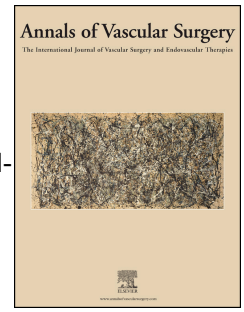
Accepted Manuscript



Drug-coated vs. Plain Balloon Angioplasty in Bypass Vein Grafts (the DRECOREST I-study)

Patrick Björkman, M.D., Tatu Kokkonen, M.D., Anders Albäck, M.D., Ph.D., Maarit Venermo, M.D., Ph.D.

PII: S0890-5096(18)30565-X

DOI: 10.1016/j.avsg.2018.04.042

Reference: AVSG 3964

To appear in: *Annals of Vascular Surgery*

Received Date: 26 February 2018

Revised Date: 20 April 2018

Accepted Date: 25 April 2018

Please cite this article as: Björkman P, Kokkonen T, Albäck A, Venermo M, Drug-coated vs. Plain Balloon Angioplasty in Bypass Vein Grafts (the DRECOREST I-study), *Annals of Vascular Surgery* (2018), doi: 10.1016/j.avsg.2018.04.042.

Title page

Drug-coated vs. Plain Balloon Angioplasty in Bypass Vein Grafts (the DRECOREST I-study)

Patrick Björkman, M.D.,[a,c], patrick.bjorkman@hus.fi

Tatu Kokkonen, M.D., [b], tatu.kokkonen@hus.fi

Anders Albäck, M.D., Ph.D., [a], anders.alback@hus.fi

Maarit Venermo, M.D., Ph.D., [a,c], maarit.venermo@hus.fi

[a]) Helsinki University Hospital, Dept. of Vascular Surgery, P.O.Box 441, 00029 HUS, Finland

[b]) Helsinki University Hospital, Dept. of Interventional Radiology, address as above

[c]) University of Helsinki, Faculty of medicine, P.O.Box 63, 00014 University of Helsinki, Finland

Corresponding Author: Patrick Björkman

Word count: 3496 (excl. abstract)

No external funding

The abstract was presented at the Annual Meeting of the European Society for Vascular Surgery in Lyon, France in September 2017. The work is accepted in the Global and Rising Stars –program at the Charing Cross meeting in London, UK in April 2018.

Keywords: peripheral arterial disease; drug-coated balloons; vein grafts; restenosis; intimal hyperplasia

Drug-coated vs. Plain Balloon Angioplasty in Bypass Vein Grafts (the DRECOREST I-study)

Abstract

Objective: Stenosis is a known complication in bypass vein grafts for peripheral arterial disease (PAD). The aim of this study was to evaluate the effect of drug-coated balloons (DCB) in the treatment of vein graft stenoses. *Summary Background Data:* DCBs may prevent restenosis in arterial lesions. One small prospective, and larger retrospective and registry studies have failed to show benefit from DCBs in vein grafts. Prospective data are scarce. *Materials and Methods:* 60 patients treated for primary or recurrent stenosis in venous bypass grafts were randomized to DCB (n=30) or standard balloon angioplasty (BA) (n=30). Follow-up was 1 year. The primary outcome measure was target lesion revascularization (TLR). Secondary outcome measures were assisted primary patency and secondary patency and graft occlusion. *Results:* Fifty-seven patients were analyzed. Three patients were excluded due to primary technical failure (2 DCB, 1 BA). Overall TLR-rate was 34.5 % and 46.4 % in the DCB and BA groups, respectively (P= .33). Five (8.8 %) grafts occluded during follow-up (1 DCB, 4 BA). Assisted primary patency was 93.1% (DCB) vs. 85.7% (BA) (P= .362) and secondary patency was 100 % (DCB) vs. 89.3% (BA) (P= .076). Subgroup analysis showed a significant benefit from DCB in the treatment of primary stenosis (TLR-rate 15.0 % vs. 18.9 %, P= .03). *Conclusions:* There was no significant benefit from DCBs for treatment of vein graft stenosis compared to BA, although a trend in favor of DCBs could be seen. *Trial registration:* ClinicalTrials.gov NCT03023098

Funding: This trial did not receive external funding.

Keywords: peripheral arterial disease; drug-coated balloons; vein grafts; restenosis; intimal hyperplasia

1. Introduction

The use of autogenous vein grafts for arterial bypass is a well-established technique in vascular surgery and remains the gold standard among revascularization techniques for long occlusive lesions in ischemic limbs.[1] These bypass grafts, typically the autologous great saphenous vein (GSV), have demonstrated remarkable longevity.[2] In contrast to prosthetic grafts, vein grafts remodel to resemble native arterial vessel wall as they are exposed to arterial pressure and blood flow.[3] The complex inflammatory processes of arterialization are associated with significant changes in the biomechanical qualities of the graft and with development of neointimal hyperplasia (NIH), stenosis and ultimately graft failure.[4,5] Vein graft stenosis typically occurs within the first year after operation, and thus warrants ultrasound guided follow-up to prevent occlusion and loss of the graft. There is on-going research into mechanical, pharmaceutical and biological treatments for prevention of NIH and stenosis.[6] Invasive treatments for developed stenoses include balloon angioplasty and in some cases surgical resection and interposition of the lesion.

