues with instent restenosis and loss of patency over time.

Currently available data do not suggest a significant difference in the rate of tar-get lesion revascularization between PTA with provisional stent placement and routine stent placement for symptomatic patients with short lesions (2–5). Moreover, recent investigations have highlighted the various forces that affect a stent when implanted into the distal femoral and popliteal artery. In this vascular territory the combination of stresses (eg, longitudinal extension, torsion, flexion, and compression at the hinge point near the adductor hiatus) may lead to stent fracture and significantly influence long-term success (6,7). Cryoplasty has been introduced as a technique aimed at the two major obstacles of angioplasty: initial technical failure by dissection or recoil and the late restenosis formation caused by negative remodeling and neointima formation. It was shown that the targeted delivery of cold thermal energy has the potential to alter the biologic response of the vessel, resulting in what may be a more benign healing process after balloon injury (8). Three main effects have been proposed as the theoretical basis for a more beneficial outcome: (*a*) a more controlled and uniform stretching of the vessel as a result of a change of the plaque micro-structure, (*b*) a reduction in elastic recoil by freeze-induced alteration of the morphology of collagen and elastin fibers with short-term loss of vessel elasticity, and (*c*) apoptosis of vascular smooth muscle cells, which has been shown to result in a reduction of neointima formation and collagen synthesis, thereby providing protection against constrictive remodeling and restenosis (9 –11). Hence, it can be hypothesized that cryoplasty might be an ideal treatment modality for lesions of the popliteal artery, in which the implantation of stents should generally be avoided (12). In this article, results from the COLD study, a prospective, randomized single-center trial to compare safety and efficacy of cryoplasty versus conventional angioplasty in the popliteal artery, are reported.

Materials and Methods

The study protocol was granted approval by the institutional review board, and informed consent was obtained from all patients. Considered for inclusion were patients with lifestyle-limiting claudication (Rutherford-Becker categories 1–3), rest pain, or ischemic skin changes of the feet (Rutherford-Becker categories 4 –5) induced by

focal atherosclerotic stenoses or occlusions of the popliteal artery (13). Patients were excluded if they had hemodynamically relevant lesions (>50% luminal steno-sis) of the arterial in- and/or outflow, previous stent or stent-graft placement into the popliteal artery, lesions induced by former vascular surgery, and fresh embolic occlusions. Patients who had contraindications to the administration of contrast media, renal failure, hyperthyroidism, or allergic diathesis were also excluded from the study.

Design and Objectives

During the past 2½ years, 86 patients with focal atherosclerotic stenoses and occlusions of the popliteal artery were randomized to receive either cryoplasty or conventional balloon angioplasty as the initial treatment strategy. Patients were randomly assigned to one of the two treatment groups by opening a sealed envelope containing the treatment modality. The primary study end-point was target lesion patency. Secondary endpoints were initial anatomic treatment success with less than 30% residual stenosis, absence of hemodynamically relevant dissection or recoil without the need for stent placement, and complications. Of the 86 patients, there were 40 men and 46 women aged 50 –94 years (mean age, 72 years). Forty patients were randomized to receive cryoplasty and 46 to receive conventional angioplasty. Follow-up with ankle brachial index (ABI) measurement and color-coded duplex ultrasonography (US) was scheduled at 3, 6, 9, and 15 months. Angiography was performed for cases of suspected restenosis.

Pretreatment Evaluation

The clinical status of peripheral vascular disease was determined by documentation of clinical symptoms and measurements of the Doppler ABI before and after a standardized treadmill exercise (5 minutes at 2 mph [3.2 km/h] on a 12° incline). The following risk factors of peripheral vascular disease were assessed: sex, age, smoking, diabetes, hypertension, hyperlipidemia, obesity, renal function, and preinterventional state of anticoagulation. For the evalua-tion of anatomic and hemodynamic factors of disease severity, intraarterial angiography (Multistar; Siemens, Erlangen, Germany) was performed with documentation of local grade and loca-tion of stenosis, presence of occlusion, length of the treated lesion, and quality of distal runoff. Local grades of stenoses were quantitatively measured on the basis of imaging with digital subtraction angiography in a posteroanterior plus left or right anterior oblique projection with electronic calipers, in comparison with the nearest normal-appearing segment of the treated artery. In cases of diffuse disease, multiple short stenoses located in close proximity within a particular segment of the popliteal artery were counted as one lesion. To account for radiographic magnification, lesion length and luminal diameter of the vessel were quantitatively assessed after internal calibration of the electronic measuring system with a ruler.

Lesions were assigned to the popliteal artery segments, which were de-fined as follows: (*a*) The superior or supraarticular popliteal artery (1st popliteal segment), extending from the adductor hiatus to the superior border of the femoral condyle. As a fluoroscopic landmark for the adduc-tor hiatus a line 3 cm above the prox-imal patella pole was defined. (*b*) The middle or articular popliteal artery (2nd popliteal segment) lying behind the femoral condyles opposite the in-tracondylar notch in the popliteal fossa extending from the superior border of the femoral condyle to the joint line; and (*c*) The lower or intraarticular popliteal artery (3rd popliteal segment) extending from the joint line to the soleus arcade, that is, to the bifurcation of the anterior tibial artery and tibioperoneal trunk (**Fig 1**). In case of a variant high origin of the anterior tibial artery, the 3rd popliteal segment was defined as the portion of the popliteal artery extending from the joint line to the bifurcation of posterior tibial and peroneal artery (14).

