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Midterm Results of Directional Atherectomy for the Treatment of Atherosclerotic Common Femoral Artery Disease

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Short title: Atherectomy of Common Femoral Artery Lesions

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Abstract

Aim: To evaluate the safety and efficacy of directional atherectomy (DA) for the treatment of common femoral artery (CFA) lesions.

Methods and Results: A retrospective analysis of patients who underwent DA of the CFA between March 2009 and June 2017 was performed. The primary efficacy endpoint was the incidence of clinically-driven target lesion revascularization (cdTLR). Secondary endpoints included the overall procedural complication rate at 30 days, change in ankle-brachial index (ABI), and Rutherford-Becker class (RBC) during follow-up.

This analysis included 250 patients. The mean follow-up period was 31.03±21.56 months (range 1-88, median follow-up period 25 months). Procedural complication rate including access site complications, target lesion perforation, and outflow embolization was 10.4% (n=26). All but one complication could be treated conservatively or endovascularly. One surgical revision was necessary. Freedom from major adverse events (death, cdTLR, myocardial infarction and major target limb amputation) at 30 days was 99.6%. CdTLR rate during follow-up was 13.6% (n=34). A significant improvement of the mean ABI and the RBC could be observed, respectively. Multivariate logistic regression analysis revealed residual target lesion stenosis >30% (p=0.005), and heavy calcification of the target lesion (p=0.033) as independent predictors for cdTLR.

Conclusion:

The use of DA for the treatment of CFA lesions leads to promising mid-term results with an acceptable complication rate.

Key words: Claudication; Critical limb ischemia; Atherectomy; Drug-eluting balloon

Condensed Abstract

For lesions involving the common femoral artery (CFA) surgical endarterectomy is still considered the gold standard. Aim of this analysis was to evaluate safety and efficacy of directional atherectomy (DA) for the treatment of CFA lesions.

This analysis included 250 patients. The procedural complication rate was 10.4% and cdTLR rate at mean follow-up period of 31.03±21.56 months was 13.6%. A significant improvement of the mean ankle-brachial index and the Rutherford-Becker class could be observed.

The use of DA for the treatment of CFA lesions leads to promising mid-term results with an acceptable complication rate.

Abbreviations:

ABI – ankle brachial index

CFA – common femoral artery

CLI – critical limb ischemia

DA – directional atherectomy

DCB – drug coated balloon

IC – intermittent claudication

PAD – peripheral artery disease

POBA – plain old balloon angioplasty

RBC – Rutherford-Becker class

TLR – target lesion revascularization

1. INTRODUCTION

In 2010 the worldwide prevalence of peripheral artery disease (PAD) was estimated at 202 million people. Between 2000 and 2010 the incidence increased by 28.7% in countries with low and middle income and by 13.1% in high-income countries. (1)

Endovascular therapy is the first line strategy for femoropopliteal obstructive disease. (2) However, for lesions involving the common femoral artery (CFA) surgical endarterectomy is still the gold standard. (3) Although satisfactory long-term results can be achieved with surgery, the procedure is associated with noteworthy major complications including redo-procedures, wound infections, and nerve damages in up to 13.8 % of the patients. (4-6)

Several studies evaluated technical and clinical outcomes of endovascular procedures for treatment of CFA lesions. (7-11) However, sufficient evidence to support endovascular techniques as an equivalent alternative to open surgery is lacking. Directional atherectomy (DA) is an established endovascular procedure for treatment of femoropopliteal and infrapopliteal lesions (12-17). Subgroup analyses and a small prospective studies revealed promising acute and mid-term results of CFA-DA (7,18,19). In addition, the reported stenting rates following DA are low ranging from 3% to 6.5%. (12,13,17)

Aim of this study was to investigate the safety and the technical and clinical outcome of consecutive patients with atherosclerotic CFA lesions treated by DA with or without additional plain balloon angioplasty (POBA) or drug coated balloon (DCB) angioplasty.

2. METHODS

2.1. Patient population

A consecutively collected and retrospectively evaluated study was established to register patients who received DA of atherosclerotic lesions of the CFA. Between March 2009 and June 2017 medical records, duplex ultrasound measurements, angiographies and endovascular procedures were examined. This trial was approved by the local ethics committee. Patients with PAD Rutherford-Becker class (RBC) 2 to 5 with a de-novo CFA stenosis ≥ 70% (estimated by duplex ultrasound with a peak systolic velocity ratio of > 3.5 and visually on angiography) were eligible for this analysis.

Major exclusion criteria included thrombus within the target lesion, acute critical limb ischemia, lesions not caused by atherosclerotic disease, PAD RBC 0, 1 and 6, and restenosis or re-occlusion after endovascular or surgical index procedure.

2.2. Study endpoints

Primary effectiveness endpoint was the clinically-driven target lesion revascularization (cdTLR)-free survival rate by Kaplan-Meier analysis. Primary safety endpoint was freedom of major adverse events (MAE) at 30 days including death, myocardial infarction, cdTLR, and major target limb amputation.

Secondary endpoints included the overall procedural complication rate, changes in RBC and ankle-brachial index (ABI). The procedural complication rate including, access site complications, target lesion perforation, and outflow embolization. The time to TLR and the type of revascularization (surgery or endovascular procedure) were documented.

2.3. Study Procedures

2.3.1. Directional atherectomy devices

The SilverHawk™, the TurboHawk™ and the HawkOne™ directional atherectomy catheters (Medtronic/ Covidien, Mansfield, USA) were evaluated for treatment of the CFA. The atherectomy catheters are licensed for commercial use by the Food and Drug Administration and the European Union.

2.3.2. Endovascular procedure

The following index procedure related criteria were documented: Sheath size, type of atherectomy catheter, use of an embolic protection device, additional target lesion procedures (plain-old balloon angioplasty, drug-coated balloon angioplasty, stenting), and inflow- and outflow non-target lesion procedures. Target lesions were evaluated in terms of extent (appendix Table 1), degree of calcification (by visual estimation, appendix Table 2), and residual stenosis post procedure. The degree of calcification was estimated visually and divided into three levels according to an own classification (appendix Table 2). The lesion required placement of a 0.014 inch guidewire. Target lesion predilatation, use of an embolic protection device, the number of lesion passes with the atherectomy device as well as potential additional treatments were left to the discretion of the operator. An angiographic residual stenosis below 30% reference vessel diameter was assumed as a successful target lesion intervention.

The interventions were performed by experienced interventionalists. To detect peripheral embolization following atherectomy, the pre- and post-interventional angiographies of the outflow were compared by two endovascular specialists [AR,PF].

2.3.3. Follow-up

According to department standard, a follow-up protocol was advised after index procedure on an outpatient basis. Follow-up visits including physical examination, estimation of the RBC,

ABI measurements and duplex ultrasound were scheduled for 6, 12, and 24 months post procedure.

2.3.4. Statistical analysis

Continuous data are presented as means ± standard deviation; categorical data are given as counts (percentages). Categorical variables were compared with the Fisher exact test, and continuous data were compared with the Student t test.

Binary logistic regression analysis was performed by means of a stepwise forward variable selection procedure to investigate the predictive value of confounding variables: age, gender, body mass index, smoking status, hypertension, dyslipidemia, diabetes mellitus, initial lesion grade (stenosis versus occlusion), initial RBC, lesion length, lesion calcification, reference vessel diameter, DCB use, and post procedural residual stenosis. Outcomes of the regression analysis are given as odds ratio with 95% confident intervals.

Event-free survival (freedom from cdTLR, and MAE) was evaluated using Kaplan-Meier analysis; the survival curves were compared using the Mantel-Cox log-rank test. Multivariate logistic regression analysis was performed to detect predictors of cdTLR.

