Peripheral Artery Disease Intervention: Drug-Coated Balloon vs Drug-Eluting Stent, A Long-Term Comparison

Nathan Marzlin, M. Fuad Jan, Louie Kostopoulos, Ana Cristina Perez Moreno, Tanvir Bajwa, and Suhail Q. Allaqaband

Aurora Cardiovascular and Thoracic Services, Aurora Sinai/Aurora St. Luke’s Medical Centers, University of Wisconsin School of Medicine and Public Health, 2801 W. Kinnickinnic River Parkway, Milwaukee, WI 53215, USA

Cardiovascular Research, Advocate Aurora Research, Advocate Aurora Health, 960 N. 12th St., Ste. 4120, Milwaukee, WI 53233, USA

Correspondence should be addressed to M. Fuad Jan; publishing18@aurora.org

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Objectives. The aim of the study is to evaluate current trends and long-term durability of both drug-eluting stents (DES) and drug-coated balloons (DCB) in the treatment of peripheral artery disease (PAD). Background. PAD affects more than 200 million people worldwide. Endovascular treatment of critical PAD has advanced in recent years. DES and DCB have demonstrated superiority compared to balloon angioplasty or bare metal stenting. The current literature lacks any long-term, direct comparison. Methods. A retrospective analysis was completed on patients who had femoral-popliteal interventions from June 2014 to June 2018 with either DCB or DES. Patient medical data and lesion characteristics were retrieved using the Vascular Quality Initiative database. Outcomes were analyzed through December 2019. Primary endpoint of time to clinical event-driven target lesion reintervention (TLR) and secondary endpoint of all-cause mortality were examined. Results. Four hundred eighty-three patients with a total of 563 interventions met the inclusion criteria. Three hundred fifty-nine DCB and 204 DES were performed. Of the DCBs, 132 required bailout stenting at the time of procedure. The mean time for TLR in the DES group was 1,277 days (SD 546), compared to 904 days (SD 330.1) for DCB. For patients requiring TLR, DES remained patent significantly longer (373 days longer on average) (p < 0.001). For all-cause mortality there was no significant difference at 50 months between DCB and DES (p = 0.06). Conclusions. In patients who required TLR, DES had a significantly longer length of time to reintervention vs DCB (average 373 days), although no difference in mortality was observed.

1. Introduction

Endovascular treatment of peripheral artery disease (PAD) has become an important part of current medical practice. With the advancement of endovascular technology, the optimal treatment strategy for femoropopliteal PAD remains somewhat unclear. Femoropopliteal lesions are often complex, lengthy, heavily calcified, and complicated by torsion and flexion from joint movement. The complexity of these lesions creates difficulty with deciding intervention strategy. Previously, endovascular options were limited to primary balloon angioplasty and bare metal stent, with the gold standard of treatment being surgical bypass [1]. In 2012, the Food and Drug Administration (FDA) approved the use of drug-eluting stents (DES) for the treatment of PAD after a randomized study demonstrated improved primary patency with the Zilver (Cook Medical, Bloomington, Ind.) paclitaxel-coated stent compared to a bare metal nitinol stent and primary balloon angioplasty at 12 months [2]. Subsequent analysis demonstrated 5-year durability of the Zilver DES compared to standard of care up to 5 years [3]. In 2014, the Lutonix (Maple Grove, Minn.) drug-coated balloon (DCB) gained FDA approval for the treatment of femoral popliteal PAD after demonstrating a higher rate of primary patency.
with the paclitaxel-coated balloon at 12 months with non-
inferior safety profile [4]. Similar results were seen in the
IN.PACT SFA (superficial femoral artery) trial comparing the
In.Pact Admiral DCB (Medtronic, Minneapolis, Minn.)
vs primary angioplasty [5]. The Admiral DCB was superior
to primary angioplasty up to 36 months [6]. Finally, in 2018
there was FDA approval of the Eluvia paclitaxel DES, which
demonstrated a higher primary patency in a non-inferiority
study compared to the Zilver DES [7]. Despite these exciting
advancements in endovascular treatment of critical PAD,
there had not been a direct comparison between paclitaxel
DCBs and paclitaxel DES. In 2019, the first randomized
controlled trial compared DES vs DCB in 150 patients with
symptomatic femoropopliteal disease. At 12 months there
was no significant difference in primary patency between
the two modalities. Although the study was not designed for
a longer time period, there was a trend toward improved
patency with DES at 36 months compared to DCB [8].
Despite the promising data on both paclitaxel-coated bal-
loons and stents for the treatment of symptomatic femo-
ropopliteal peripheral vascular disease, there remains a lack
of data with direct comparison of long-term patency be-
tween the two modalities.