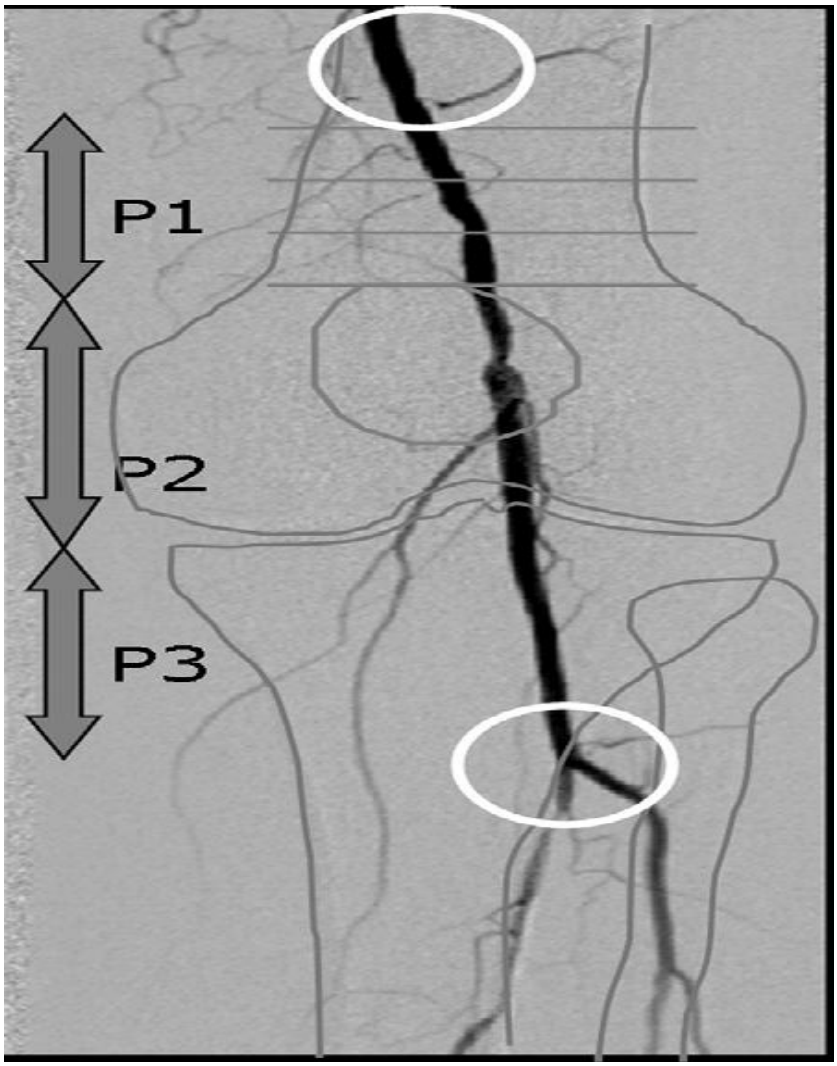

Figure 1. Topographic anatomy of the popliteal artery for lesion stratification. The borders of the 1st, 2nd, and 3rd popliteal segments (*P1*, *P2*, and *P3*, respectively) are shown (14). As a fluoroscopic landmark to locate the adductor hiatus, a line 3 cm above the upper patella pole was used. Approximate location of adductor hiatus and bifurcation of the anterior tibial artery and tibioperoneal trunk are marked with white circles.

Procedural Details

Details of the procedure and suc-cess rates were gathered from the an-giographic images and extracted from the interventional protocols. These in-cluded duration of fluoroscopy; dose-area product; amount of contrast me-dium used; location, grade, and length of stenosis; presence of total occlusion; presence of calicification if visible at fluoroscopy; technical and anatomic success (residual stenosis <30%); rate of dissection and/or need for bail-out stenting, and periprocedural complications. Indication for stent implantation was residual stenosis of more than 30% and/or hemodynamically relevant dissection. Dissection was graded by using the Na-tional Heart, Lung and Blood Institute classification system for intimal tears (15). Hemodynamically significant dissection was defined by grade C or greater and/or a more than 50% residual luminal stenosis. Grade of residual stenosis was measured on the basis of imaging with digital subtraction angiography in a posteroanterior plus left or right anterior oblique projection with electronic calipers in comparison with the nearest normal-appearing segment of the treated artery.

Complications were documented according to the published SIR reporting standards (16). Minor complications were defined as adverse events without clinical consequence that required no or only nominal therapy. Minor groin hematoma, for instance, would fall into this category. Major complications were defined as events requiring further medical or interventional therapy or complications leading to prolonged hospitalization (>48 hours), major therapy, an un-planned increase in the level of care, permanent adverse sequelae, or death. For example, distal embolization with the need for aspiration thrombectomy and/or locoregional lysis or false aneurysm requiring thrombin injection or surgery would fall into this category.

Treatment Description

Cryoplasty.—All interventions were performed with the patient under local anesthesia (lidocaine 1%, 10 mL) from an ipsilateral antegrade puncture of the common femoral artery. After placement of a 7-F sheath (Terumo, Tokyo, Japan), preprocedural measurements of vessel and lesion dimensions were as-sessed as described earlier. Lesions were recanalized with use of a 0.018-inch guide wire (V18; Boston Scientific, Watertown, Massachusetts) and a 5-F re-canalization catheter (Berenstein; Cor-dis, Roden, The Netherlands). After passage of the lesion, the correct intralu-minal position of the catheter was verified with the injection of contrast medium, and the guide wire was ex-changed for a 0.35-inch Radiofocus Glidewire (Terumo). Before cryoplasty was performed, 5,000 IU of heparin was administered intraarterially. Cryoplasty-balloon sizes were chosen to be the same size as the reference vessel diameter and allowed to exceed the luminal diameter of the nearest normal-appearing vessel lumen by 20%, thereby achieving balloon-to-vessel ratios rang-ing from 1.15:1 to 1.25:1, depending on initial vessel size. Once the balloon was positioned into the lesion, the procedure was carried out with the PolarCath cryoplasty system (Boston Scientific) ac-cording to the instructions for use. A treatment cycle of simultaneous dilation and cooling lasts 20 seconds, and, after passive warming of the catheter by body temperature and surrounding blood flow, the balloon is manually de-flated and repositioned or removed. Multiple ”runs” of cryoplasty were al-lowed (maximum of five), with each inflation requiring a separate nitrous oxide cylinder. In case of residual stenosis or grade C dissection after cryoplasty, a conventional balloon of the same diameter was introduced and long-term angioplasty performed for a period of 3–5 minutes and a pressure of 8 atm controlled with a manometer (Encore, Bos-ton Scientific). If anatomic treatment success was still not achieved, the bal-loon catheter was exchanged for one of the next higher diameter and inflated again for another 3–5 minutes. In case of persistent failure with more than 30% residual stenosis or luminal narrowing by dissection, a self-expandable stent was implanted (Absolute; Guidant, Indianapolis, Indiana). Stents were oversized to up to 1 mm compared to the reference vessel diameter. **Figures 2** and **3** show examples of two cryoplasty procedures, the first (**Fig 2**) with an optimal result after a single run of cold balloon therapy; the second case (**Fig 3**) shows a failed procedure with need for long-term angioplasty by using a conventional balloon catheter.

Conventional angioplasty.—All inter-ventions were performed with the pa-tient under local anesthesia (lidocaine 1%, 10 mL) from an ipsilateral ante-grade or retrograde crossover approach. After placement of a 5- or 6-F sheath (Terumo), lesions were recanalized by using a 0.018-inch guide wire (V18) in combination with a 5-F recanalization catheter (Cordis). After passage of the lesion, the correct intraluminal position of the catheter was verified with the injection of contrast medium. Before angioplasty (Sterling Balloon, Boston Scientific) was performed, 5,000 IU of narheparin was administered intraarterially.