All hypothesis testing was 2-tailed for comparison of pre- and postinterventional measurements; $p<0.05$ was considered to indicate significance. Analyses were performed using SPSS software (version 23.0; SPSS, Chicago, IL, USA).

3. RESULTS

Between March 2009 and June 2017 2197 patients with arteriosclerotic lesions of the CFA were treated by an endovascular approach. Of these patients, 250 received a DA and were included in this analysis. Baseline characteristics are shown in Table 1. Two hundred and eighteen patients (87.2%) suffered from intermittent claudication (IC, RBC 2 and 3), and 32 patients (12.8%) had critical limb ischemia (CLI, RBC 4 and 5, Table 1; appendix Figure 1-4). There were 153 CFA-bifurcation lesions (61.2%), and 97 isolated CFA lesions (38.8%). Following suspected intraluminal lesion crossing eight CFA- occlusions (3.2%) were included in this analysis.

The DA procedure was performed with either SilverHawk™ device in 16.4% (n=41), TurboHawk™ device in 70.8% (n=177) or HawkOne™ device in 12.8% (n=32), respectively. In 75.6% (n=189) a distal protection device was used to avoid distal debris embolization.

Adjunctive angioplasty following DA was performed in all cases, POBA in 39.6% (n=99), and DCB in 60.4% (n=151), respectively. Bail-out stenting was performed in 8.0% (n=20), and endoprosthesis placement was necessary in 1.2% (n=3) (Table 2). Used DCB's and stents are shown in appendix Table 3.

3.1. Acute and 30-days outcomes

The technical success rate was 92.4% (n=231, Table 3). Twenty-six procedure-related adverse events (10.4%) were documented. Perforations of the target lesion following atherectomy in 10 (4.0%) patients could be treated by prolonged POBA (n=2, 0.8%), nitinol stenting (n=5, 2.0%) or stent graft implantation (n=3, 1.2%) during the index procedure. In six patients (2.4%) an outflow embolization was documented. Three of these embolizations (1.2%) occurred in procedures without the use of a distal protection device. All embolization events were treated

successfully by catheter-aspiration. Six patients (2.4%) with postinterventional access site pseudoaneurysms underwent ultrasound guided compression or local thrombin injection.

Two patients (0.8%) developed a target lesion aneurysm, one was covered with an endoprosthesis during index procedure. The second aneurysm became noticeable by ultrasound 51 days post procedure and was treated by open repair.

All but one complication could therefore be treated conservatively or endovascularly.

All-cause 30-day mortality rate was 0.4% (n=1). (Table 4) This one patient died 28 days post-procedure of unknown cause.

The mean pre-interventional ABI was 0.46±0.23 and increased significantly to 0.82±0.21 ($p<0.001$) at discharge. (Table 3)

Primary safety endpoint, freedom from MAE at 30 days, was 99.6%.

3.2. Mid-term outcomes

During mean follow-up of 31.03 ± 21.56 months (range 1-88, median follow-up period 25 months), 34 patients (13.6%) had to undergo a cdTLR, resulting in a cdTLR-free survival rate of 86.4%. (Figure 1a)

Noteworthy 8 (42.1%) out of 19 patients with a >30% residual target lesion stenosis had a cdTLR.

During follow-up there was no significant difference concerning TLR-free survival neither between patients with CLI and IC (91.7% vs. 84.2%, p=0.277) at baseline, nor between patients with additional POBA or DCB angioplasty following DA (87.2% vs. 83.9% p=0.44), respectively. (Figure 1b) In patients with additional stenting of the target lesion (n=20) the cdTLR-free survival rate was 88.9%.

Multivariate logistic regression analysis revealed residual target lesion stenosis >30% (p=0.005), and heavy calcification of the target lesion (p=0.033) as independent predictors for

TLR. Noteworthy, for mild, moderate, and severely calcified lesions the cdTLR free survival was 94%, 87.9% and 80.6% (p=0.02), respectively (Figure 2).

A significant improvement of the mean ABI and mean RBC values from 0.46±0.23 and 3.2±0.68 to 0.8±0.20 and 2.0±0.64 (p<0.001) could be observed during mean follow-up. The freedom from MAE rate and limb salvage during follow-up was 71.6%, and 100%, respectively. (Figure 3, Table 3).

4. DISCUSSION

Atherectomy and DA in particular is an established treatment option for atherosclerotic femoropopliteal and infrapopliteal artery lesions. (12-17) However, only a few studies are supporting the applicability of DA for the treatment of arteriosclerotic CFA lesions. (7,18,19) The present analysis represents the largest study evaluating the safety, the technical-, and clinical outcomes of patients with CFA lesions treated with DA.

The primary effectiveness endpoint freedom from cdTLR was 86.4% during a mean follow-up of 31±21.6 months. The cdTLR rate (13.6%) is comparable to the results of previous studies ranging from 14.1% and 23% using POBA with provisional stenting or primary stenting for CFA treatment. (7, 8, 19, 20) In the TECCO trial, a prospective, randomized, multi-center study comparing primary stent placement and open surgical reconstruction for CFA treatment, comparable TLR rates at 2-year follow-up (stent cohort 14.4±5.1%, surgical cohort 15.2±5.0%) could be documented (11).

In the last decade the use of DCBs lead to impressive results after femoropopliteal interventions. Although there is no class effect most DCBs showed significantly lower TLR rates at midterm follow-up in comparison to POBA. (21-23) In the present study predictors of TLR were residual target lesion stenosis ≥30%, and severe target lesion calcification. This corresponds to the

results of the DEFINITIVE AR study investigating the effect of DA prior to DCB angioplasty in femoropopliteal lesions. (13) The use of DCBs following DA of the CFA did not reduce the TLR rate in comparison to POBA.

A small prospective, single-center study including 30 patients showed an impressive 1-year TLR rate of only 3.3% for DA plus DCB for CFA treatment (18). A possible explanation for the lack of DCB impact on cdTLR in the present study could be the degree of target lesion calcification, which might prevent sufficient drug-uptake and may result in subacute vessel recoil. Two studies found the degree of target vessel calcification as a predictor for reduced effectiveness of DCBs in femoropopliteal artery lesions, displaying an inverse relationship between primary patency, late lumen loss and the grade of calcification (24-26). Another reason for the lack of superiority of DCBs in this CFA cohort might be the mismatch between vessel size and DCB diameter available leading to an insufficient vessel apposition. In fact, after evaluation of the angiographies and the procedure reports, a mismatch between target lesion reference diameter of up to 10mm and the DCB diameter of maximum 7mm was found in a considerable number of interventions.

The same limitation may be true for the use of vascular lithotripsy, another CFA treatment strategy under clinical evaluation in order to avoid stent placement. Lithotripsy has been shown to achieve acute luminal gain comparable to nitinol stent placement in calcified femoropopliteal lesions (27). However, lithotripsy balloon diameters are also limited to 7mm. An international prospective observational registry study is ongoing evaluating the potential benefit of lithotripsy in CFA interventions besides other indications.

Regarding clinical outcomes a significant improvement in ABI and RBC could be achieved in the vast majority of the patients (84.8%). The limb salvage rate was 100%. These findings are roughly equivalent to other trials dealing with endovascular therapy of the CFA and the femoropopliteal arteries. (8,14,28)

In the present study the procedural complication rate was 10.4%. The target lesion perforation rate was 4.0% (n=10), and comparable to previous femoropopliteal studies (2.3-4.4%). (13-15) All perforations could be treated within the index procedure either by prolonged balloon dilatation or by implantation of bare nitinol stents or covered stents. There was no periprocedural open surgical revision. The overall incidence of target lesion aneurysm formation was low (n=2; 0.8%). Outflow embolization is a dreaded complication of DA. (29-31) Depending on the use of distal embolic protection devices the reported rates range from 2.3% to 5.3%. (12-14) In this study distal embolization was observed in 2.4% (n=6) of the patients. Performing catheter aspiration all emboli could be removed during the index procedure. The 30-day freedom from MAE rate was 99.6%.

