The COBRA Trial

How will cryotherapy compare to conventional balloon angioplasty in peripheral vascular interventions?

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Peripheral artery disease (PAD) affects 12% to 20% of Americans aged 65 years or older.[1] In the Framingham cohort, the presence of diabetes increased the risk of claudication by 3.5-fold in men and 8.6-fold in women and is the cause of most nontraumatic lower extremity amputations in the United States. The relative risk for lower extremity amputation in patients with diabetes was 12.7% (95% confidence interval [CI], 10.9–14.9) compared with that of nondiabetic patients in the Medicare population and as high as 23.5% (95% CI, 19.3–29.1) for diabetic patients aged 65 to 74 years.[2] A population-based study[3] has shown the prevalence of PAD in the diabetic population to be as high as 30%.

Although medical treatment with antiplatelet agents continues to be the mainstay for treating PAD, in patients with advanced symptomatic disease, revascularization is crucial. Currently, percutaneous transluminal angioplasty (PTA) is the preferred first-line approach for interventional treatment for patients with symptomatic PAD, with optional secondary stenting. However, the high restenosis rates of approximately 40% to 60% in treated segments at 1 year[4-6] and rates > 70% at 1 year in lesions > 10 cm[7] remain major limitations. Endovascular stenting avoids the complications of early elastic recoil, residual stenosis, and flow-limiting dissection of the vessel, which may occur after PTA.[8]

An initial study of nitinol stents in the superficial femoral artery (SFA) showed promising results with a patency rate of 85% at 18 months.[8] However, many subsequent randomized studies comparing PTA alone versus PTA plus stent placement in the SFA failed to show the benefit of stenting over PTA alone.[9-11] Zdanowski et al found a higher rate of restenosis in the stent group compared to the group with PTA alone.[12] A more recent study in 2006 showed that primary nitinol stenting yielded superior results compared to conventional PTA with optional secondary stenting[13] and stainless steel stents.[14]

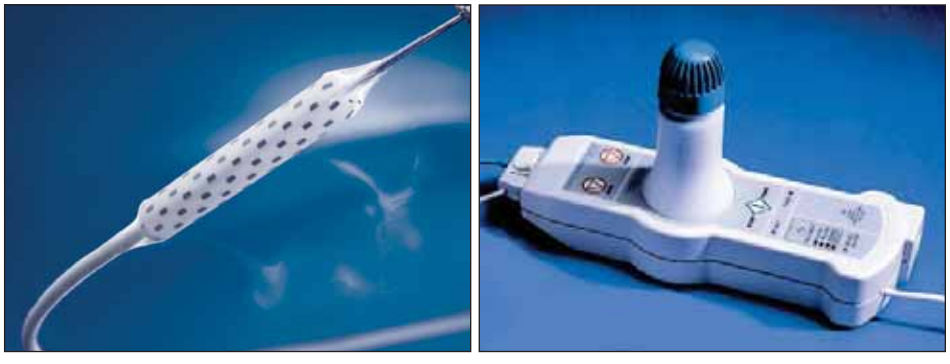

Figure 1. PolarCath inflation and balloon catheter (Boston Scientific Corporation, Natick, MA).

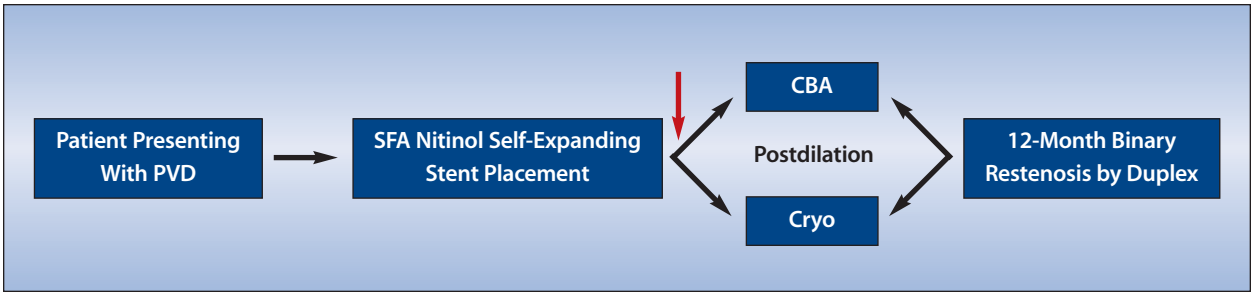

Figure 2. COBRA trial scheme. Red arrow indicates randomization. Abbreviations: CBA, conventional balloon angiography; Cryo, cryoplasty; PVD, peripheral vascular disease; SFA, superficial femoral artery.

Even though nitinol stents appear to yield better results than PTA alone, the rate of in-stent restenosis is still quite high, with approximately 40% of patients developing in-stent restenosis in the 8-month median follow-up period.[15] This study also showed cumulative freedom from restenosis rates of 79% and 54% at 6 and 12 months, respectively; for the same time periods, these rates were 84% and 71% in nondiabetic patients (n = 41) versus 68% and 22% in diabetic patients (n = 24) (adjusted hazard ratio, 3.8; *P* = .01). This shows that in-stent restenosis remains a major limitation with nitinol stents in SFA revascularization, especially in symptomatic diabetic patients.