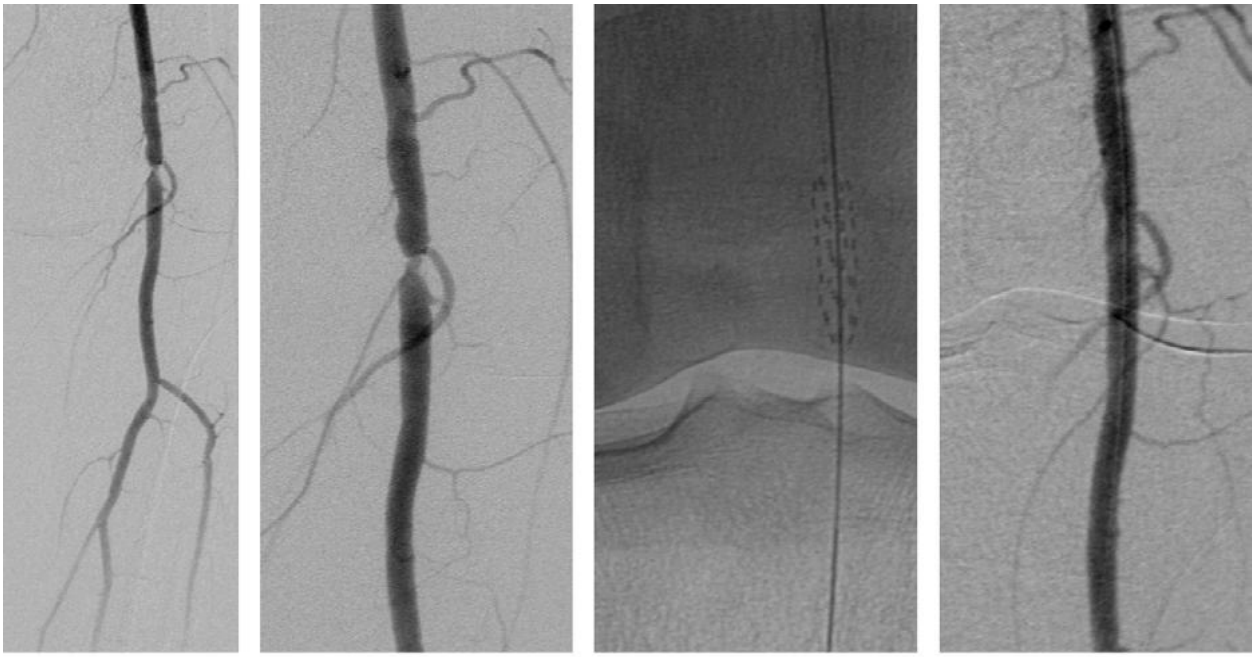

Figure 2. Digital substraction angiography and fluoroscopy images in a 78-year-old woman for whom an optimal result of cryoplasty was achieved. **(a,b)** Preprocedural images show a focal high-grade stenosis of the 2nd popliteal segment. After one cryoplasty procedure with a 5-mm device **(c)**, no residual stenosis or dissection is present **(d)**.

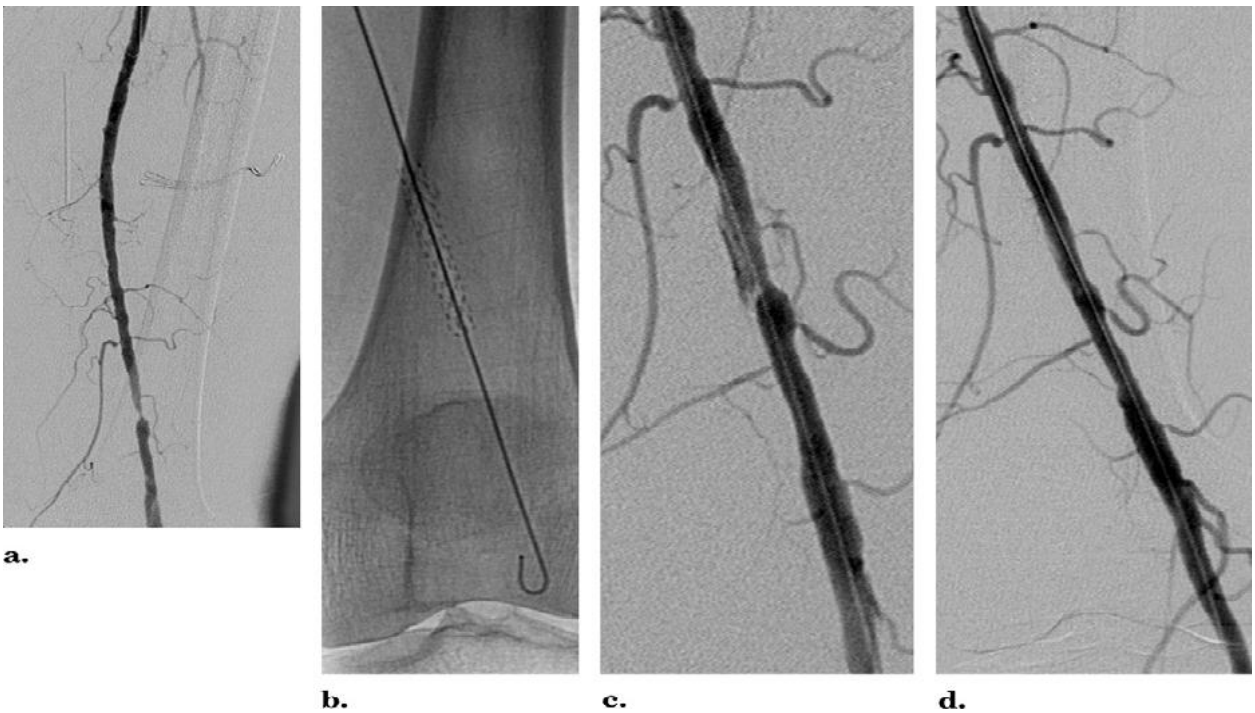

Figure 3. (a) Digital substraction angiography obtained in a 69-year-old man with high grade stenosis in the 1st popliteal segment of the left leg. **(b)** Fluoroscopy image of the inflated cryoplasty balloon in the lesion. Image obtained after three cryoplasty balloon procedures shows that grade C dissection is still present, prompting the need for prolonged angioplasty **(c)**. Control angiography **(d)** shows the result after treatment of the residual stenosis with long-term PTA with a conventional balloon.