There is growing evidence that endovascular procedures possibly have the potential to replace open surgery as the gold standard for CFA treatment. The TECCO trail showed comparable technical results during 2-year follow-up including freedom from TLR and primary patency. However, the perioperative morbidity rate that caused or prolonged hospitalization and/or re-intervention was significantly higher (26% versus 12.5%, p=0.05) and the time to discharge was significantly longer in the surgical group (6.3±3.0 days versus 3.2±2.9 days, p<0.001). (11) Moreover, in a study by Nguyen et al. including 1846 patients with open endarterectomy of the CFA, redo surgery procedures at 30-days (due to e.g. acute target lesion occlusions, bleeding, infections) were necessary in 10.2% of the patients.(5) These results were confirmed by reports from other studies, showing wound infections, nerve injuries, haematoma and lymphatic fistulas in up to 13.6% of cases in patients treated with open endarterectomy. (4,6,32)

The number of patients included in the TECCO trial was too small to draw meaningful conclusion concerning the primary patency rates and TLR presented between the treatment groups (stenting vs. open endarterectomy). Although confirmed by smaller studies and subgroup analyses (7-11), long-term results of CFA stenting are missing. Moreover, stenting of

an access artery might lead to limitations concerning future endovascular procedures. In the present study the rate of CFA stenting was low (8%) and the overall freedom from cdTLR rate was comparable to the results reported for stent placement. Therefore, DA offers a "leave-no-metal-behind" strategy in order to preserve the native artery. The small cohort of patients with CFA stenting in this study (n=20) showed a noticeably low TLR rate of 10% during mean follow-up period of 2 years.

Open endarterectomy of CFA lesions is associated with a 30-day mortality rate of 1.5 to 3.4% (5,31), whereas the mortality rate in the present study was 0.4%. The ongoing prospective, randomized, multi-center PESTO-trial (Percutaneous Intervention Versus Surgery in the Treatment of Common Femoral Artery Lesions) will add evidence to the question whether DA followed by DCB angioplasty has the potential to compete with endarterectomy as the gold standard of CFA treatment. (33)

Limitations

Even if derived from a prospective database the study represents a retrospective single arm analysis without a control group. Moreover, the assumable mismatch of the target lesion reference diameter and the diameter of the DCBs used following DA potentially has an impact on the performance of the DCB cohort.

Conclusion

In experienced hands DA of atherosclerotic CFA lesions provides promising results with a low cdTLR rate in a mid-term follow-up. DA complication rates are acceptable. Severely calcified lesions and a residual stenosis >30% are predictors of cdTLR.

Randomized prospective studies are required to clarify the potential role of this endovascular procedure in CFA treatment compared to the open surgical reconstruction.

Impact on daily practice

DA of atherosclerotic CFA lesions provides promising results. Even if further investigations are necessary, DA should be considered as an alternative therapy option for the treatment of arteriosclerotic lesions of CFA.

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5. DISCLOSURES

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6. REFERENCES

1. Fowkes FG, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, Norman PE, Sampson UK, Williams LJ, Mensah GA, Criqui MH. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. Lancet 2013; 382: 1329-40.
2. Rooke TW, Hirsch AT, Misra S, Sidawy AN, Beckman JA, Findeiss L, Golzarian J, Gornik HL, Jaff MR, Moneta GL, Olin JW, Stanley JC, White CJ, White JV, Zierler RE; American College of Cardiology Foundation Task Force; American Heart Association Task Force. Management of patients with peripheral artery disease (compilation of 2005 and 2011 ACCF/AHA Guideline Recommendations): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013; 61: 1555-1570.
3. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG; TASC II Working Group. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). Eur J Vasc Endovasc Surg 2007; 33: S1eS70.
4. Kang JL, Patel VI, Conrad MF, Lamuraglia GM, Chung TK, Cambria RP. Common femoral artery occlusive disease: contemporary results following surgical endarterectomy. J Vasc Surg 2008; 48: 872-877.
5. Nguyen BN, Amdur RL, Abugideiri M, Rahbar R, Neville RF, Sidawy, AN. Postoperative complications after common femoral endarterectomy. J Vasc Surg 2015; 61: 1489-1494.
6. Wieker CM, Schönefeld E, Osada N, Lührs C, Beneking R, Torsello G, Böckler D. Results of common femoral artery thromboendarterectomy evaluation of a traditional surgical management in the endovascular era. J Vasc Surg 2016; 64: 995-1001.

7. Bonvini RF, Rastan A, Sixt S, Noory E, Schwarz T, Frank U, Roffi M, Dorsaz PA, Schwarzwälder U, Bürgelin K, Macharzina R, Zeller T. Endovascular treatment of common femoral artery disease: medium-term outcomes of 360 consecutive procedures. J Am Coll Cardiol 2011; 58: 792-798.
8. Azéma L, Davaine JM, Guyomarch B, Chaillou P, Costargent A, Patra P, Gouëffic Y. Endovascular repair of common femoral artery and concomitant arterial lesions. Eur J Vasc Endovasc Surg 2011, 41: 787-793.
9. Stricker H, Jacomella V. Stent-assisted angioplasty at the level of the common femoral artery bifurcation: midterm outcomes. J Endovasc Ther 2004; 11: 281-286.
10. Bath, J, Avgerinos, E. A pooled analysis of common femoral and profunda femoris endovascular interventions. Vascular 2016, 24: 404-413.
11. Gouëffic Y, Della Schiava N, Thaveau F, Rosset E, Favre JP, Salomon du Mont L, Alsac JM, Hassen-Khodia R, Reix T, Allaire E, Ducasse E, Soler R, Guyomarc'h B, Nasr B. Stenting or surgery for de novo common femoral artery stenosis. J Am Coll Cardiol Intv 2017; 10: 1344-1354.
12. McKinsey JF, Zeller T, Rocha-Singh KJ, Jaff MR, Garcia LA, DEFINITIVE LE Investigators. Lower extremity revascularization using directional atherectomy: 12-month prospective results of the DEFINITIVE LE study. J Am Coll Cardiol Intv 2014; *7*: 923-933.
13. Zeller T, Langhoff R, Rocha-Singh KJ, Jaff MR, Blessing E, Amann-Vesti B, Krzanowski M, Peeters P, Scheinert D, Torsello G, Sixt S, Tepe G, DEFINITIVE AR Investigators. Directional atherectomy followed by a paclitaxel-coated balloon to inhibit restenosis and maintain vessel patency: twelve-month results of the DEFINITIVE AR Study. Circ Cardiovasc Interv 2017; 10, e004848.
14. Roberts D, Niazi K, Miller W, Krishnan P, Gammon R, Schreiber T, Shammas NW, Clair D ; DEFINITIVE Ca++Investigators. Effective endovascular treatment of

calcified femoropopliteal disease with directional atherectomy and distal embolic protection: final results of the DEFINITIVE Ca++ trial. Catheter Cardiovasc Interv 2014; 84: 236-244.