Neointimal proliferation plays a major role in in-stent restenosis. Vascular tissue, when exposed to any injury, responds with inflammation/neointimal proliferation.[16] During stenting/angioplasty, the stretching leads to endothelial injury and a break in the internal elastic membrane. This triggers the inflammatory cascade, leading to migration of smooth muscles from the media and recruitment of circulating smooth muscle precursors, resulting in deposition and proliferation in the intima. This neointimal proliferation and hyperplasia leads to restenosis.[17] Diabetic patients have an exaggerated response to injury with deposition of advanced glycation end products that bind to smooth muscle cells, leading to relatively increased smooth muscle proliferation, neointimal hyperplasia, and in-stent restenosis.[18]

During the last decade, modifications and refinement of existing therapies for PAD and newer techniques such as brachytherapy, excimer laser therapy, ultrasonographic therapy, cutting/scoring balloon angioplasty, and atherectomy have been introduced.[19] Despite these advances, the efficacy of these newer approaches in the reduction of neointimal hyperplasia has not yet been determined in treating femoropopliteal arterial disease. Late clinical failure/restenosis of endovascular treatment of infrainguinal arterial obstruction remains a major concern.

Cryotherapy literally means cold therapy. It has been used to treat neoplastic and nonneoplastic conditions (eg, prostate cancer, skin lesions, and cervical lesions). The mechanism of cryotherapy is causing programmed cell death (apoptosis) through a freezing and rethawing process.

Cryoplasty involves the use of nitrous oxide in place of standard saline and contrast medium to inflate and cool the balloon to the desired temperature. By using the nitrous oxide, the area of contact is cooled to -10º Celsius, the ideal temperature at which apoptosis sets in. Evidence shows that cryoplasty is a safe and effective treatment modality when used in combination with other procedures[20] and as primary treatment.[21-24] However, its role in reducing in-stent restenosis has never been tested.

HYPOTHESIS

Our hypothesis is that the use of cryotherapy for nitinol stent postdilation in the SFA of symptomatic diabetic patients will reduce neointimal proliferation compared to the use of a conventional balloon, thereby reducing the in-stent restenosis rate.

DESIGN

The COBRA (PolarCath Cryoplasty Versus Conventional Balloon Postdilation of Nitinol Stents for Peripheral Vascular Interventions) study is a randomized, multicenter, prospective, efficacy trial using the PolarCath peripheral dilatation system (Figure 1).

METHOD

A total of 86 individual treatment limbs are to be randomized to conventional balloon angioplasty or cryoplasty for postdilation of self-expanding nitinol stents in the SFA of symptomatic diabetic patients (see *Study Inclusion and Exclusion Criteria* sidebar). The use of pharmacological agents, need for stent implant, lesion debulking or predilation strategy, and predilation or

STUDY INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria

- Diabetic patients, insulin or noninsulin dependent older than 21 years
- Ability to provide an informed consent
- Life expectancy > 1 year
- Presenting with severe intermittent claudication (Rutherford category 3), chronic critical limb ischemia with pain while the patient is at rest (Rutherford category 4), or chronic critical limb ischemia with ischemic ulcers (Rutherford category 5)
- Placement of self-expanding nitinol stent > 5 mm in diameter in the SFA
- Placement of self-expanding nitinol stent > 60 mm in length in the SFA

Exclusion Criteria

- Serum creatinine of < 2 mg/dL
- Presence of iodinated contrast allergy
- Presence of allergy to aspirin and clopidogrel
- Pregnancy
- Relative or absolute contraindication for anticoagulation
- History of allergy to unfractionated heparin or heparin-induced thrombocytopenia
- White blood count < 3,000; platelet count < 100,000; and baseline hemoglobin < 10 g/dL
- Absence of at least one infrapopliteal vessel with brisk runoff to the foot
- Left ventricular ejection fraction < 25%

postdilation balloon size will be at the discretion of the operator. Patient follow-up will be at 24 hours (optional), 6 months, and 12 months after the procedure with duplex ultrasonography, measurement of ankle-brachial index, and a walking impairment questionnaire (Figure 2).

ENDPOINTS

The primary endpoint is the rate of binary restenosis determined by a > 2.5 times increase in peak systolic velocity in the treated segment and 10 mm beyond its proximal and distal end at 12 months after the procedure. The secondary endpoints are improved hemodynamic endpoint at 6 and 12 months (assessed by resting ankle-brachial index measured), a lowered rate of anatomical restenosis of > 50% at 6 months (determined by duplex ultrasonography), and the angiographic degree of restenosis at 12 months (percent reduction in diameter in the stented segment and 10 mm beyond its proximal and distal edges). Angiographic evaluation for restenosis will be performed at 12 months with the use of either > 16-slice computed tomographic angiography or conventional digital subtraction angiography for all patients with an abnormal duplex ultrasound study.

CURRENT STATUS

This study, which has 70 participants, is currently enrolling patients and has an anticipated completion date of December 2010. ■

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