Concomitant Drug-Coated Balloon Angioplasty With Bail-Out Use of Eluvia Drug-Eluting Stent: Is There Any Downside to a Double Dose of Paclitaxel?

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Peripheral artery disease (PAD) of the lower extremities is frequently due to atherosclerotic lesions of the femoropopliteal artery,[1] which may result in disabling claudication and rest pain with or without tissue loss.[2-4] More than 50% of the patients presenting with disabling claudication have occlusion of the superficial femoral artery (SFA).[5] In the majority of such cases, an endovascular procedure is performed.[6,7] During the last decade, drug-coated balloon (DCB) angioplasty has been an attractive alternative to bare-metal stent (BMS) and/or conventional plain old balloon angioplasty (POBA), promising better patency and/or limb-salvage rates.[8-13] Thus, over time, DCB angioplasty utilization has expanded due to a sustained benefit, especially for short femoropopliteal lesions.[11-14] However, the effectiveness of DCB angioplasty at the femoropopliteal artery is often challenged by moderate/severe calcification, long target-lesion length, recoil, and/or the presence of chronic total occlusion (CTO).[15-17] Additionally, angiographically visible dissections after POBA or DCB angioplasty are estimated to occur in up to 88% of cases,[17-19] with higher-grade dissections associated with worse prognosis.[20] Adequate target-vessel preparation (eg, POBA, atherectomy, intravascular lithotripsy [IVL], cutting/scoring balloons, etc) prior to DCB angioplasty could further facilitate acute luminal gain, limiting the risk for recoil, residual stenosis, and/or postangioplasty dissections.[21-25] However, the application of these combined approaches has been challenged due to limited reimbursement and the lack of randomized controlled trials (RCTs) regarding their benefit.[21-23,26] Therefore, in daily clinical practice, DCB angioplasty often correlates to an increased dependence on provisional stenting, with rates of bail-out stenting reported to be 7.3%-40%.[17,27,28]

Generally, provisional stenting after DCB angioplasty has involved BMS placement.[10,29-31] Nonetheless, animal studies have provided significant evidence that DES implantation could be also used as bail-out, offering an additional dose of paclitaxel at the same arterial level where the DCB angioplasty result is suboptimal, without increasing the risk for adverse effects.[32-34] The Eluvia drug-eluting vascular stent system (Boston Scientific) is composed of a nitinol self-expanding stent (closed cells on the ends and open cells in the middle) coated with paclitaxel.[35-37] The stent is designed to provide uniform drug coverage along the artery length and sustained paclitaxel elution over time, while also exhibiting increased resistance to stent fractures.[35-37] Thus, the paclitaxel-coated Eluvia stent has been designed to overcome the burden of in-stent restenosis associated with older stent devices (ie, BMS or DES).[37] In this study, we aimed to summarize our experience on the safety and efficacy outcomes of Eluvia stenting after suboptimal DCB angioplasty for the treatment of symptomatic femoropopliteal disease.

Methods

Study design and patient population. This was a single-center, retrospective study of 22 consecutive patients (23 limbs) who underwent DCB angioplasty followed by DES stenting for the treatment of femoropopliteal lesions at the Rocky Mountain Regional Veterans Affairs Medical Center in Aurora, Colorado between 2019 and 2020. The protocol of the current study was approved by the institutional review board and the study was conducted in accordance with the Declaration of Helsinki. Experienced abstractors collected demographic, baseline lesion, and procedural and outcome data by reviewing the electronic medical records and angiographic images of all eligible cases.

Endovascular treatment. All procedures were performed according to the standards of femoropopliteal artery endovascular revascularization, via either a contralateral or an ipsilateral approach. The type of anesthesia, access site, crossing guidewires, support catheters, the type/number of DCBs used, as well as the adjuvant use of cutting balloons, employed atherectomy devices, utilization of distal filter, and/or IVL application, were at the discretion of the operator. Additionally, bail-out stenting with DES occurred at the discretion of the operator in cases of severe flow-limiting dissections or suboptimal angiographic results with significant recoil and/or residual stenosis. Moreover, significant inflow and/or outflow disease were treated at the discretion of the operator. For intraprocedural anticoagulation, heparin was used, with a targeted activated clotting time of >250 seconds. The stents and/or balloons utilized were chosen based on availability and operator's preference. The DCBs were used with inflation to nominal pressures for at least 3 minutes in all cases. Final angiography was performed in all cases to determine procedural success and/or the need for further adjunctive therapies.