15. Rastan A, McKinsey JF, Garcia, LA, Rocha-Singh KJ, Jaff MR, Noory E, Zeller T, DEFINITIVE LE Investigators. One-year outcomes following directional atherectomy of infrapopliteal artery lesions: subgroup results of the prospective, multicenter DEFINITIVE LE Trial. J Endovasc Ther 2015; 22: 839-846.
16. Rastan A, McKinsey JF, Garcia, LA, Rocha-Singh KJ, Jaff MR, Harlin S, Kamat S, Janzer S, Zeller T. One-Year Outcomes Following Directional Atherectomy of Popliteal Artery Lesions: Subgroup Analysis of the Prospective, Multicenter DEFINITIVE LE Trial. J Endovasc Ther 2018; 25: 100-108.
17. Cioppa A, Stabile E, Popusoi G, Salemme L, Cota L, Pucciarelli A, Ambrosini V, Sorropago G, Tesorio T, Agresta A, Biamino G, Rubino P. Combined treatment of heavy calcified femoro-popliteal lesions using directional atherectomy and a paclitaxel coated balloon: one-year single centre clinical results. Cardiovasc Revasc Med 2012; 13: 219-223.
18. Cioppa A, Stabile E, Salemme L, Popusoi G, Pucciarelli A, Iacovelli F, Arcari A, Coscioni E, Trimarco B, Esposito G, Tesorio T. Combined use of directional atherectomy and drug-coated balloon for the endovascular treatment of common femoral artery disease: immediate and one-year outcomes. EuroIntervention 2017; 12: 1789-1794.
19. Bonvini RF, Rastan A, Sixt S, Beschorner U, Noory E, Schwarz T, Roffi M, Dorsaz PA, Schwarzwälder U, Bürgelin K, Macharzina R, Zeller T. Angioplasty and provisional stent treatment of common femoral artery lesions. J Vasc Interv Radiol 2013; 24: 175-183.

20. Davies RS, Adair W, Bolia A, Fishwick G, Sayers RD, McCarthy MJ. Endovascular treatment of the common femoral artery for limb ischemia. Vasc Endovascular Surg 2013; 47: 639-644.
21. Tepe G, Zeller T, Albrecht T, Heller S, Schwarzwälder U, Beregi JP, Claussen CD, Oldenburg A, Scheller B, Speck U. Local delivery of paclitaxel to inhibit restenosis during angioplasty of the leg. N Engl J Med 2008; 358: 689-699.
22. Tepe G, Laird J, Schneider P, Brodmann M, Krishnan P, Micari A, Metzger C, Scheinert D, Zeller T, Cohen DJ, Snead DB, Alexander B, Landini M, Jaff MR, IN.PACT SFA Trial Investigators. Drug-Coated Balloon Versus Standard Percutaneous Transluminal Angioplasty for the Treatment of Superficial Femoral and Popliteal Peripheral Artery Disease CLINICAL PERSPECTIVE: 12-Month Results From the IN. PACT SFA Randomized Trial. Circulation 2015; 131: 495-502.
23. Sixt S, Cancino OGC, Treszl A, Beschorner U, Marcharzina R, Rastan A, Krankenberg H, Neumann FJ, Zeller T. Drug-coated balloon angioplasty after directional atherectomy improves outcome in restenotic femoropopliteal arteries. J Vasc Surg 2013; 58: 682-686.
24. Fanelli F, Cannavale A, Gazzetti M, Lucatelli P, Wlderk A, Cirelli C, d'Adamo A, Salvatori FM. Calcium burden assessment and impact on drug-eluting balloons in peripheral arterial disease. Cardiovasc Intervent Radiol 2014; 37: 898-907.
25. Tzafriri AR, Garcia-Polite F, Zani B, Stanley J, Muraj B, Knutson J, Kohler R, Markham P, Nikanorov A, Edelman ER. Calcified plaque modification alters local drug delivery in the treatment of peripheral atherosclerosis. J Control Release 2017; 264: 203-210.
26. Tepe G, Beschorner U, Ruether C, Fischer I, Pfaffinger P, Noory E, Zeller T. Drug-eluting balloon therapy for femoropopliteal occlusive disease: predictors of outcome with a special emphasis on calcium. J Endovasc Ther 2015, 22: 727-733.

27. Brodmann M, Werner M, Holden A, Tepe G, Scheinert D, Schwindt A, Wolf F, Jaff M, Lansky A, Zeller T. Primary outcomes and mechanism of action of intravascular lithotripsy in calcified, femoropopliteal lesions: Results of Disrupt PAD II. Catheter Catheter Cardiovasc Interv. 2019 Feb 1;93(2):335-342. doi: 10.1002/ccd.27943
28. Baumann F, Ruch M, Willenberg T, Dick F, Do DD, Keo HH, Baumgartner I, Diehm N. Endovascular treatment of common femoral artery obstructions. J Vasc Surg 2011; 53: 1000-1006.
29. Suri R, Wholey MH, Postoak D, Hagino RT, Toursarkissian B. (2006). Distal embolic protection during femoropopliteal atherectomy. Catheter Cardiovasc Interv 2006; 67: 417-422.
30. Shammas NW, Dippel EJ, Coiner D, Shammas GA, Jerin M, Kumar A. Preventing Lo wer Extremity Distal Embolization Using Embolic Filter Protection: Results of the PROTECT Registry. J Endovasc Ther 2008; 15: 270-276.
31. Lam RC, Shah S, Faries PL, McKinsey JF, Kent KC, Morrissey NJ. Incidence and clinical significance of distal embolization during percutaneous interventions involving the superficial femoral artery. J Vasc Surg 2007; 46: 1155-1159.
32. Siracuse JJ, Gill HL, Schneider DB, Graham AR, Connolly PH, Jones DW, Meltzer AJ. Assessing the perioperative safety of common femoral endarterectomy in the endovascular era. Vasc Endovascular Surg 2014; 48: 27-33.
33. Rastan A, Boehme T, Zeller T. Percutaneous Intervention Versus Surgery in the Treatment of Common Femoral Artery Lesions. The PESTO-Trial. www.clinicaltrials.org. NCT02517827.
34. Medina A, de Lezo JS, Pan M. A new classification of coronary bifurcation lesions. Revista espanola de cardiologia 2006; 59: 183-183.

7. Figure legends

Figure 1a.

Title: Freedom from cdTLR entire cohort

Legend: Kaplan-Meier plot of survival free from cdTLR.

cdTLR – clinically-driven target lesion revascularization

Figure 1b.

Title: Freedom from cdTLR stratified to Drug Coated Balloon vs. Plain Old Balloon Angioplasty following Directional Atherectomy

Legend: Kaplan-Meier analysis of survival free from cdTLR for patients treated with POBA and DCB following atherectomy

cdTLR – clinically-driven target lesion revascularization

Figure 2.

Title: Freedom from cdTLR depending on the degree of calcification

Legend: Kaplan-Meier analysis of survival free from cdTLR depending on the degree of calcification. cdTLR – clinically-driven target lesion revascularization

Figure 3.

Title: Freedom from MAE

Legend: Kaplan-Meier analysis of survival free from MAE

MAE - major adverse events. MAE including death, myocardial infarction, TLR, and major target limb

8. Tables

Table 1.

Baseline Characteristics	n=250
Age, yrs	70±9.2
Male sex	170 (68)
Hypertension	226 (90.4)
Diabetes mellitus	86 (34.4)
Hyperlipidemia	225 (90)
Smoker	77 (30.8)
Coronary heart disease	125 (50)
Myocardial infarction	43 (17.2)
Cerebral vascular disease	66 (26.4)
Stroke	30 (12)
Chronic obstructive pulmonary disease	28 (11.2)
Renal insuffciency*	61 (24.4)
Claudication	218 (87.2)
Critical limb ischemia	32 (12.8)
Rutherford-Becker class	
2	23 (9.2)
3	195 (78)
4	12 (4.8)
5	20 (8.0)

Values are n (%). * defined as clearance < 60 ml/min

Table 2.