Balloon sizes were chosen to be the same size as the reference vessel diameter but were allowed to exceed the luminal diameter of the nearest normalappearing vessel lumen by 20%, thereby achieving balloon-to-vessel ratios rang-ing from 1.15:1 to 1.25:1, depending on the initial vessel size. Balloons were inflated with nominal pressure of 8 atm for 30 – 60 seconds under manometer control (Encore). In case of residual ste-nosis or hemodynamically relevant dis-section, either the balloon catheter was exchanged for one of the next higher diameter or the device last used was inflated again for 3–5 minutes. In case of persistent angioplasty failure, a self-expandable stent was implanted (Absolute). Stents were oversized to up to 1compared to the reference vessel diameter.

Anticoagulation.—For anticoagulation, all patients received 1,000 mg of acetyl-salicylic acid (Bayer, Leverkusen, Ger-many) intravenously and 5,000 IU of heparin intraarterially before cryoplasty and/or conventional angioplasty, fol-lowed by a regimen of 1,000 IU heparin per hour intravenously for at least 24 hours (partial thromboplastin time, 60 – 80 seconds). On discharge, a life-time regimen of oral acetylsalicylic acid (100 mg/d) and an 8-week course of clopidogrel (75 mg/d) were initiated. A loading dose of 300-mg clopidogrel was administered on the day of the intervention.

Follow-up

Postprocedural examinations included ABI measurements and arterial duplex US within 24 hours. At 3, 6, 9, and 15 months, patients were scheduled to re-turn for clinical assessment, ABI measurements, and arterial duplex US. The degree of improvement of claudication was assessed with use of the grading system of the Society of Vascular Surgery and the International Society of Cardiovascular Surgery (17,18), ranging from -3 (markedly worse) to +3 (markedly improved). Peak systolic velocity and peak systolic velocity ratios were recorded for all patients. Peak systolic velocity ratios were calculated by dividing the peak systolic velocity (in centimeters per second) in the treated segment by the peak systolic velocity in the preceding normal segment. The criteria for target lesion restenosis was a more than 2.5-fold increase in the peak systolic velocity ratio across the treated segment, which is indicative of luminal narrowing of more than 50% (19). Patients with clinical evidence of recurrent disease and typical symptoms, but without restenosis in the treated segment found at color Doppler US, were scheduled for control angiography to rule out the development of in- and/or outflow disease.

Statistical Analysis

The primary endpoint of the study was analyzed on an intention-to-treat basis. For continuous variables, the arithmetic mean and standard deviation were calculated, and comparisons were performed with the two-sided Wilcoxon rank-sum test. For categoric variables, the absolute and relative frequencies were calculated, and comparisons were performed with the Fisher exact test. Target lesion patency was calculated with use of Kaplan-Meier life table anal-ysis and is expressed as the percentages of survival (patency) probability including standard error. The log-rank test was used to evaluate for statistical differences. Differences were considered significant at a *P* value less than.05. All analyses were carried out with software (version 9.1; SAS, Cary, North Carolina).

Results

Patient Demographics, Comorbidities, and Lesion Details

Eighty-six patients (40 men and 46 women; mean age, 72 years; age range, 50 –94 years) were enrolled in this study. Forty patients were randomized to receive cryoplasty and 46 to receive conventional angioplasty. Demographics with sex distribution, age, risk factors, renal function, and clinical stage of disease were comparable in both groups. Most patients had claudication (72.5% [29/40] in the cryoplasty group vs 80.4% [37/46] in the angioplasty group, *P* = not significant).

The location of the treated lesions did not differ significantly between groups, with most lesions being located in the 1st and 2nd segments of the popliteal artery.

In approximately one-quarter of cases, more than one segment of the popliteal artery was involved (25% [10/40] in the cryoplasty group vs 28%[13/46] in the angioplasty group, *P* = not significant). The length and grade of stenosis, presence of calcification, and number of total occlusions were similar in both groups (23% [9/40] oc-clusions in the cryoplasty group vs 30% [14/46] in the angioplasty group, *P* = not significant; 45% [18/40] calci-fication in the cryoplasty group vs 52% [24/46] in the angioplasty group, *P* = not significant). The mean lesion length was 35 mm ± 28.8 in the cryo-plasty group and 36.5 mm ± 28.5 in the angioplasty group (*P* = not signif-icant). The mean grade of stenosis was 91% ± 10 for the cryoplasty group and 90% ± 12.2 for the angioplasty group (*P* = not significant). The mean distal run-off was 2.0 patent calf vessels in both groups (*P* = not significant). All data are summarized in **Table 1.**

Table 1 Patient Demographics, Comorbidities, and Lesion Details

Parameter	Cryoplasty (*n* = 40)		Conventional Angioplasty (*n* = 46)		*P* Value
Age (y)	73.6 ± 9.7		70.6 ± 10.2		.09
Male sex	43	(17/40)	49	(23/46)	.12
Obesity	53	(21/40)	41	(19/46)	.39
History of smoking	38	(15/40)	46	(21/46)	.33
Hyerlipidemia	48	(19/40)	46	(21/46)	.46
Arterial hypertension	85	(34/40)	78	(36/46)	.82
Diabetes mellitus	28	(11/40)	33	(15/46)	.52
Mean serum creatinine level (mg/dL)	1.19 ± 1.14		1.07 ± 1.18		.33
Mean prothrombin time (% of quick value)	96 ± 11.3		96.1 ± 9.3		.4
Mean partial thromboplastin time (sec)	32.8 ± 10.5		30.6 ± 6.9		.1
Claudication	72.5	(29/40)	80.4	(37/46)	.33
Critical limb ischemia (rest pain, ulceration)	27.5	(11/40)	19.6	(9/46)	.21
No. of patent calf vessels	2	± 0.8	2	± 0.7	.87
Right leg	35	(14/40)	35	(16/46)	.49
Popliteal segment					
1st	73	(29/40)	61	(28/46)	.13
2nd	45	(18/40)	59	(24/46)	.1
3rd	14	(4/40)	9	(4/46)	.42
Multisegmental disease	25	(10/40)	28	(13/46)	.37
Mean lesion length (mm)	35 ± 28.8		36.5 ± 28.5		.41
Mean grade of stenosis (%)	91±10		90 ± 12.2		.28
Chronic total occlusion	23	(9/40)	30	(14/46)	.16
Calcified lesion at fluoroscopy	45	(18/40)	52	(24/46)	.26

Note.—Except where indicated, data are given as percentages. Hypertension was defined as more than 140/80 mm Hg examined repeatedly or documented in the history with regard to the patient's antihypertensive therapy. Diabetes mellitus was defined as a blood glucose level of more than 126 mg/dL (7.0 mmol/L). Furthermore, a glycosylated hemoglobin level of more than 6.5% was accepted as indicative of diabetes mellitus. Hyperlipidemia was defined as hypercholesterolemia (cholesterol level >200 mg/dL [5.17 mmol/L] or LDL cholesterol level >130 mg/dL [3.36 mmol/L]) and was assumed to be present in all patients taking lipid-lowering medications.