Additionally, antithrombotic therapy with antiplatelet agents (eg, aspirin, clopidogrel) and/or anticoagulants was administered pre- and post procedurally based on the preference of the operator. Specifically, 18 patients were on dual-antiplatelet therapy (DAPT) post procedure, with 3 of these 18 patients also on low-dose rivaroxaban. In the remaining patients, 3 were given low-dose aspirin or clopidogrel combined with low-dose rivaroxaban and 1 patient (deemed to be at increased risk for bleeding) was placed on aspirin monotherapy. Additionally, all but 2 patients were on moderate- or high-intensity statin therapy based on operator's preference post procedure.

Study outcomes. Procedure success was determined when the lesion could be crossed and treated with a final residual stenosis <30% in the final angiographic images. Major adverse limb event (MALE) was defined as the composite of 1 of the following: endovascular or surgical target-lesion revascularization (TLR) for clinically significant femoropopliteal lesions, all-cause mortality, and/or limb loss. Routine duplex ultrasound follow-up, ankle-brachial index (ABI), and clinical examination were used to identify restenosis or reocclusion during follow-up. The primary outcome of this study was the 2-year MALE rate. Secondary outcomes included procedural success and limb loss, TLR, and all-cause mortality, as well as arterial aneurysm formation at sites of Eluvia stent placement during follow-up.

Statistical analysis. Categorical variables were presented as absolute and relative frequencies (ie, percentages), while continuous variables were presented as means ± standard deviations. Additionally, the cumulative incidence of primary and secondary outcomes was presented with absolute and relative frequencies. Moreover, the Kaplan-Meier (KM) method was used to estimate 2-year freedom from primary and secondary revascularization outcomes. All analyses were performed using STATA software, version 14.1 (STATA Corporation).

Results

Patients and lesion characteristics. Details regarding patients' baseline demographics are presented in Table 1 [available online, please scan the QR code at the end of the article]. Most of the patients were males and presented with lifestyle-limiting claudication. In all cases, the SFA was involved, with the disease extending into the popliteal artery in 7 cases and a mean lesion length of 321 ± 130 mm. In the majority of cases, a CTO with moderate/severe calcification was present. Overall, in 9 and 4 cases, inflow and outflow disease were treated with standard endovascular recanalization techniques, respectively. DCB angioplasty was performed with the Stellarex DCB (Philips) in 6 cases and the In.Pact Admiral DCB (Medtronic) in the remaining cases. Provisional stenting with DES was required due to

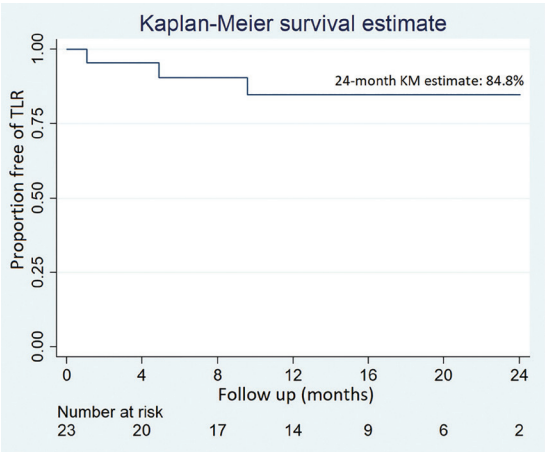

Figure 1. Freedom from target-lesion revascularization (TLR) during follow-up.

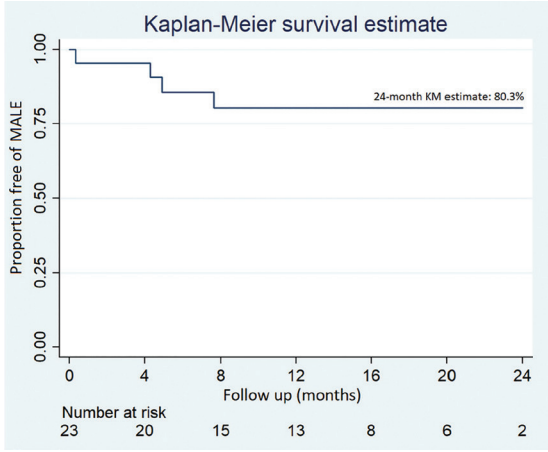

Figure 2. Freedom from major adverse limb event (MALE) during follow-up.

flow-limiting dissection (grade C or higher) in 10 cases and due to suboptimal angiographic result due to significant residual stenosis and/or recoil in 13 cases. Multiple Eluvia DESs were used in 8 cases.

