İstanbul Med J 2019; 20(1): 44–8
**DOI:** 10.4274/imj.galenos.2018.46693

# Drug-Eluting Balloon Angioplasty for Complex Femoropopliteal Lesions in Patients with End-Stage Renal Disease

## Son Dönem Böbrek Yetersizliği Hastalarında Kompleks Femoropopliteal Lezyonların İlaç Salınımlı Balon Anjiyoplasti ile Açılması

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## ABSTRACT

**Introduction:** The aim of this study was to investigate the safety and efficacy of drug-elicited balloon (DEB) use in the interventional treatment of patients with end-stage renal disease (ESRD) and complex femoropopliteal artery lesions.

**Methods:** A retrospective chart review identified 30 ESRD patients who were treated for symptomatic peripheral artery disease with DEB angioplasty between September 2012 and February 2016. The inclusion criteria were having Rutherford class 2 to 6 symptoms and a critical stenosis or occlusion of the femoropopliteal artery. While restenosis or reocclusion was the primary end point, major or minor amputation was the secondary end point.

**Results:** A total of 36 diabetic patients with complex femoropopliteal lesions who underwent endovascular therapy with DEB were identified. Four patients were lost during follow-up and 30 patients were included in the study. The mean lesion length was 114.6±27.8 mm. Primary patency was 73.1% and the secondary end point was 10.7% at 1-year. After a mean follow-up of 16.0±5.0 months, all-cause mortality was 7.1% (n=2). Ankle-brachial index increased from 0.42±0.04 to 0.88±0.05 postoperatively.

**Conclusion:** DEB angioplasty is efficient and safe even in long and calcified obstructive lesions including the distal superficial femoral and popliteal artery in patients with ESRD.

**Keywords:** Balloon angioplasty, drug-eluting balloon, end-stage renal disease, peripheral interventions

## ÖZ

**Amaç:** Bu çalışmada son dönem böbrek yetersizliği (ESRD) ve kompleks femoropopliteal arter lezyona sahip hastaların girişimsel tedavisinde ilaç salınımlı balon (DEB) kullanımının güvenilirliği ve etkinliğini araştırmaktadır.

**Yöntemler:** Kabul edilme kriterleri, Rutherford sınıf 2 veya üstü semptoma sahip olmak ile birlikte hastalarda femoropopliteal arterde kritik darlık veya tıkanıklık olması idi. Hedef damar tıkanıklığı veya daralması primer sonlanma iken majör ve minör amptütasyon sekonder sonlanım olarak kabul edildi.

**Bulgular:** Eylül 2012 ve Şubat 2016 tarihleri arasında, diyabetik ve kompleks femoropopliteal lezyonu olan ve girişimsel tedavide DEB kullanılmış 36 hasta tanımlandı. Dört hasta takibi bıraktığından dolayı 30 hasta ile devam edildi. Ortalama lezyon uzunluğu 114,6±27,8 mm idi. On iki ay sonunda primer açık kalım %73,1 sekonder sonlanım %10,7 gözlendi. Ortalama 16,0±5,0 aylık takip sonrası tüm sebeplere bağlı mortalite %7,1 olarak gözlendi (n=2). Ayak bileği brakial indeksi operasyon öncesi 0,42±0,04'den operasyon sonrası 0,88±0,05'e yükseldi.

**Sonuç:** ESRD ile birlikte uzun kalsifik ve distal yüzeyel femoral ve popliteal darlığı olan hastalarda dahi girişimsel tedavisinde DEB kullanımı etkilidir.