Lesion and Index Procedure Characteristics	
Lesion anatomy	
CFA	97 (38.8)
CFA + DFA	17 (6.8)
CFA + SFA	42 (16.8)
CFA + DFA + SFA	94 (37.6)
Degree of calcification	
Mild	57 (22.8)
Moderate	63 (25.2)
Severe	130 (52.0)
Atherectomy	
SilverHawk	41 (16.4)
TurboHawk	177 (70.8)
HawkOne	32 (12.8)
Filter device used	189 (75.6)
Adjunctive target lesion therapy	
Plain old balloon angioplasty	99 (39.6)
Drug coated balloon	151 (60.4)
Stent implantation	20 (8.0)
Non-target lesion interventions	
Inflow (CIA, EIA)	38 (15.2)
Outflow (SFA, DFA, Popliteal)	195 (78)

Values are n (%)

CFA – common femoral artery, DFA – deep femoral artery, SFA – superficial femoral artery, CIA – common iliac artery, EIA – external iliac artery

Table 3.

Clinical and Procedural Outcomes	
Residual stenosis ≤ 30%	231 (92.4)
Degree of stenosis	
Baseline *	81.44±7.9
Post-procedure *	21.82±9.4 (p=0.021)
Ankle-Brachial-Index	
Baseline	0.46±0.23
Post-procedure	0.82±0.21 (p<0.001)
Follow-up	0.8±0.22 (p<0.001)
Rutherford-Becker Class	
Baseline	3.2±0.68
Follow-up	2.04±0.64 (p<0.001)
cdTLR	34 (13.6)
Endovascular reintervention	21 (8.4)
Open, surgical treatment	13 (5.2)
Time to cdTLR (in months)	27.41±13.77
Major amputation	0
Minor amputation	2 (0.8)
Freedom from Major adverse events	249 (99.6)

Values are n (%) or mean ± SD

* By visual estimation

cdTLR – clinically-driven target lesion revascularization

Table 4.

Procedural Complications	
Access site pseudoaneurysm	6 (2.4)
Perforation (target lesion)	10 (4.0)
- Successful endovascular treatment	10 (4.0)
Distal Embolization	6 (2.4)
- Without protection device	3 (1.2)
- Successful endovascular treatment	6 (2.4)
Aneurysm	2 (0.8)
- Endovascular treatment	1 (0.4)
- Surgical treatment	1 (0.4)
Technical complications	2 (0.8)
- Conservative treatment	2 (0.8)

Values are n (%)

9. Figures

Figure 1a.

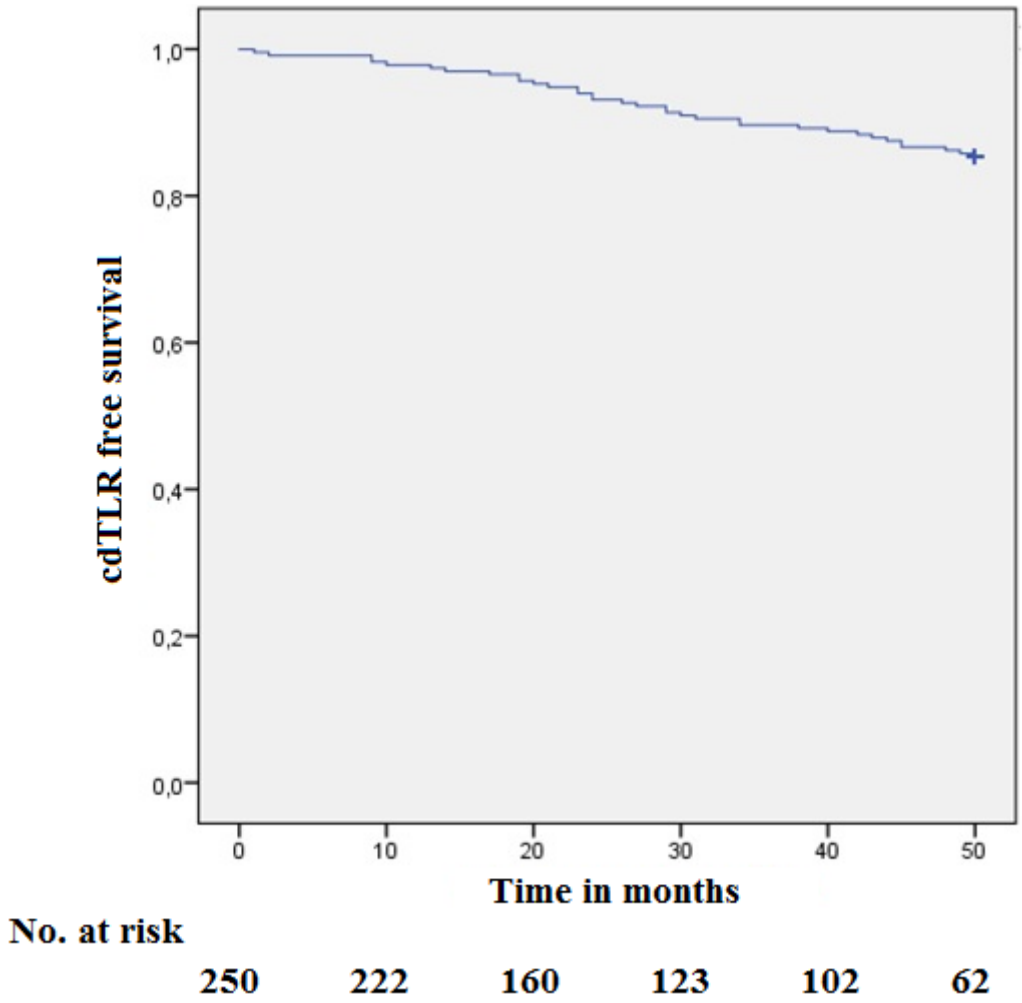
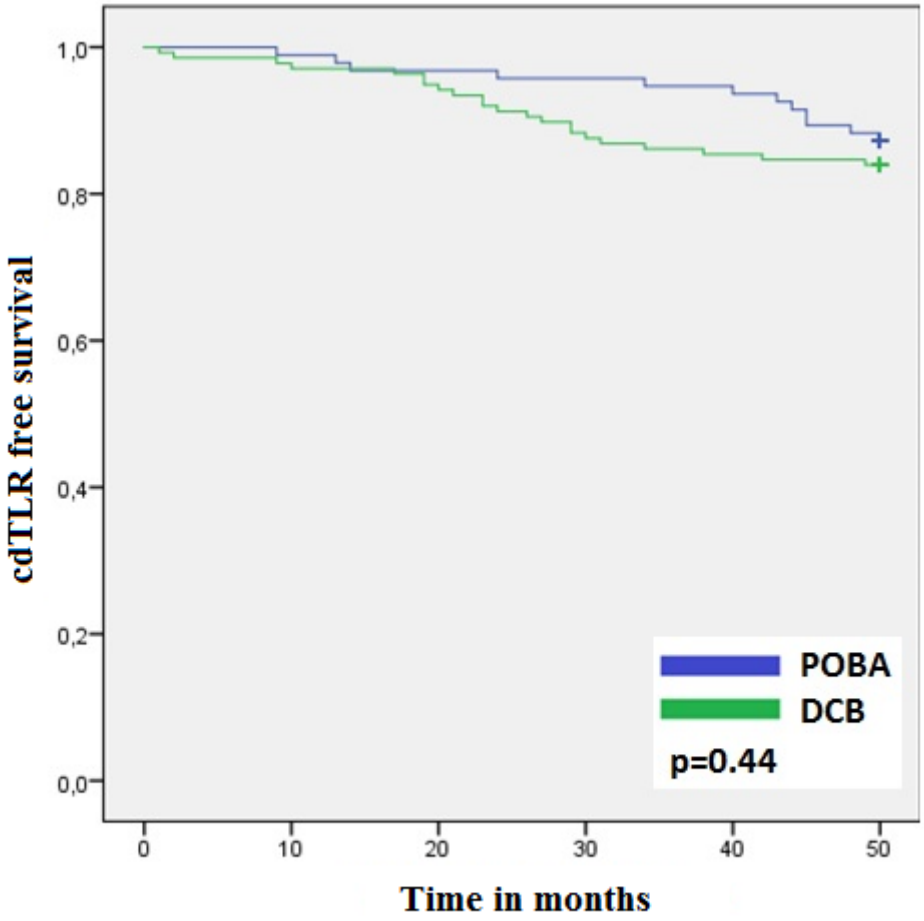


Figure 1b.