All but 1 limb was successfully revascularized with <30% residual stenosis. The 1 procedural failure was due to a case of severely calcified SFA-CTO that showed persistent mild recoil on final angiography. There were no procedural deaths, strokes, or myocardial infarctions observed. In 1 patient, distal embolization to infrapopliteal vessels occurred intraprocedurally. However, this was treated successfully with aspiration thrombectomy, with final angiography showing no residual thrombus in the run-off vessels. Additionally, 1 patient developed an access-site hematoma that was treated conservatively and resolved a few weeks post procedure. ABI improved from a mean baseline value of 0.55 ± 0.20 to a postprocedural value (within 30 days) of 0.96 ± 0.17. The mean toe-brachial index (TBI) was 0.31 ± 0.21 preprocedure and 0.75 ± 0.51 post procedure. Important lesion and procedural characteristics are summarized in Table 2 [available online, please scan the QR code at the end of the article].

The average follow-up was 15 ± 7 months. At 12-month follow-up, the mean ABI and TBI values were 0.95 ± 0.16 and 0.77 ± 0.10, respectively. Restenosis or reocclusion of the target vessel, detected by duplex ultrasound, was observed in 6 cases (26.1%), although only 3 patients required revascularization (13.0%). The 6-, 12-, and 24-month rates of freedom from TLR were 90.4% (95% confidence interval [CI], 66.8-97.5), 84.8% (95% CI, 59.6-94.9), and 84.8% (95% CI, 59.6-94.9), respectively. Freedom from TLR is presented in Figure 1. One additional patient, with CLI at baseline, underwent major amputation 7.6 months post procedure. Another patient who presented with CLI at baseline also required multiple interventions and eventually severe disease progression led to limb loss and death. No other deaths were observed. The 6-, 12-, and 24-month rates of freedom from MALE were 85.6% (95% CI, 61.7-95.1), 80.3% (95% CI, 55.5-92.2), and 80.3% (95% CI, 55.5-92.2), respectively (Figure 2). Additionally, 2 patients underwent coronary artery revascularization during follow-up, while 1 patient suffered a stroke 12.7 months after the index procedure. Moreover, routine duplex ultrasound during follow-up failed to show any aneurysmal formation at sites of Eluvia stent placement (ie, sites of double paclitaxel dose). The cumulative incidences of primary and secondary outcomes with the corresponding CIs are presented in Supplemental Table S1 [available online, please scan the QR code at the end of the article].

Discussion

This single-arm pilot study included 22 patients with very long-length femoropopliteal lesions (mostly CTOs) who underwent provisional stenting with the Eluvia DES after suboptimal DCB angioplasty result. The endovascular procedure was challenged by the presence of CTOs, calcification, and/or severe disease (ie, CLI) in almost all cases. The reason for bail-out stenting was flow-limiting dissections in approximately half of the cases, while the other half required DES deployment for significant residual stenosis and/or recoil. The procedure was successful in 22 out of 23 limbs, with no evidence of distal embolization, dissection, or perforation post procedure. In 1 case, blood flow restoration was incomplete due to mild recoil. During an average follow-up of 15.2 months, only 1 death and 1 major amputation occurred, likely attributed to disease progression. Both events occurred in patients who presented with CLI at baseline. Thus, this study provides encouraging results that double-dose paclitaxel approach with DCB followed by DES might have a role in the management of complex femoropopliteal disease.

