Peripheral Drug-Eluting Technology

Anna Franzone, MD, Eugenio Stabile, MD, PhD*, Bruno Trimarco, MD, Giovanni Esposito, MD, PhD

KEYWORDS

• Peripheral artery disease • Drug-eluting balloon • Restenosis • Femoropopliteal • Below-the-knee • Drug-coated balloons • Drug-eluting stents • In-stent restenosis

KEY POINTS

- Drug-eluting devices have been developed to overcome restenosis, the major limitation of conventional angioplasty, by achieving effective drug transfer into the arterial wall and by exerting antirestenotic effects.
- A large body of evidence supports the safety and efficacy of drug-eluting stents in below-the-knee arteries.
- Drug-eluting balloons are found to be superior to conventional angioplasty for the treatment of de novo femoropopliteal and below-the-knee diseases.
- Accurate lesion preparation before use of drug-eluting balloons is essential for effective drug transfer into the arterial wall.
- The use of drug-eluting technologies (drug-eluting stents and drug-eluting balloons) for the treatment of femoropopliteal in-stent restenosis seems to provide good long-term patency rates, as reported by registries and a randomized clinical trial.

INTRODUCTION

The endovascular approach has emerged as a valid therapeutic option for patients with peripheral artery disease (PAD), causing intermittent claudication or critical limb ischemia (CLI), with reduced morbidity and costs compared to surgical bypass grafting.[1] Despite marked improvements in materials and techniques, maintaining long-term patency after percutaneous transluminal angioplasty (PTA) of femoropopliteal (FP) or below-the-knee (BTK) lesions is still a real challenge because of the occurrence of restenosis. Indeed, mechanical stresses, heavy calcification, and extensive atherosclerotic lesions make the FP bed typically prone to PTA failure. Patency at 1 year after balloon angioplasty (plain old balloon angioplasty, POBA) is only near 40%.[2] Superior vessel scaffolding provided by nitinol stents has markedly improved the patency rates (65%–80%) over conventional angioplasty or atherectomy.[3,4] In-stent restenosis (ISR), however, has been reported to occur in up to 40% of FP lesions treated with bare metal stents (BMS) within 1 year of treatment, with an increasing number of patients requiring re-intervention.[5] Moreover, the diffuse nature of atherosclerotic disease and compromised general status make patients with BTK lesions more difficult to treat. In this scenario, drug-eluting technologies seem to offer promising tools to overcome the limitations of peripheral POBA or stenting and to manage ISR. Because drug-eluting balloons (DEB) and drug-eluting stents (DES) have major application in the treatment of FP or BTK tracts, this review

The authors have no conflict to disclose.
Division of Cardiology, Department of Advanced Biomedical Sciences, University of Napoli "Federico II", Via S. Pansini 5, Napoli 80131, Italy
* Corresponding author.
E-mail address: geko50@hotmail.com

Cardiol Clin 33 (2015) 151–162
http://dx.doi.org/10.1016/j.ccl.2014.09.005

focuses on the currently available evidence of their use in these arterial territories.

PERFORMANCE OF CONVENTIONAL PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY DEVICES

Low complication rates (0.5%–4%) and high technical success (90%) are the major advantages of the percutaneous approach to PAD over surgery.[6]

Conventional Balloon Angioplasty

POBA has been the cornerstone of endovascular therapy for the FP region. However, despite good early angiographic results, balloon injury is associated with the occurrence of adverse events such as elastic recoil, negative remodeling, and vessel dissection accounting for disappointing long-term primary patency.[7] For these reasons, as a standalone therapy, POBA is indicated for short, focal lesions (<4 or 5 cm).

Low-profile, long balloons with long inflation times provide good acute angiographic results when used in BTK arteries of patients suffering from CLI. Despite a 90% rate of limb salvage, restenosis at 6 months is extremely high (up to 80%) with a 1-year re-intervention rate of 59%.[1]

Stents

Because of their peculiar features (radial strength and crush recoverability), self-expanding nitinol stents have been found to improve the patency rates compared with PTA only in the treatment of long lesions (≥8 cm) of the FP tract.[4,8,9] Growing evidence from randomized trials has changed the previous common paradigm that limited stenting of shorter FP lesions to bailout indications (flow-limiting dissections, acute or subacute recoil, or reocclusion) after POBA. Primary nitinol stenting now represents the first-line strategy for the treatment of intermediate-length superficial femoral artery (SFA) lesions with a restenosis rate at 1 and 2 years 20% to 30% lower than conventional angioplasty.[10] Technologic advances in stent design provide more flexibility and crush resistance to second-generation nitinol stents that is associated with improved clinical and angiographic outcomes.[11,12] Furthermore, covered stent grafts may be a valid option for longer and more complex SFA lesions, showing results comparable to those of prosthetic bypass surgery.[13]

The role of metal stents (mostly balloon-expandable coronary stents) for BTK lesions has been historically restricted to bailout indications after failure of PTA. In a small, randomized trial comparing the performance of different metal stents and balloon-only angioplasty in 38 limbs, no difference in survival, limb salvage, and primary and secondary patency was seen at 1 year.[14] In a pooled analysis of 640 patients treated with infragenicular stent implantation, sirolimus-eluting stents showed superiority in terms of binary restenosis and primary patency over BMS.[15]

RATIONALE FOR DRUG-ELUTING TECHNOLOGIES

Successful application of drug-eluting devices in coronary vasculature has encouraged their use in peripheral arteries. The addition of a drug layer to common endovascular devices (balloons or stents) aims mainly to hinder the occurrence of restenosis.

Balloon injury–induced arterial recoil, negative remodeling, and vessel dissection can limit the acute gain of conventional angioplasty. Improved mechanical scaffolding provided by nitinol stents, however, is associated with an increased risk of late vessel injury and neointimal hyperplasia.[16] Regardless of the underling mechanism, the occurrence of neointimal hyperplasia is caused by smooth muscle cell (SMC) proliferation as a result of sustained inflammatory response and therefore invalidates long-term patency of PTA. Against this background, the concept of drug delivery directly into the vessel wall is attractive for 2 main reasons: (1) it ensures effective and steady concentration of chemotherapeutic drugs able to prevent neointimal hyperplasia by inhibiting SMC migration and proliferation of pharmacologic agents and (2) there is minimal associated risk of systemic toxicity.[17]

DRUG-ELUTING STENTS

The introduction of DES has added substantial benefit to the clinical outcomes of patients undergoing percutaneous coronary revascularization, driven mainly by a significant reduction of target lesion revascularization (TLR) rates compared with those of BMS.[18] DES combine sustained local drug delivery with vessel scaffolding to prevent recoil and to solve vessel dissection.

An extensive, off-label use of balloon-expandable coronary stents has been made for the treatment of BTK lesions. Furthermore, dedicated self-expanding stents were developed for the FP arteries.

Two categories of antiproliferative (chemotherapeutic) drugs can be eluted on stent platform: macrolide antibiotics (rapamycin), such as sirolimus and its analogues (everolimus, zotarolimus, tacrolimus, biolimus A9) or paclitaxel. Rapamycin