**Anahtar Kelimeler:** Balon anjiyoplasti, ilaç kaplı balon, son dönem böbrek yetersizliği, periferik girişim

## Introduction

Peripheral arterial disease (PAD) is more common in patients with end-stage renal disease (ESRD) undergoing hemodialysis compared to the general population. By-pass surgery is mostly not suitable since most patients with ESRD have multiple comorbidities with distal occlusions (1). Endovascular treatment (EVT) is the preferred method of revascularization in patients with femoropopliteal lesions. Percutaneous transluminal angioplasty (PTA) is mostly preferred for revascularization of femoropopliteal disease due to its relatively low risk. However, the results of balloon angioplasty alone for the complex femoropopliteal disease have been disappointing (2,3). The possibility of treating superficial femoral artery obstruction and maintaining patency rates has dramatically increased because of further device and technique

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**Received/Geliş Tarihi:** 17.01.2018
**Accepted/Kabul Tarihi:** 16.08.2018

**Cite this article as/Atıf:** Teymen B, Aktürk S. Drug-Eluting Balloon Angioplasty For Complex Femoropopliteal Lesions in Patients with End-Stage Renal Disease. İstanbul Med J 2019; 20(1): 44-8.

development in recent years (4). Recently, drug-eluting balloon (DEB) angioplasty has been introduced to reduce femoropopliteal restenosis compared to plain old balloon (POB) angioplasty. Therefore, we analyzed our experiences with 30 femoropopliteal DEB angioplasties in ESRD patients.

## Methods

### Patient Population

This study was a retrospective single-center study of 34 ESRD patients (hemodialysis patients, four patients lost to follow up leaving 30 patients) with femoropopliteal arterial disease and life-style-limiting claudication who underwent DEB angioplasty between September 2012 and February 2016. The presence of Rutherford Becker class 2 or greater (Fontaine IIB) symptoms and femoropopliteal critical lesions were the inclusion criteria for our study. Mean age was 58.4±6.2 years, and 55% of patients were men. Hypertension (83.3%) and diabetes (66.7%) were the most common risk factors in this patient cohort. Baseline characteristics are summarized in Table 1.

The present study complies with the principles outlined in the Declaration of Helsinki and was approved by the Emsey Hospital Ethics Committee (no: AEK 17/009) and consent was obtained from all patients for participation in the study.

### Procedures

Arterial access was obtained by antegrade puncture in 24 patients and contralateral femoral puncture in 4 patients. In 2 patients, retrograde popliteal approach was preferred because of failed antegrade approach. Duplex ultrasonography (USG) and digital subtraction angiography were used for evaluation of infra-inguinal vessel calcifications. Ankle-brachial index (ABI) was measured before and after the intervention.

Intravenous heparin (100 IU/kg) was given after diagnostic angiography was performed (Figure 1A-C, 2A, 2B). Atherectomy was preferred by operator's choice in severely calcified six lesions with suitable vessel diameter. We used a support catheter with hydrophilic guide wire for chronic total occlusions. All lesions were pre-dilated before treatment with DEB angioplasty (3 minutes inflation time, 4-7 mm 20-120 mm). The ratio of DEB to vessel diameter was planned to be 1:1. The overlap zone was more than 10 mm if multiple balloons were used per lesion. Another dilation of up to 3 minutes was performed if flow-limiting dissection or residual stenosis of more than 50% was seen. A self-expandable stent was deployed when there was flow-limiting dissection or >50% residual stenosis after DEB angioplasty. A completion angiogram concluded the procedure (Figure 2C, 3A, 3B). Patients with additional below the knee lesions were treated with DEB angioplasty (n=5). Arterial access site was managed with digital pressure. Procedural details are summarized in Table 2. Proper medication for risk factors (coronary artery disease, hypertension, and hyperlipidemia) was given with dual antiplatelet therapy (DAPT) (3 months with aspirin 100 mg + Clopidogrel 75 mg then with aspirin alone). At each follow-up visit, a duplex USG of the treated femoropopliteal site (peak systolic velocity ratio 2.5 and >50% decrease in vessel diameter was an angiography indication) and additional peripheral angiography was performed when indicated.