Endovascular revascularization has been increasingly utilized for the treatment of PAD,[6] as it has been associated with fewer periprocedural complications and similar amputation-free survival compared with surgical repair, even when treating patients with advanced PAD.[38-41] However, as endovascular procedures with conventional balloon angioplasty have been associated with high restenosis rates,[42-45] alternative endovascular treatment approaches have been developed, utilizing drug-coated technology (DCB, DES, etc) that offers lower risk of restenosis and improved long-term outcomes.[9,40,42] DCB compared with POBA has demonstrated promising 1- and 2-year results in terms of safety and efficacy and has greatly expanded in many practices.[10,46-48] Specifically, DCB technology combines the characteristics of POBA and delivery of an antiproliferative agent (ie, paclitaxel) in the vessel wall, targeting smooth muscle cells and inhibiting as such neointima formation. In vitro studies have shown that balloon inflation for up to 45 seconds is enough for proper drug delivery,[49] although longer inflation times and progressive balloon dilation are recommended in order to decrease the risk for periprocedural dissections and/or elastic recoil, thereby limiting the need for bail-out procedures.[50-52]

Interestingly, several clinical trials have demonstrated promising results with both the DCB + BMS and the DCB-only approaches.[28,53-55] More specifically, the In.Pact Global study, which enrolled 1535 patients with symptomatic PAD attributed to femoropopliteal lesions, demonstrated that DCB + provisional stenting with BMS vs DCB alone exhibited similar patency rates over a 13-month follow-up, especially when treating long-length or complex lesions.[56] Thus, the need for bail-out stenting has been questioned when using DCBs due to the antirestenotic effect of drug-eluting technology. Additionally, as the femoropopliteal artery undergoes repetitive deformations during movements (ie, crosses both the hip and knee joint),[57] the stents deployed at the femoropopliteal segment are prone to fractures and/or loss of the patency due to thrombosis.[28,58-60] Therefore, the deployment of stents after DCB might be challenging. Nonetheless, despite advancements in angioplasty algorithms, POBA and/or DCB angioplasty for lower-limb PAD in daily clinical practice often correlates to an increased dependance on provisional stenting for optimization of angiographic result and improvement of overall outcomes, especially when flow-limiting dissections or significant elastic recoil occur.[17,27,28,61] Therefore, it has been necessary to investigate alternative approaches to bail-out stenting with BMS, including but not limited to DES.

The Eluvia drug-eluting vascular stent system is composed of a nitinol, self-expanding stent coated with a formulation of paclitaxel contained in a polymer matrix. The base stent is designed to provide enough force and flexibility to the scaffold, with closed cells on the ends and open cells in the middle, offering improved resistance to fracture forces and better patency compared with older BMS or DES devices.[36,62] Additionally, the specific design of the coating (a primer layer that adheres the layer with the polymer and paclitaxel), promises uniform drug coverage along the artery length and sustained paclitaxel elution over time.[35] Several investigators have confirmed the favorable outcomes of the Eluvia stent and its durability to stress forces of the femoropopliteal artery.[26,36,62,63] In general, DES have been associated with superior primary patency and higher sustained clinical benefit compared with BMS, when used as provisional stents after failed

POBA.[64,65] Therefore, it could be hypothesized that bail-out Eluvia stenting after DCB suboptimal angioplasty result would be a reasonable approach, likely offering better outcomes compared with DCB + BMS. Our study supported this idea, showing that DCB + provisional stenting with the Eluvia DES is feasible and safe in terms of mortality and limb loss during an average follow-up of 15.2 months.

However, there are several potential concerns regarding the double paclitaxel dose at the same target area in the femoropopliteal artery. Experimental research on animal models has shown that paclitaxel-coated stents exert a dose-dependent effect, inhibiting neointimal hyperplasia, with higher levels of the antiproliferative agent (eg, overlapping of DES, combination of DCB and DES, DCB followed by DCB, etc) associated with greater fibrin deposition, medial cell loss, inflammation within the arterial wall, and paradoxically late neointimal formation.[33,66] Nonetheless, these techniques were deemed safe, with delayed healing being the only limitation of their application.[33,66] Specifically, regarding the DCB + DES approach, Torii et al showed in a preclinical study that there were no significant differences in safety, endothelial, and/or medial cell damage and inflammation among DCB + DES vs conventional POBA + DES approach, although clinically nonsignificant small-particle downstream embolization might occur with the DCB + DES technique.[32] Thus, the authors suggested that deployment of DES after DCB angioplasty might be a reasonable approach for patients requiring additional treatment due to suboptimal angioplasty result.[32]