No. at risk

250	222	160	123	102	62

Figure 2.

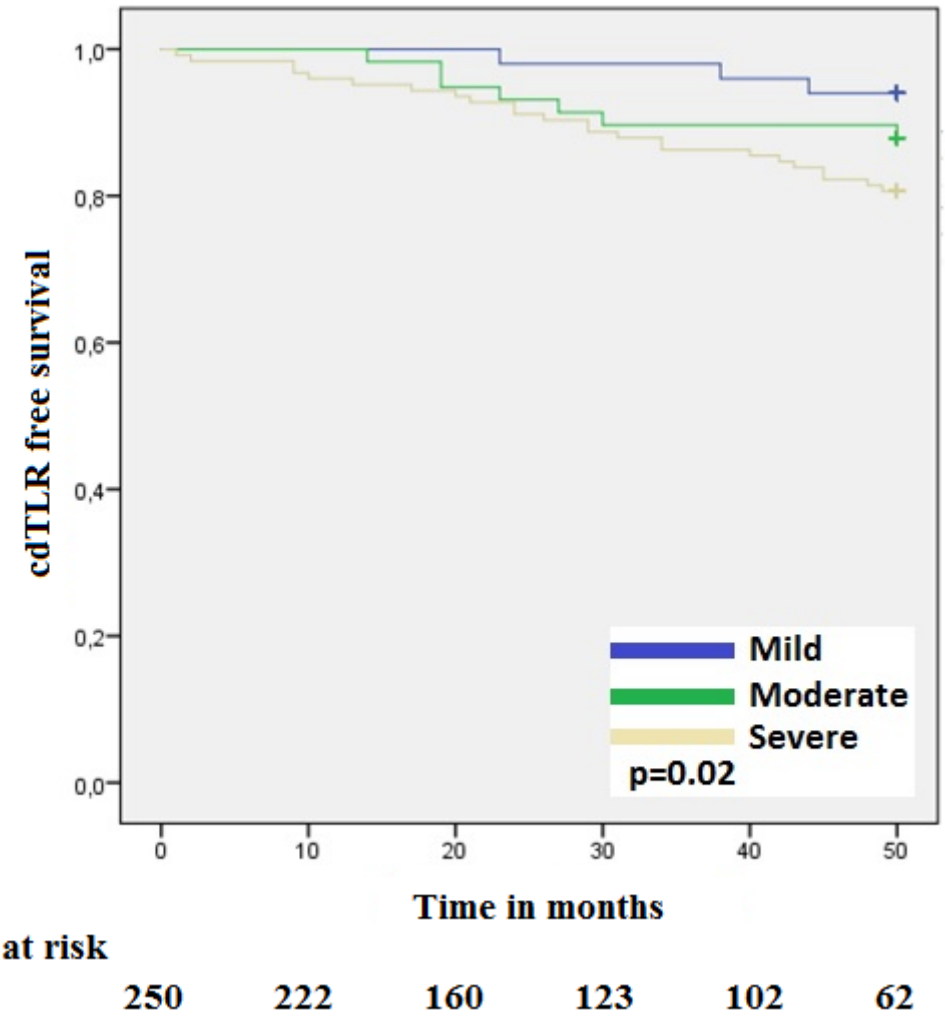
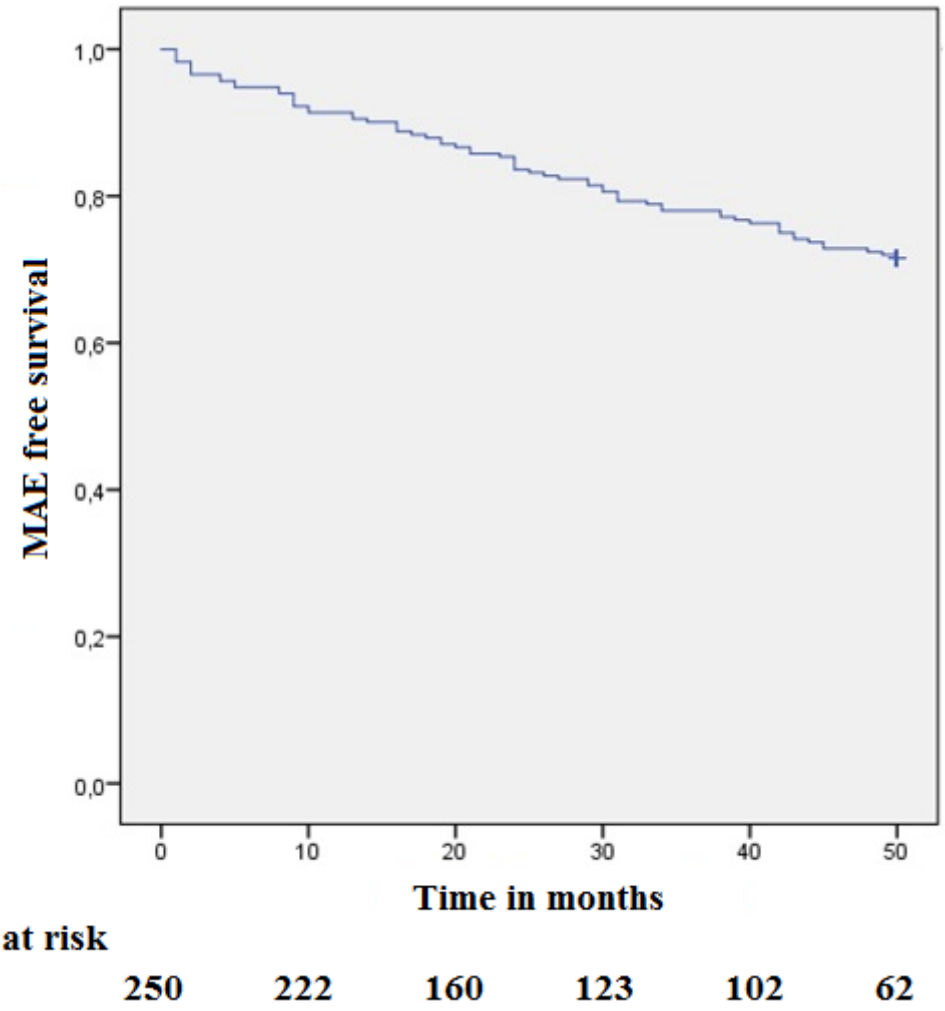
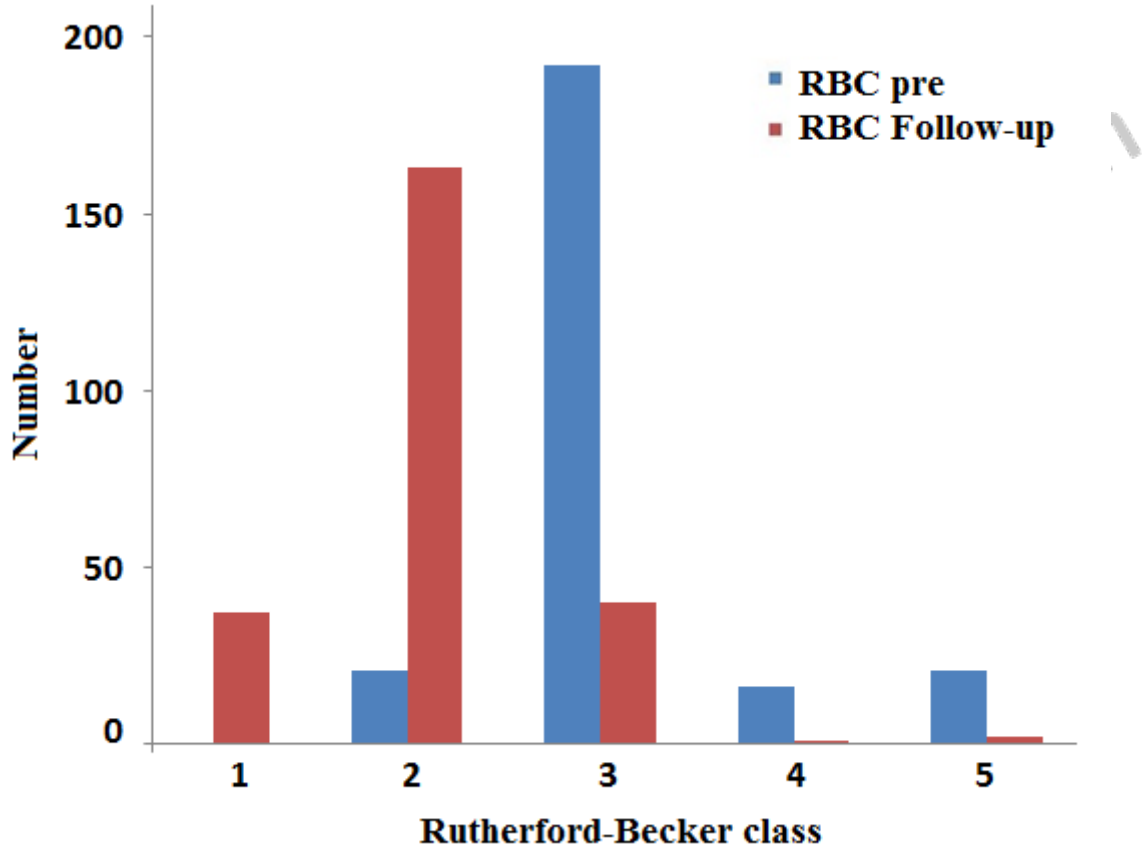