Procedure Details

There were no differences in the mean size of balloons used for dilation, with a diameter of 5 mm most frequently used in both groups (63% [25/ 40] of the cryoplasty group and 67% [31/46] of the angioplasty group, *P* =

not significant). In the angioplasty group, long-term dilation with inflation times of more than 60 seconds was performed in 78.3% (36/46) of cases, with a mean inflation time of 166 seconds ± 82.6. Long-term angioplasty representing crossover treatment was performed in 58% (23/40) of cryoplasty procedures. The mean number of cryoplasty procedures performed per lesion was 2.0 ± 0.86 (range, 1–4). There were no differences in the amount of contrast medium used, the fluoroscopy times, or the dose-area product between the two groups. All data are summarized in **Table 2**.

Table 2
Procedure Details

Parameter	Cryoplasty (n = 40)	Conventional Angioplasty (n = 46)	P Value
Balloon size			
4 mm	10 (4/40)	17.4 (8/46)	.33
5 mm	63 (25/40)	67.4 (31/46)	.64
6 mm	28 (11/40)	15.2 (7/46)	.57
Long-term inflation (>60 sec)	58 (23/40)	78.3 (36/46)	.03
Mean inflation time (sec)	NA	166 ± 82.6	. . .
Mean no. of cryoplasty runs	2 ± .86	NA	. . .
Mean amount of contrast medium used (mL)	93 ± 35	99.9 ± 50.2	.28
Mean fluoroscopy time (min)	9 ± 5.7	12.2 ± 9.9	.1
Mean dose-area product (cGy/cm^2)	805 ± 527.4	1,259 ± 1,406	.07

Note.—Except where indicated, data are given as percentages. NA = not applicable.

Table 3
Summary of Results

Parameter	Cryoplasty (n =40)	Conventional Angioplasty (n = 46)	P Value
Intention-to-treat success	35 (14/40)	54 (25/46)	.02
Grade 4 dissection	35 (14/40)	26 (12/46)	.4
Residual stenosis >30%	20 (8/40)	20 (9/46)	.3
Bail-out stent placement	30 (12/40)	39 (18/46)	.34
Minor complications	2.5 (1/40)	2.7 (1/46)	.46
Major complications	5 (2/40)	2.7 (1/46)	.24
Mean ABI	0.63 ± 0.2	0.71 ± 0.2	.08
At baseline			
After the proceduret	0.89 ± 0.38	0.94 ± 0.2	.2

Note.—Except for the ABI, data are given as percentages.

Table 4
Results of Hemodynamic Follow-up

Parameter and Follow-up Time	Cryoplasty (n = 40)	Conventional Angioplasty (n = 46)	P Value
ABI			
<24 h	0.89 ± 0.14	0.94 ± 0.22	.2
3 mo	0.96 ± 0.19	0.83 ± 0.33	.1
6 mo	1.06 ± 0.24	0.92 ± 0.21	.08
9 mo	0.94 ± 0.18	0.92 ± 0.19	.9
PSV ratio*	1.1 ± 0.38	1.2 ± 0.86	.4
<24 h			
3 mo	1.3 ± 0.8	1.7 ± 1.5	.21
6 mo	1.4 ± 1.3	1.5 ± 0.8	.75
9 mo	1.2 ± 0.5	1.5 ± 1.45	.44

Note.—Data are given as means ± standard deviations.
* Mean peak systolic velocity ratio measured across the target lesion.

Treatment Success

On an intention-to-treat basis, initial treatment success was 35% (14/40) for cryoplasty versus 54% (25/46) for angioplasty with optional long term dilation (P = .02). The rate of grade 4 dissection after cryoplasty alone was 35% (14/40), versus 26% (12/46) following angioplasty (P = .4). Residual stenosis or recoil was equal in both groups and occurred in 20% of cases. In 58% (23/40) of the patients who underwent cryoplasty, additional long-term angioplasty with a conventional balloon was performed. The rate of bail-out stent placement for persistent dissection and/or residual stenosis was 30% (12/40) after cryoplasty (including per-protocol long-term dilation) and 39% (18/46) after angioplasty (P = .34). Complication rates were similar for both groups. In the cryoplasty group, there were two cases of distal embolization, requiring aspiration thrombectomy, and one case of minor groin hematoma, for which there was no need for therapy (major complication rate, 5% [2/40]; minor complication rate, 3% [1/40]). In the angioplasty group, there was one groin hematoma (minor complication rate, 2.7% [1/46]) and one case of side branch perforation that was treated with coil embolization (major complication rate, 2.2% [1/46]). The baseline ABI improved from 0.63 ± 0.2 to 0.89 ± 0.38 after cryoplasty and from 0.71 ± 0.2 to 0.94 ± 0.2 after angioplasty (P = not significant). Procedure results are summarized in **Table 3**.

Follow-up

Twenty-three of the 40 patients who underwent cryoplasty (58%) and 23 of the 46 patients who underwent angioplasty (50%) have reached 9-month follow-up. The mean follow-up time is 9 months ± 7 (range, 1–32 months). Postoperative ABI development and/or mean peak systolic velocity ratios measured across the target lesion were not different between the two treatment arms (data are summarized in **Table 4** and **Fig 4**). At 9 months, improvement of the clinical stage of peripheral vascular disease was +2.73 ± .55 for after cryoplasty (P = .29) and +2.43 ± 1.16 after angioplasty (P = not significant). Following cryoplasty,