2. Methods

A retrospective analysis was done using the Vascular Quality
Initiative (VQI) database at a single high-volume center [9].
Patients who were 18 years and older who underwent pe-
ripheral vascular interventions from June 2014 through June
2018 were included. Patients included underwent paclitaxel
DCB or DES of the superficial femoral artery and/or pop-
liteal artery. Patients with previous interventions of the
lesion or previous vascular surgery were excluded. Patients
who received both DES and DCB to the same lesion were
also excluded from the study. Using the VQI database,
baseline characteristics, past medical history, lesion size, and
location were recorded. Baseline characteristics were ana-
lyzed between the two groups. Through retrospective chart
review, patients were followed through December 2019.
Repeat angiography, peripheral interventions, surgical in-
terventions, and all-cause mortality were examined and
analyzed between each modality.

3. Results

A total of 483 patients with a total of 563 procedures from
June 2014 through June 2018 were included. Baseline
characteristics, including smoking history, renal dysfunc-
tion, hypertension, coronary artery disease, cerebral vascular
disease, age, and sex, were compared. A statistical com-
parison between the modalities is demonstrated in Table 1.
Higher rates of previous stroke and renal disease were seen
in the DES group ($p < 0.001$). Additionally, a slightly higher
prevalence of hypertension was seen in the DES group
($p = 0.04$), but otherwise, no significant difference was
demonstrated between the treatment groups. Lesion size and
location were compared between DES and DCB. Vessel
location for DES (Figure 1) and DCB (Figure 2) are shown
below. Length of lesion tended to be longer in DCB than
DES. A breakdown of lesion size for DES and DCB is shown
in Table 2. The majority of patients presented with signifi-
cant claudication or non-healing ischemic wounds. A mi-
nority of patients had ischemic rest pain or acute limb
ischemia. The distribution of presenting symptoms is dis-
played in Figure 3.

Given the earlier FDA approval of DES for the treatment of
PAD, there were higher rates of DES usage in 2014 and
2015. We observed a paradigm shift in the treatment of PAD
(Figure 4) after the FDA approval of the Lutonix DCB in
2014 followed by the Admiral DCB. Usage of DCB increased
significantly, with numbers surpassing DES in the years
2016–2018. After the FDA approval of DCB, standard
practice shifted from primarily using stenting to a DCB-first
approach. If the lesion was not successfully treated by DCB
alone, then the operator would deploy a stent to correct any
residual stenosis or treat underlying flow-limiting dissection.

A retrospective review was done on each patient. Repeat
angiography, intervention, surgical procedure, and ampu-
tation of limbs were reviewed on each patient. Patient
mortality was also recorded and analyzed. Two hundred
and four DES and 359 DCB were used in the treatment if sig-
nificant femoropopliteal PAD was observed. Of the 359
lesions that were treated with DCB, 132 received bailout
stenting at the time of the procedure; of these, 103 were
deployed for residual stenosis, 28 were deployed for arterial
dissection, and one covered stent was placed for perforation
(Figure 5). Univariate Cox regression was used to compare
the two modalities in terms of all-cause mortality. There was
no statistical difference between the two groups at 50
months; hazard ratio (HR) 1.38 (95% CI 0.98–1.95) $p = 0.07$.
The survival curve is demonstrated in Figures 6 and 7.

Due to the significant practice shift observed from DES
to DCB during the timeframe of the study, a dispropor-
tionate amount of stenting was observed at the beginning of
the study compared to DCB. Given the uneven distribution
throughout the study, the risk of failure was not even be-
tween the two modalities. This meant that univariate Cox
regression could not be used to evaluate clinically driven
target lesion reintervention (TLR) between each modality
because the proportional hazard assumption was not
fulfilled.

To correct for the disparity in risk between the two
modalities, we separated all patients who underwent clini-
cally driven TLR. Time to reintervention was then compared
between the two groups. In the DES group, 40 of the 204
patients did not maintain primary patency at the end of the
study; in the DCB group, 58 of the 359 patients did not. The
patients who failed the primary endpoint were evaluated in
terms of time from procedure to TLR. The mean time to TLR
in the DES group was 1,277 days (standard deviation 546
days). In the DCB group, mean time to TLR was 904 days
(standard deviation 330.1 days). This demonstrated a sig-
nificant increase in length of patency in the DES group of an
average of 373 days ($p < 0.001$). Results are shown in Fig-
ures 6 and 7. A multivariate analysis was then performed to
evaluate for additional factors related to TLR. Increased age
was associated with increased TRL ($p = 0.0148$), but all
other variables were not statistically significant. A breakdown of this analysis can be seen in Table 3.

4. Discussion

Although interventions of severe femoropopliteal PAD with paclitaxel-coated devices have shown superiority to standard balloon angioplasty or bare metal stenting, there is a lack of data in the direct comparison between DES and DCB. This study aimed to look at the long-term primary patency and mortality between DCB and DES. Limitations of the study include being a retrospective analysis at a single high-volume center, as well as an uneven distribution of interventions throughout the time period. We acknowledge the limitations; however, the data reflect a real-world comparison between the two modalities.