When using a drug-coated device, distal embolization could theoretically happen due to detachment of particles from the excipient coating and the crystalline formulation.[32,67] However, no cases of distal embolization associated with the use of drug-coated devices have been reported in the large RCTs investigating DCB and DES for femoropopliteal disease. Additionally, newer drug-coated devices (Eluvia DES, Stellarex DCB, etc) might be safer than older DES or DCB devices due to improved coating design and optimization of paclitaxel dose. Interestingly, a prospective, single-center pilot study by Fanelli et al investigated 15 patients with symptomatic femoropopliteal disease who were treated with DCB angioplasty followed by provisional stenting with DES due to suboptimal angiographic result.[68] The study demonstrated that no local or systemic complications occurred that could be attributed to the use of a double dose of paclitaxel, confirming previous reports from animal studies.[68] The study also showed that there was no significant increase in inflammatory markers periprocedurally, indicating that double-dose paclitaxel might not have a significant clinical effect in humans when treating lower-limb PAD.[68]

Additionally, the study demonstrated primary patency rates of 93.3% and 92.9% at 12 and 24 months, respectively, with reintervention required for only 2 cases.[68] As such, the study provided significant evidence that DCB + DES might be a reasonable treatment approach when angioplasty alone fails to achieve optimal angiographic result.[68] Similarly, in the present study, restenosis/reocclusion was observed in 6 cases, with only 1 death observed over a mean follow-up of 15 months. Additionally, only 1 patient who presented with CLI required major amputation during follow-up, showing that treatment with DCB + bail-out DES might not increase the risk for limb-related adverse events. Moreover, in our study, endovascular therapy of lower-extremity PAD with double-dose paclitaxel was not associated with local aneurysm formation, indicating that it might not significantly affect the arterial vessel wall. However, as it is still unclear to what extent drug-eluting technology could affect the long-term outcomes of endovascular procedures, additional research is warranted to better investigate the benefits and risks of a double paclitaxel dose approach. Additionally, future research efforts should focus on better understanding of the pharmacokinetics and pharmacodynamics as well as the actual risks associated with these devices.[69-71] Last, it should be determined which would be the most optimal paclitaxel concentration for coating of balloons and stents used for the endovascular treatment of lower-extremity PAD and whether this should be dependent on lesion characteristics (eg, CTO, calcification, long-length lesion, etc) and/or patient characteristics (eg, diabetes mellitus, chronic kidney disease, isolated infrapopliteal disease, ischemic wounds of the lower limb at baseline, etc) known to be associated with worse outcomes.[69-71]

Study limitations. The results of this study should be interpreted within the context of several limitations. This analysis shares the limitations of all retrospective, nonrandomized, observational studies, including selection and operator biases. Data were retrieved from a Veteran Affairs hospital, which limits the generalizability of the study results, particularly given the predominantly male study demographic. Additionally, the angiographic images of the included patients were not adjudicated by a core laboratory. Also, certain adjuvant interventions (eg, atherectomy, cutting balloons, IVL) were used at the discretion of the operator, which might have affected the outcomes. Moreover, in several cases the overall segment of the artery treated with DCB was longer than the segment treated with additional DES. Last, multiple DCBs, with overlapping of the corresponding areas treated at each time, were used in longer lesions at the discretion of the operator. However, no adjustments could be made to account for this extra dose of paclitaxel. Therefore, additional studies are needed to better evaluate the safety efficacy of DCB + DES approach and determine the most optimal paclitaxel dose for endovascular therapy of femoropopliteal lesions.

Conclusion

In daily clinical practice, DCB angioplasty often correlates to an increased dependance on provisional stenting for optimal result. This study confirmed previous reports that provisional stenting with DES after DCB angioplasty might be safe, while also promising improved outcomes during follow-up. Nonetheless, additional research is warranted to better determine the risks and benefits of double-dose paclitaxel approach and to identify populations (eg, patients with long lesions, severely calcified lesions, and CTOs, diabetic patients, etc) that would benefit the most from this approach. Last, cost-effective analyses should help develop optimized DCB angioplasty algorithms, determining when a bail-out intervention should be performed. ■

Scan this QR code to view Tables 1 and 2, Supplemental Table 1, and the article references.

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