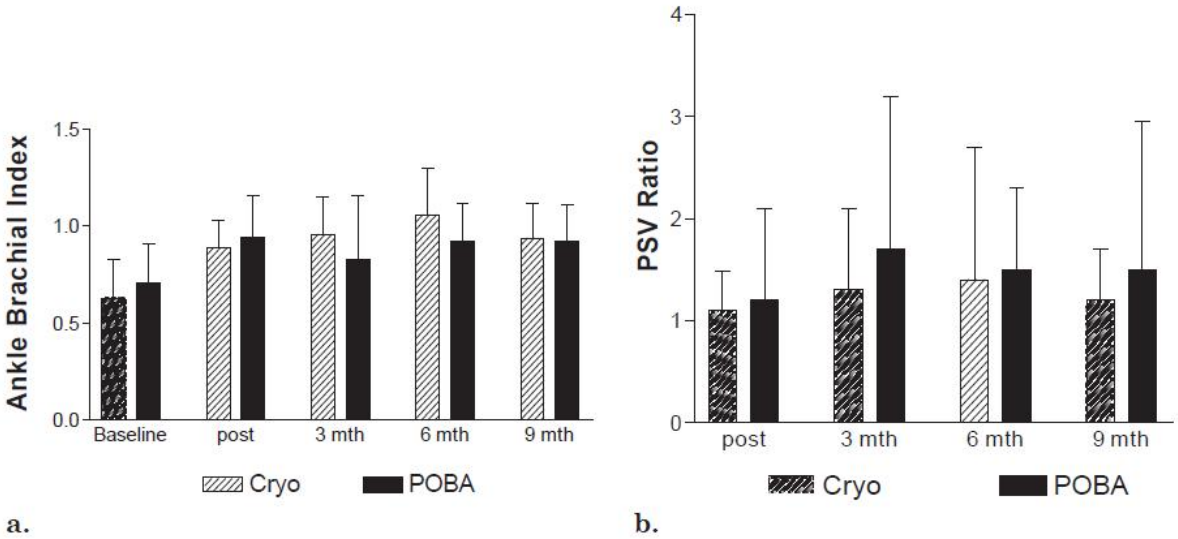

Figure 4. (a) Bar chart shows the postoperative development of ABI after cryoplasty (*cryo*) and conventional angioplasty (*POBA*). *P* = not significant. **(b)** Bar chart shows the postoperative development of the peak systolic velocity (*PSV*) ratio after cryoplasty (*cryo*) and conventional angioplasty (*POBA*). *P* = not significant.

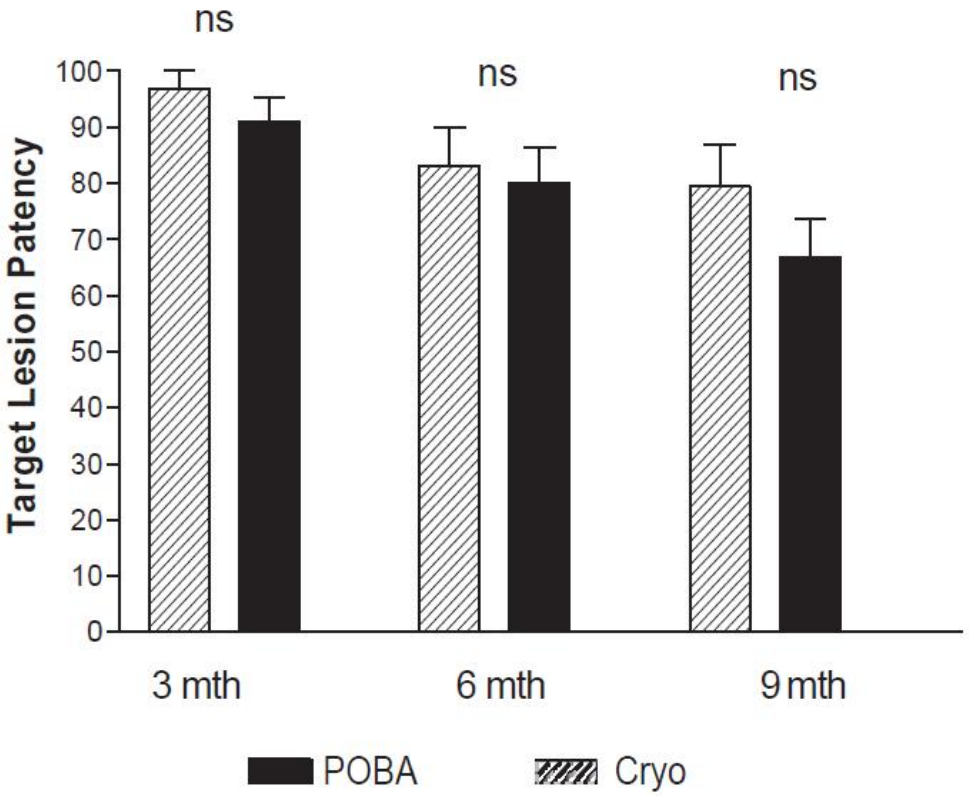

Figure 5. Bar chart shows the target lesion patency after cryoplasty (*cryo*) and conventional angioplasty (*POBA*) at 3, 6, and 9 months. *ns* = not significant.

target lesion patency was 96.8% ± 3.2, 82.9% ± 7.0, and 79.3% ± 7.5 at 3, 6, and 9 months, respectively. After angioplasty, target lesion patency was 90.8% ± 4.4, 79.8% ± 6.4, and 66.7% ± 8.1 at 3, 6, and 9 months, respectively. Results of Kaplan-Meier life table analysis did not show a statistically significant difference for survival (patency) probability (P = .14) (**Fig 5**, **Table 5**).

Table 5
Target Lesion Patency

	Cryoplasty			Conventional Angioplasty		
Follow-ups	Target Lesion Patency	Standard Error	No. of Patients at Risk	Target Lesion Patency	Standard Error	No. of Patients at Risk
3 mo	96.8	3.2	31.0	90.8	4.4	37.0
6 mo	82.9	7.0	27.0	79.8	6.4	33.0
9 mo	79.3	7.5	23.0	66.7	8.1	23.0

Note.—Comparison of survival curves with log-rank test: χ^2 = 2.182; 1 *df* *P* value = .1397 (not significant); hazard ratio = 1.995; 95% confidence interval of ratio = 0.7949, 5.122.

Discussion

To date, PTA is the preferred minimally invasive treatment for infrainguinal arterial disease. Despite recent refinements in catheter and guide wire technology with improved pushability, lesion crossing potential, and steerability, the technique continues to be limited by local dissection, vascular recoil, and neointimal hyperplasia that limits long-term efficacy of the procedure. After conventional balloon angioplasty, restenosis takes place in approximately 30%– 40% of cases within the first 6--12 months (20,21).

Stents have shown to improve the immediate outcome of angioplasty by addressing dissection, residual steno-sis, and elastic recoil, but local inflammation with activation of neointimal proliferation is still a major limitation. In addition, the superficial femoral ar-tery is exposed to longitudinal stretching, external compression, torsion, and flexion, factors that may all contribute to stent fractures and eventually lead to restenosis. This issue is even more pronounced in the distal aspect of the superficial femoral and especially in the popliteal artery, where dynamic modifications of the arterial axis in the sagittal plane produce hinge points during knee flexion that challenge any implanted foreign material (12).

In this situation, cryoplasty theoretically offers a solution to the problem. Three potential benefits of the procedure have been identified: (*a*) a cold-induced alteration of arteriosclerotic plaque and surrounding tissue, which may reduce intimal dissection and dam-age of subendothelial structures; (*b*) a change of the subintimal collagen and elastic fibers' ultrastructure as protec-tion against elastic recoil; and (*c*) the induction of smooth muscle cell apopto-sis that may lead to reduced neointimal hyperplasia and, thus, lower restenosis rates (22).