**Table 1. Baseline characteristics**

| Variable | | n=30 |
|---|---|---|
| | | n (%) |
| Age, years | Mean ± SD | 57.4±6.1 |
| Gender | Male | 19 (63) |
| | Female | 11 (37) |
| Diabetes mellitus | | 21 (70.0) |
| Hypertension | | 26 (86.7) |
| Hypercholesterolemia | | 15 (50.0) |
| Coronary artery disease | | 22 (73.3) |
| Cerebrovascular disease | | 1 (3.3) |
| Congestive heart failure | | 4 (15.9) |
| Current smoker | | 18 (60) |

SD: standard deviation

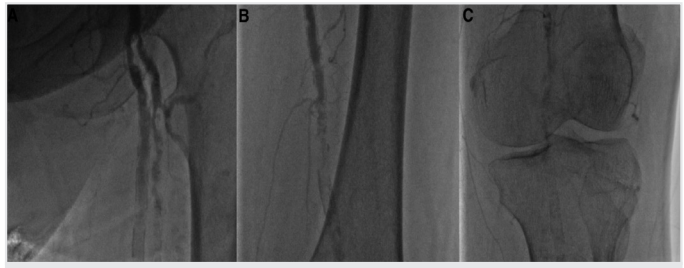


**Figure 1.** Preinterventional angiogram of superficial femoral artery with critical osteal stenosis and severe calcification (A). Femoropopliteal artery with critical stenosis and severe calcification (B) and popliteal artery occlusion (C)

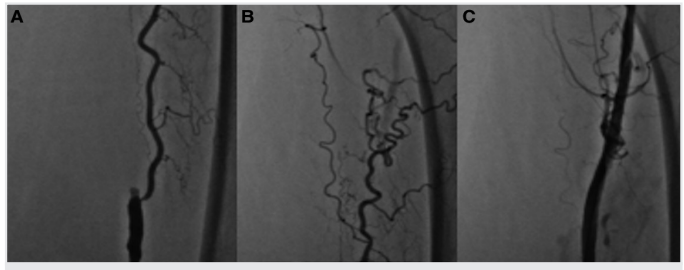


**Figure 2.** Superficial femoral artery chronic total occlusion (A). Popliteal artery is barely visible with collaterals (B). Superficial femoral artery after intervention (C)

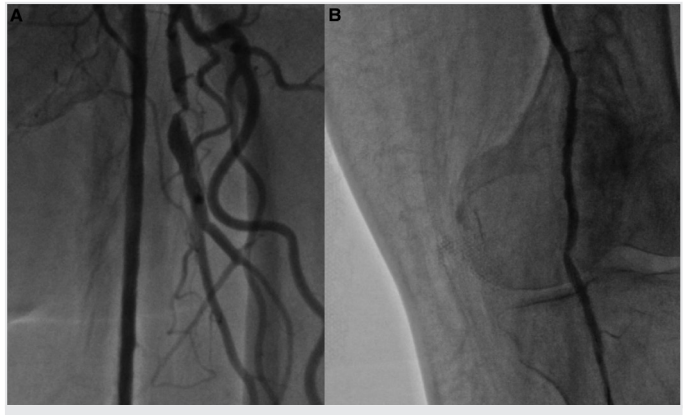


**Figure 3.** Superficial femoral artery after intervention (A). Popliteal artery after intervention (B)

**Table 2. Procedural details**

| Variable | | n=30 |
|---|---|---|
| | | n (%) |
| Mean length, mm | Mean ± SD | 135.56±46.02 |
| Total occlusion | | 11 (36.7) |
| Atherectomy performed | | 6 (20.0) |
| Severe calcification | | 14 (46.7) |
| TASC | A | 4 (13.3) |
| | B | 11 (36.7) |
| | C | 10 (33.3) |
| | D | 5 (16.7) |
| Lesion type | De novo | 25 (83.3) |
| | Restenosis | 3 (10.0) |
| | In-stent stenosis | 2 (6.7) |
| BTK lesion that needed intervention | | 5 (16.7) |
| Multiple DEB | | 16 (53.3) |