Figure 3.



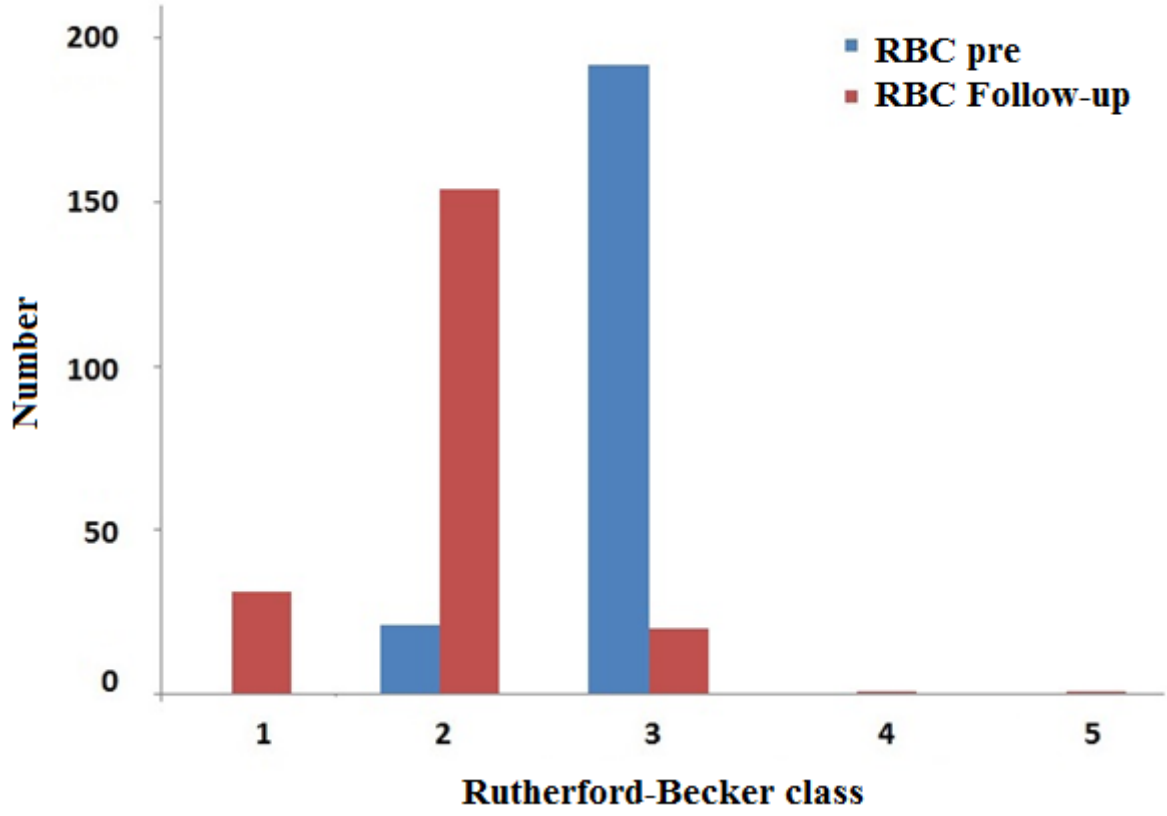
aAppendices

Appendix Figure 1. Distribution of the Rutherford-Becker category preinterventional and Follow-up for the overall cohort