Although the overall clinical suc-cess of cryoplasty for patients with peripheral vascular disease happens to be promising, with midterm clin-ical patency rates of 82%–92%, high-level evidence for the safety and efficacy of the procedure is still lacking. Currently, only small series of clinical trials, mainly single- or multicenter registries, have been published and randomized comparative studies are miss-ing (9,23–27). In a recent reappraisal of a single-center experience (92 lesions in 64 consecutive patients) with long-term data now becoming available, freedom from restenosis on an intention to treat basis was only 47% and 38% at 12 and 24 months (28).

In this article, we present results from the COLD study, a prospective, randomized single center trial to com-pare the safety and efficacy of cryoplasty versus conventional angioplasty for the treatment of symptomatic focal de-novo stenoses and occlusions restricted to the popliteal artery. The the-oretical advantages of simultaneously cooling and dilating a vessel portray an attractive treatment concept for this particular vascular territory because material implanted into the region is subject to high degrees of biomechanical stress, which is known to limit long-term out-come. A novel technique that could facilitate higher initial technical success (in comparison to conventional angioplasty) with fewer dissections and/or recoil would help avoid the implantation of stents in the first place. If adjunct stent placement was still needed, however, the induction of apoptosis with the inhibition of neointimal hyperplasia could potentially create a favorable basis by reducing the proliferative response to the device, which might improve long-term success.

The results of this study show that, in the popliteal artery, cryoplasty as the primary treatment strategy does not result in higher initial success rates when compared with conventional balloon angioplasty. In fact, intention-to-treat analysis demonstrated that conventional angioplasty was significantly more successful (54% for angioplasty vs 35% for cryoplasty, P = .02). Rates of dissection and residual steno-sis were similar after both treatment modalities. However, the angioplasty strategy included optional long-term dilation, which has proved to enhance the treatment success of failing angio-plasty (29). Overall, the frequency of adjunct stent placement in our study was not higher after cryoplasty, apparently because prolonged balloon dila-tion could be performed as crossover treatment and was done in 58% of the cases. Reports of adjunct stent placement after suboptimal/failed cryoplasty published in the literature are inconsistent and inconclusive. Laird et al (9), for instance, reported a low overall bail-out stent rate of 8.8%; however, in a subgroup of 15 patients with occluded vessels the stent rate was as high as 33.3%. Other data from the literature available today also do not support the notion that cryoplasty reduces the need for stent placement after dilation when compared with conventional balloon angioplasty in the superficial femoral artery, a territory where additional stent placement is needed in up to 35% of cases (30,31). Our data suggest that cryoplasty and angioplasty are equally safe, with low complication rates. Despite the need for larger sheath sizes with cryoplasty (7 F vs 5– 6 F), major bleeding complications were not encountered more often. The rate of distal embolization was also not significantly higher, although there are marked size differences between the over-the-wire-cryoplasty balloon and the low-profile rapid-exchange bal-loon catheters available today, which are known to enhance technical success of femoropopliteal interventions (32). Overall treatment success in our series was 100% for both groups, and both interventional strategies led to continuous improvement of the ABI and the clinical stage of the disease. This represents an important finding of our study because it shows that revascularization of the popliteal artery can be performed safely and has sim-ilar success rates when compared with interventions in the superficial femoral artery (3).

Target vessel patency has been pro-posed as a robust endpoint when com-paring two treatment strategies for peripheral vascular disease because it is decision-driven by both the clinical status and the angiographic or Doppler evidence of restenosis (2,33). For the COLD study, target lesion patency was selected as the primary endpoint. Both treatments were aimed at anatomically defined target lesions restricted to popliteal arterial segments, and local restenosis development could be directly as-sessed with duplex US. Although patients with in- and/or outflow disease were initially excluded from the study, the postinterventional development of in- and outflow stenosis cannot be ruled out. However, a primary objective of the study was to test the hypothesis that delivery of cold thermal energy would lead to a reduction of neointimal hyperplasia with consecutive restenosis. Thus, target lesion patency is a more appropriate endpoint for the study.

Our data demonstrate that cryoplasty in the popliteal artery leads to promising target lesion patency of 96.8% ± 3.2, 82.9% ± 7.0, and 79.3% ± 7.5 at 3-, 6-, and 9-month follow-up. The target lesion patency with cryoplasty was slightly higher than that after conventional angioplasty, which had patency rates of 90.8% ± 4.4, 79.8% ± 6.4, and 66.7% ± 8.1 at 3, 6, and 9 months, respectively. However, Kaplan-Meier life table analysis did not find a statistically significant difference between the two treatment strategies. Hence, on the basis of our data, the notion that cryoplasty is substantially more effective than conventional angioplasty cannot be supported at this point.

The COLD study represents a non controlled single-center trial that is limited in scope and observation period. Because the evaluation of follow-up imaging stud-ies to determine target lesion patency was not performed by an independent core laboratory, inherent bias cannot be ruled out. However, randomization does guar-antee equal distribution of demographic data, risk factors, and lesion details. More-over, the procedures were standardized with comparable balloon-to-vessel ratios, dilation pressures, stent type used, and anticoagulation regimen; thus, an environment with controlled variables was created and allows us to draw evidence-based conclusions. Of course, additional and larger trials will be necessary to determine the future effect of cryoplasty in the treatment of peripheral vascular disease.

In conclusion, midterm results of the COLD study demonstrate that cryoplasty as a primary treatment strategy in the popliteal artery has a higher rate of dissection and lower initial anatomic success rate when compared to conventional angioplasty with optional long-term dilation. In combination with pro-longed conventional PTA, however, adjunctive stent placement is not needed more often. There is a trend to-ward higher target lesion patency after the procedure, but results are not statistically significant and long-term fol-low-up has to be awaited. This study also shows that results of modern revascularization techniques in the popliteal artery are comparable to those at the superficial femoral artery level. In light of the high technical success rates of 100%, complication rates of less than 5%, and target lesion patency of up to 79%, a primary minimally invasive treatment approach for isolated popliteal arterial disease may be justified, not only for patients with critical limb ischemia but also for those with claudication. Full clinical review has been done according to New Medical Device Regulation MDR (2017/745/EC), MDD 93/42/EEC and BS EN ISO 14155:2020. Clinical data was sufficient to address clinical performance, safety and benefits of the device and compliance with relevant applicable regulatory requirements.