TASC: the Trans-Atlantic Inter-Society Consensus document on management of peripheral arterial disease
BTK: below the knee, DEB: drug eluting balloon, SD: standard deviation

**Table 3. Clinical outcomes, 12 months**

| Variable | n (%) |
|---|---|
| Primary endpoint | 19 (73.1) |
| All-cause mortality | 2 (6.7) |
| Minor amputation | 2 (7.7) |
| Major amputation | 1 (3.8) |

### Definitions

Technical success was defined as restoration of straight line of blood flow to the foot with a residual stenosis less than 30%. Restenosis is defined as >%50 lesion. Major amputation was defined as limb loss above the ankle, whereas minor amputation referred to below the ankle amputation or removal of more distal parts of the lower extremity.

### Statistical Analysis

NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for the statistical analysis. Data were reported as mean, standard deviation, median, frequency, and ratio. Wilcoxon signed-ranks test was used to test the difference between preop and postop values. The results were evaluated in 95% confidence interval and at a significance level of $p<0.05$.

## Results

Thirty ESRD patients (hemodialysis patients, four patients were lost during follow-up) who underwent EVT with DEB angioplasty for femoropopliteal lesions were enrolled. The mean follow-up time was 16.0 months. The technical success rate was 93.3%. Procedural details are summarized in Table 2. Stent implantation was needed in 2 patients because of flow limiting dissection. Two patients died due to acute myocardial infarction (10th, 11th month). These four patients were excluded from the primary and secondary end points. Seven patients with restenosis and reocclusion (73.1% patency in 26 patients, >%50 at narrowest point) were diagnosed by clinical investigation and duplex USG (Table 3). Peripheral angiography was performed in these cases after diagnosis. These patients were revascularized with EVT where bailout stent was not needed in any of them. Three amputations involving three patients were seen in this patient cohort (two minor and one major). Minor extravasation occurred when crossing a total occlusion with guide-wire in two patients. Obviously these extravasations were not seen after normal treatment protocol with balloon angioplasty. Access related hematoma occurred in three patients that resolved with manual digital pressure. The mean baseline ABI increased after the intervention, which demonstrated a hemodynamic success, and a clinical improvement with significant decrease in rutherford becker classification was seen in the patients (0.43±0.06, $p<0.001$) (Tables 4, 5).

**Table 4. Rutherford becker classification pre-post (12 months) treatment**

| | | n (%) |
|---|---|---|
| Preop RBC | 0.1 | 0 (0) |
| | 2 | 5 (16.7) |
| | 3 | 17 (56.7) |
| | 4 | 5 (16.7) |
| | 5 | 2 (6.7) |
| | 6 | 1 (3.3) |
| Mean ± SD | | 3.33±0.60 |
| 12 months follow up RBC | 0 | 0 (0) |
| | 1 | 3 (11.5) |
| | 2 | 20 (77) |
| | 3 | 3 (11.5) |
| Mean ± SD | | 2±0.49 |
| | | p<0.01 |

RBC: rutherford becker classification, SD: standard deviation *p<0.01

**Table 5. Change in ankle brachial index**

| ABI | n=30 |
|---|---|
| | Mean ± SD |
| Before procedure | 0.45±0.04 |
| After procedure | 0.88±0.05 |
| | p 0.001** |
| Difference | 0.43±0.06 |

**p<0,01 ABI: ankle brachial index, SD: standard deviation

## Discussion

ESRD is a strong determinant of atherosclerotic vascular disease and is associated with a high incidence of cardiovascular diseases. EVT of infra-inguinal lesions in ESRD patients remains a controversial issue; thus we examined the clinical and procedural outcomes of DEB angioplasty of femoropopliteal lesions in this patient cohort.