First, our study demonstrated a significant shift in the standard of care for the treatment of femoropopliteal PAD. Throughout the course of the study, the FDA approval of DCB led to a significant shift to a DCB-first strategy. During the last 3 years, DCB was overwhelmingly used compared to DES. DCB has the appeal of proven durability, at least up to 36 months. It also gives the operator the ability to treat lengthy lesions while minimizing the amount of foreign material left in the vasculature. This strategy includes bailout stenting of any residual stenosis with a shorter nitinol stent.

Table 1: Baseline demographics between the drug-eluting stent and drug-coated balloon treatment groups.

| Factor                              | Drug-eluting stents n = 177 | Drug-coated balloons n = 306 | p value |
|-------------------------------------|-----------------------------|-----------------------------|---------|
| Age at procedure, mean (SD)         | 68.53 (11.71)               | 68.65 (11.10)               | 0.91    |
| Sex                                 |                             |                             |         |
| Female                              | 88 (49.7%)                  | 146 (47.7%)                 | 0.67    |
| Male                                | 89 (50.3%)                  | 160 (52.3%)                 |         |
| Diabetes                            | 108 (61.0%)                 | 163 (53.3%)                 | 0.10    |
| Hypertension                        | 167 (94.4%)                 | 271 (88.6%)                 | 0.04    |
| Pre-op statin                       | 143 (80.8%)                 | 241 (78.8%)                 | 0.59    |
| Coronary artery disease             | 50 (28.2%)                  | 101 (33.0%)                 | 0.28    |
| Cerebrovascular disease             | 140 (79.1%)                 | 85 (27.8%)                  | <0.001  |

Table 2: Lesion lengths compared between drug-eluting stents and drug-coated balloons.

| Lesion length | Drug-eluting stent | Drug-coated balloon |
|---------------|--------------------|---------------------|
| 0–5 cm        | 25                 | 44                  |
| 6–10 cm       | 99                 | 81                  |
| 11–15 cm      | 31                 | 115                 |
| 16–20 cm      | 29                 | 47                  |
| >20 cm        | 20                 | 72                  |
Any patients with a combination of DES and DCB to the same lesion were excluded from our study, so we are not able to comment on that specific strategy.

Previous studies have demonstrated a possible superior long-term durability of DES compared to DCB in the treatment of PAD. The goal of this study was to compare each modality at up to 5 years. While there was an appropriate number of patients in each arm, as previously stated, the distribution throughout the course of the study was not even. Given this, the risk of failure was also distributed unevenly between DES and DCB. To adjust this, we separated and analyzed time to intervention for the patients who required symptom-driven TLR.

The mean time for TLR in the DES group was 1,277 days (SD 546), while the mean time for TLR in the DCB group was 904 days (SD 330.1). In patients requiring TLR, DES remained patent significantly longer than DCB (373 days longer on average) ($p < 0.001$). This suggests that DES may have a longer durability, particularly after 36 months.
5. Conclusion

This five-year comparison of DES vs DCB in the treatment of femoropopliteal PAD demonstrated a longer TLR time in the DES group compared to the DCB counterparts. Although this was a single-center retrospective study, it provides a real-world comparison of not only drug-coated modalities but of the trend of PAD intervention. DCB provides the operator the ability to treat femoropopliteal lesions without the need for lengthy stents and the use of bailout stenting when indicated. This study suggests improved long-term patency in DES vs DCB. A long-term randomized trial between DES and DCB is needed to further investigate the optimal treatment of peripheral vascular disease.

Abbreviations

CAD: Coronary artery disease  
CVD: Cardiovascular disease  
DCB: Drug-coated balloons  
DES: Drug-eluting stents  
FDA: Food and Drug Administration  
HR: Hazard ratio  
PAD: Peripheral artery disease  
PTA: Percutaneous transluminal angioplasty  
SD: Standard deviation  
SFA: Superficial femoral artery  
TLR: Target lesion reintervention  
VQI: Vascular Quality Initiative

Data Availability

The datasets created and used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest regarding the publication of this paper.

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Table 3: Subsequent analysis of additional factors related to clinical event driven target lesion reintervention.

| Predictors                  | Univariate analysis |          |          | Multivariate analysis |          |          |
|-----------------------------|---------------------|----------|----------|-----------------------|----------|----------|
|                             | Odds ratio          | (95% CI) | p value  | Odds ratio            | (95% CI) | p value  |
| Age                         | 0.970               | 0.946–0.994 | 0.0140  | 0.970                 | 0.947–0.994 | 0.0148  |
| Sex                         | 1.306               | 0.722–2.363 | 0.3775  |                       |          |          |
| Current smoking             | 1.304               | 0.703–2.419 | 0.4004  |                       |          |          |
| Diabetes                    | 1.550               | 0.836–2.873 | 0.1643  |                       |          |          |
| Hypertension                | 1.158               | 0.386–3.478 | 0.7934  |                       |          |          |
| Coronary artery disease     | 1.070               | 0.574–1.994 | 0.8311  |                       |          |          |
| Cerebrovascular disease     | 1.171               | 0.55–2.494 | 0.6830  |                       |          |          |