References

1. Jeans WD, Armstrong S, Cole SE, Hor- rocks M, Baird RN. Fate of patients undergoing transluminal angioplasty for lower-limb ischemia. Radiology 1990; 177:559 –564.
2. Kasapis C, Henke PK, Chetcuti SJ, et al. Routine stent implantation vs. percuta- neous transluminal angioplasty in femo- ropopliteal artery disease: a meta-analy- sis of randomized controlled trials. Eur Heart J 2009; 30:44 –55.
3. Adam DJ, Bradbury AW. TASC II document on the management of pe-ripheral arterial disease. Eur J Vasc En-dovasc Surg 2007; 33:1–2.
4. Muradin GS, Bosch JL, Stijnen T, Hunink MG. Balloon dilation and stent implantation for treatment of femoropopliteal arterial disease: metaanalysis. Radiology 2001; 221:137–145.
5. Cejna M, Thurnher S, Illiasch H, et al. PTA versus Palmaz stent placement in femoropopliteal artery obstructions: a multicenter prospective randomized study. J Vasc Interv Radiol 2001; 12:23–31.
6. Machan L. Drug eluting stents in the infrainguinal circulation.
7. Scheinert D, Scheinert S, Sax J, et al. Prevalence and clinical impact of stent fractures after femoropopliteal stenting. J Am Coll Cardiol 2005; 45:312–315.

8. Gage A, Fazekas G, Riley E. Freezing injury to large blood vessels in dogs. Surgery 1967; 61:748 –754.
9. Laird J, Jaff MR, Biamino G, et al. Cryoplasty for the treatment of femo-ropopliteal arterial disease: results of a prospective, multicenter registry. J Vasc Interv Radiol 2005; 16:1067–1073.
10. Soloff BL, Nagle WA, Moss AJ, Henle KJ, Crawford JT. Apoptosis induced by cold shock in vitro is dependent on cell growth phase. Biochem Biophys Res Commun 1987; 145:876 – 883.
11. Tatsutani KN, Joye JD, Virmani R, Tay- lor MJ. In vitro evaluation of vascular endothelial and smooth muscle cell survival and apoptosis in response to hypothermia and freezing. Cryo Lett 2005; 26:55– 64.
12. Diaz JA, Villegas M, Tamashiro G, et al. Flexions of the popliteal artery: dy- namic angiography. J Invasive Cardiol 2004; 16:712–715.
13. Rutherford RB. Standards for evalu- ating results of interventional therapy for peripheral vascular disease. Circu- lation 1991; 83(Suppl):1–11.
14. Avisse C, Marcus C, Ouedraogo T, De-lattre JF, Menanteau B, Flament JB. Anatomo-radiological study of the popliteal artery during knee flexion. Surg Radiol Anat 1995; 17:255–262.
15. Huber MS, Mooney JF, Madison J, Mooney MR. Use of a morphologic classification to predict clinical outcome after dissection from coronary angio- plasty. Am J Cardiol 1991; 68:467– 473.
16. Sacks D, Marinelli DL, Martin LG, Spies JB; Society of Interventional Radiology Technology Assessment Committee. Reporting standards for clinical evalua- tion of new peripheral arterial revascu- larization devices. J Vasc Interv Radiol 2003; 14:395–404.
17. Standards of Practice Committee of the Society of Cardiovascular and Inter-ventional Radiology. Angioplasty stan-dard of practice. J Vasc Interv Radiol 1992; 3:269 –271.
18. Hiatt WR, Hirsch AT, Regensteiner JG, Brass EP, the Vascular Clinical Trial- ists. Clinical trials for claudication: as- sessment of exercise performance, func- tional status, and clinical endpoints. Circulation 1995; 92:614 – 621.
19. Leng GC, Whyman MR, Donnan PT, et al. Accuracy and reproducibility of duplex ultrasonography in grading femoro-popliteal stenoses. J Vasc Surg 1993; 17:510 – 517.
20. Laird JR. Limitations of percutaneous transluminal angioplasty and stenting for the treatment of disease of the su- perficial femoral and popliteal arteries. J Endovasc Ther 2006; 13:II30 –II40.
21. Wyttenbach R, Gallino A, Alerci M, et al. Effects of percutaneous transluminal an-gioplasty and endovascular brachyther- apy on vascular remodeling of human femoropopliteal artery by non-invasive magnetic resonance imaging. Circulation 2004; 110:1156 –1161.
22. Joye JD. The clinical application of cryoplasty for infrainguinal peripheral arterial disease. Tech Vasc Interv Ra- diol 2005; 8:160 –164.
23. Fava M, Loyola S, Polydorou A, et al. Cryoplasty for femoropopliteal arterial disease: late angiographic results of ini- tial human experience. J Vasc Interv Radiol 2004; 15:1239 –1243.
24. Laird JR, Biamino G, McNamara T, et al. Cryoplasty for the treatment of femoropopliteal arterial disease: ex- tended follow-up results. J Endovasc Ther 2006; 13:II52–II59.
25. Karthik S, Tuite DJ, Nicholson AA, et al. Cryoplasty for arterial restenosis. Eur J Vasc Endovasc Surg 2007; 33:40 – 43.
26. Samson RH, Showalter DP, Lepore MR Jr, Ames S. Cryoplasty therapy of the superficial femoral and popliteal arter- ies: a single center experience. Vasc En-dovascular Surg 2006; 40:446 – 450.
27. Das T, McNamara T, Gray B, et al. Cryoplasty therapy for limb salvage in patients with critical limb ischemia. J Endovasc Ther 2007; 14:753–762.
28. Samson RH, Showalter DP, Lepore M Jr, Nair DG, Merigliano K. CryoPlasty therapy of the superficial femoral and popliteal arteries:

a reappraisal after 44 months' experience. J Vasc Surg 2008; 48:634 – 637.
29. Zorger N, Manke C, Lenhart M, et al. Peripheral arterial balloon angioplasty: effect of short versus long balloon infla- tion times on the morphologic results. J Vasc Interv Radiol 2002; 13:355–359.
30. Schillinger M, Mlekusch W, Haumer M, Sabeti S, Ahmadi R, Minar E. Angioplasty and elective stenting of de novo versus recurrent femoropopliteal lesions: 1-year follow-up. J Endovasc Ther 2003; 10:288 – 297.
31. Schillinger M, Sabeti S, Loewe C, et al. Balloon angioplasty versus implantation of nitinol stents in the superficial femoral artery. N Engl J Med 2006; 354:1879–1888.
32. Jahnke T, Schäfer JP, Bolte H, et al. Retrospective study of rapid-exchange monorail versus over-the-wire technique for femoropopliteal angioplasty. Cardio- vasc Intervent Radiol 2008; 31:854–859.
33. Saxon R, Dake MD, Volgelzang RL, Kat- zen BT, Becker GJ. Randomized, mul- ticenter study comparing expanded polytetrafluoroethylene– covered endo- prosthesis placement with percutaneous transluminal angioplasty in the treat- ment of superficial femoral artery occlu- sive disease. J Vasc Interv Radiol 2008; 19:823– 832.

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