ESRD patients on dialysis with DM, frequently have calcific, long and diffuse arteriosclerotic disease in the femoropopliteal site. Therefore, these patients are often not suitable for surgery due to other comorbidities and advanced age, thus making EVT preferable. However, primary patency rate of POB angioplasty is low in multiple studies compared to DEB (3,5-8). Therefore we preferred DEB angioplasty for the treatment of femoropopliteal lesions in this study.

Nitinol or drug-eluting stents have provided better results compared to standard PTA for femoropopliteal disease, but they change the structure of the vessel and it still carries a relevant risk of restenosis, especially in long and complex lesions commonly seen in ESRD patients (5,6). Another important issue is that in-stent restenosis is more difficult to treat than restenosis in non-stented segments. Studies with DEB angioplasty have patency outcomes at least similar to stents but without leaving permanent metallic implants (9-11). Due to these facts, we preferred DEB angioplasty instead of stent deployment in our study.

EVT for PAD in ESRD patients may be technically hard because of the calcified nature of very tight stenosis or mostly occlusion, which makes the crossing by a balloon catheter and even with guide wire problematic. Through mostly antegrade femoral approach (80.0%) with using a support catheter and a hydrophilic guide wire, we crossed the lesions with a high technical success rate of 93.3% in this setting of patients.

Revascularization for peripheral arterial lesions in patients with ESRD has been controversial because of the low rates of limb preservation and short life expectancy and increased risk of dissection in this patient cohort with severe calcification (12-14). EVT, particularly with DEB angioplasty is costly. Although it seemed expensive, in a cost-effectiveness study, it appears to be better compared to local wound care alone, primary amputation or even surgical approach, especially in patients with non-healing foot wounds. (15). A recent analysis came to the conclusion that DEB angioplasty offers the lowest budget impact in the treatment of femoropopliteal lesions (16).

An alternative concept to potentially improve DEB efficacy in lesions with severe calcification (instead of pre-dilatation with a standard balloon) is to combine DEB angioplasty with directional atherectomy. After reducing plaque burden, paclitaxel can potentially inhibit cell proliferation more effectively. The DEFINITIVE AR, which is a pilot study, suggest that there is a benefit with adjuvant directional atherectomy in patients with long and calcified femoropopliteal lesions prior to using a DEB in comparison to the DEB angioplasty alone. However, the study was not sufficiently powered to detect differences in clinical outcomes. In our study, there was only one patient who needed re-intervention out of 6 patients treated with atherectomy before DEB angioplasty (16.7%). Studies with larger population are needed to evaluate the efficacy, safety, and cost-effectiveness of atherectomy as an adjuvant therapy in this patient cohort.

There is still no consensus about the duration of DAPT following DEB angioplasty (ranging from 1 to 3 months or more in different studies) (17,18). We administered a 3-month DAPT in our study. Such duration appeared safe and no acute thrombosis or major bleeding was observed during the follow-up period.

**Study Limitations**

This study has some limitations. First, it was a retrospective study with relatively small patient population lacking a control group. Second, we could not perform follow-up angiography in all patients and third, toe brachial index was not measured although it is needed for reliable diagnosis for PAD in this patient group (19).

## Conclusion

DEB seems efficient and safe in the treatment of complex femoropopliteal lesions in ESRD patients. Larger and longer studies are needed to evaluate the efficacy, safety and cost-effectiveness of DEB angioplasty in this patient cohort.

**Ethics Committee Approval:** The present study complies with the principles outlined in the Declaration of Helsinki and was approved by the Emsey Hospital Ethics Committee.

**Informed Consent:** Consent was obtained from all patients for participation in the study.

**Peer-review:** Externally and internally peer-reviewed.

**Author Contributions:** Concept - B.T., S.A.; Design - B.T., S.A.; Supervision - B.T., S.A.; Resources - B.T., S.A.; Materials - B.T., S.A.; Data Collection and/or Processing - B.T., S.A.; Analysis and/or Interpretation - B.T., S.A.; Literature Search - B.T., S.A.; Writing Manuscript - B.T., S.A.; Critical Review - B.T., S.A.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

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