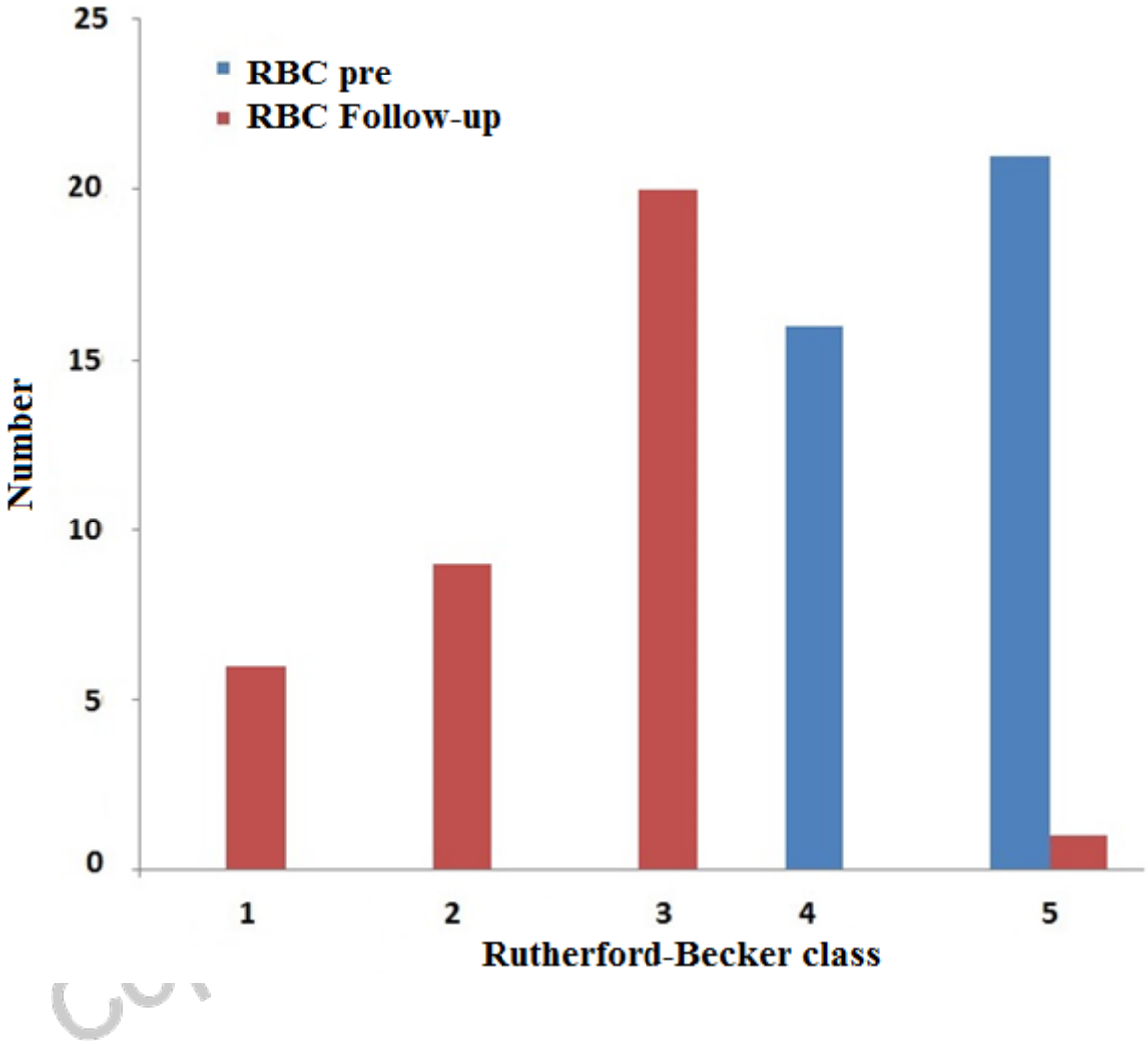
RBC- Rutherford-Becker class

Appendix Figure 2. Distribution of the Rutherford-Becker category preinterventional and Follow-up for the claudicants



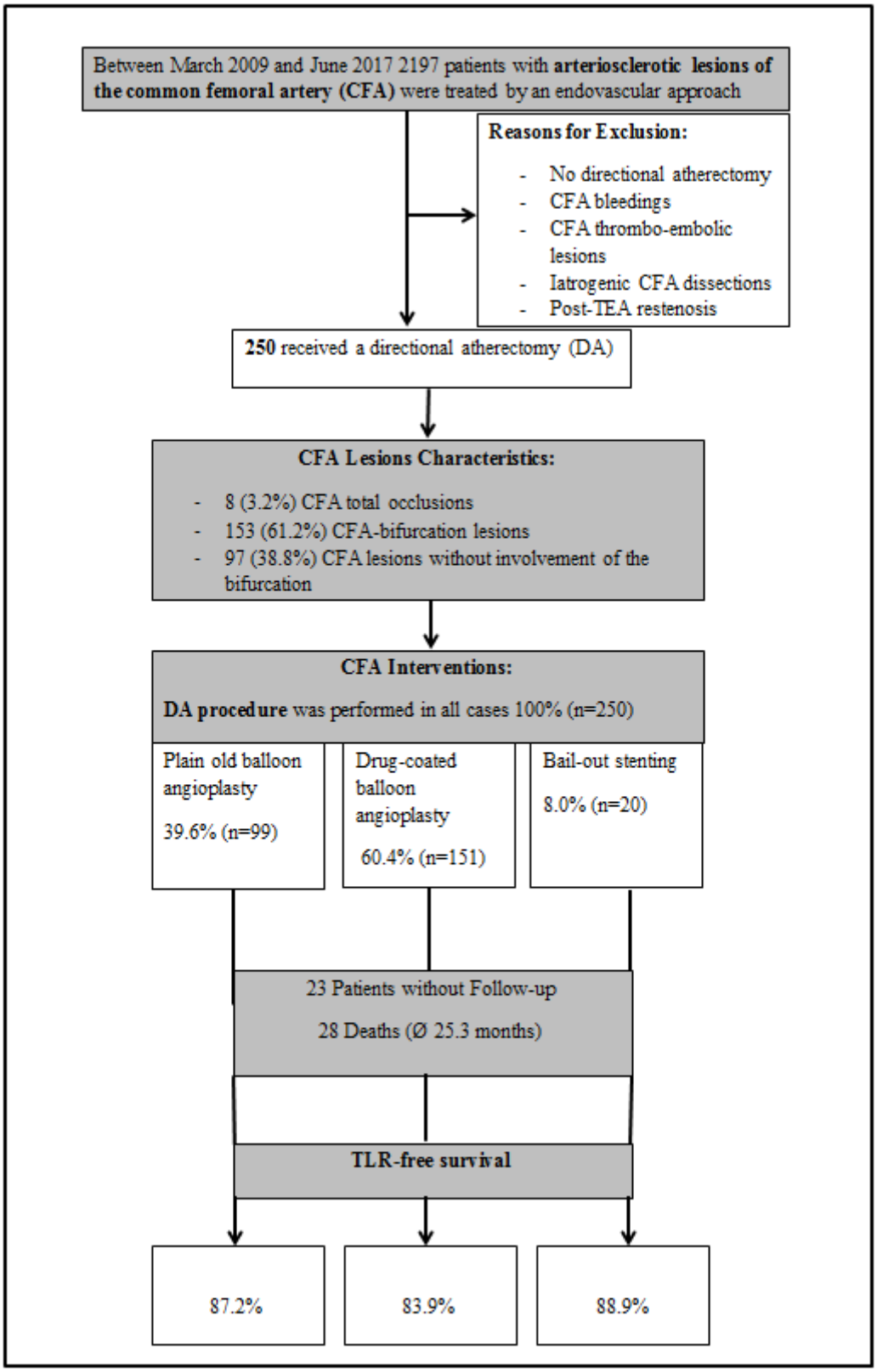
RBC- Rutherford-Becker class

Appendix Figure 3. Distribution of the Rutherford-Becker category preinterventional and Follow-up for the patients with critical ischaemia



RBC- Rutherford-Becker class

Appendix Figure 4. Patient Flow Diagram



DA Directional atherectomy, CFA common femoral artery

Appendix Table 1. Medina classification (34)

Medina classification (34)	
1-0-0	CFA only
1-0-1	CFA and ostial DFA
1-1-0	CFA and ostial SFA
1-1-1	CFA, ostial DFA and ostial SFA

CFA – common femoral artery, DFA – deep femoral artery, SFA – superficial femoral artery

Appendix Table 2. Degree of calcification

Degree of calcification		(x-ray based visual estimation)
1	None/Mild	Concentric or eccentric calcification, calcification contributes ≤30% to the target lesion stenosis.
2	Moderate	Concentric or eccentric calcification, calcification contributes >30% - ≤50% to the target lesion stenosis.
3	Severe	Concentric or eccentric calcification, calcification contributes >50% to the target lesion stenosis.

Appendix Table 3. Used Drug Coated Balloons and Stents

Drug coated balloon	151 (60.4)
Inpact	140 (56)
Lutonix	7 (2.8)
Freeway	2 (0.8)
Passeo	1 (0.4)
Stellarex	1 (0.4)
Stents	20 (8.0)
Smart (2*)	7 (2.8)
Absoulte (2*)	3 (1.2)
Supera	3 (1.2)
Viabahn (1*)	2 (0.8)
BeGraft (2*)	2 (0.8)
Scuba	1 (0.4)
Complete (1*)	1 (0.4)
LifeStent	1 (0.4)
Location of stenting	
CFA	16 (6.4)
SFA	1 (0.4)
CFA and DFA	2 (0.8)
CFA, DFA and SFA	1 (0.4)
Stent diameter	
7 mm	6 (2.4)
8 mm	6 (2.4)
9 mm	3 (1.2)

10 mm	3 (1.2)
12 mm	2 (0.8)

* used in case of perforation

CFA – common femoral artery, DFA – deep femoral artery, SFA – superficial femoral artery