Endovascular strategies have dramatically changed the approach to limb ischaemia in recent years.[7] Drug-eluting stents have already proven their worth in coronary artery lesions and to some degree in superficial femoral artery (SFA) occlusions.[8] Drug-coated balloons (DCB) are emerging as a promising way of treating recurrent stenosis in peripheral arteries. Conventional percutaneous transluminal angioplasty (PTA) mechanically dilates the stenosis in the vessel, but simultaneously causes intimal injury to the site of the balloon angioplasty (BA). Biological repair processes of intimal injury are associated with NIH and eventually restenosis and occlusion of the vessel. This is known as late lumen loss (LLL). As a consequence, repeat

interventions (target lesion revascularization, TLR) are common. The drug-eluting devices are coated with a cytostatic drug, usually paclitaxel or everolimus, to target the development of NIH. DCBs deliver the drug to the site of injury without leaving potentially thrombogenic stent material intraluminally.

We designed and conducted a prospective, single-center, controlled trial including patients with stenoses in infrainguinal venous bypass grafts. The patients were randomized to BA or DCB and followed up for a year. The objective of the study was to investigate potential benefit from DCBs with respect to restenosis, repeat interventions and bypass failure when compared to conventional balloon angioplasty.

2. Materials & Methods

Patients with restenosis in above or below-knee femoropopliteal, femorocrural, or femoropedal vein grafts were randomized between March 2013 and December 2015. Chart 1 shows the design of the study. Inclusion and exclusion criteria are listed in table 1. Perianastomotic (<15 mm from an anastomosis) stenoses were excluded. The autogenous grafts included single-segment and spliced great saphenous and arm veins. All bypasses were-performed using translocated, non-reversed and valvulectomized vein. At our institution grafts are routinely monitored with ultrasound check-ups for 12 months postoperatively. Both groups included stenoses that were detected under routine graft surveillance and symptomatic patients with bypass vein grafts who presented at the emergency department. Both groups included *de novo* lesions that had not been treated before, as well as restenosis. Grafts were examined with duplex-ultrasound; graft diameter, cross-section area and peak systolic velocity ratio (PSVR) was measured at the stenosis. The threshold for intervention was a PSVR of 2.5. Clinical presentation did not affect inclusion, as the intervention

is purely prophylactic regarding graft salvage. The interventions were performed in the angio suite with ipsilateral or crossover access from common femoral artery or direct graft puncture. In cases of concomitant lesions, the index lesion was always defined as the most proximal lesion. The lesion was crossed after angiography and thereafter predilated with a conventional balloon (90 sec.), and then treated again with DCB or BA according to randomization (90 sec.). Sizing was performed intraoperatively from the angiography images by the treating interventionist. All patients were administered 5000 IU heparin at intervention start. The DCB used in this trial had a paclitaxel dose of 3.5 $\mu g/mm^2$ and used urea as excipient (Medtronic IN.PACT, Medtronic, Minneapolis, MN, USA). Technical success was defined as residual stenosis <30% and no graft rupture. All patients, except those on warfarin, were started on dual antiplatelet therapy (DAPT) postoperatively (ASA 100 mg + Clopidogrel 75 mg). DAPT was continued for 3 months, after which the patients returned to their original drug regime. Patients on warfarin received conjunctive ASA 50 mg for three months. Patients and outcome assessors were blinded to the groups. A specially trained vascular nurse performed follow-up at 1, 6, and 12 months after intervention. The follow-up protocol included clinical evaluation (symptoms, ABI) as well as duplex ultrasound assessment of the graft and the index lesion (diameter, PSVR). Reinterventions were triggered by a PSVR of >2.5 regardless of clinical findings.

The primary endpoint was any revascularization of the same lesion (target lesion revascularization, TLR). Secondary outcome measures were graft occlusion, assisted primary patency and secondary patency. Assisted primary patency is defined in relation to the index intervention, i.e. not for the graft itself, and was defined as graft patency maintained by repeated PTA. Secondary patency was defined as time to

restored patency after surgical or endovascular thrombectomy and/or angioplasty. Based on the published literature on arterial stenosis at the time of trial design, we assumed that the 12-month TLR-rate for the BA and DCB groups is 30% and 10%, respectively.[9] With a two-sided 5% significance level and a statistical power of 80% the necessary sample size was 140 (70+70). The study was approved by the Ethical Committee of Helsinki and Uusimaa Hospital District (297/13/03/02/2012). This paper reports the results of a registered study, which can be accessed at ClinicalTrials.gov NCT03023098.

2.1 Randomization

Randomization was done after the stenosis was successfully crossed and predilated with a conventional balloon. 1:1 block randomization by sequenced concealed envelopes was used. A research nurse performed patient inclusion and allocation, as well as postoperative follow-up.

2.2 Statistical analysis

Statistical analysis was performed with SPSS version 22 (IBM, Armonk, NY, USA). Continuous variables are expressed as mean (SD) and dichotomous variables as proportions. Baseline analysis was performed with Student's t-test and Mann-Whitney analysis. Patency comparison was performed using Kaplan-Meier survival curves and log-rank (Mantel-Cox) testing. The analyses and 95% confidence intervals (CI) were calculated using SPSS. Relative risk was calculated by $RR = (a/(a+b))/(c/(c+d))$. There were no missing TLR data. Missing data for baseline analysis was managed by pairwise deletion.

3. Results

254 patients were evaluated for eligible stenosis. 194 patients were excluded due to perianastomotic stenosis or unavailable research personnel. The CONSORT flow diagram is shown in chart 2. The trial was discontinued due to slow recruitment at 60 patients. No interim analysis was performed prior to the discontinuation. Fifty-seven cases were ultimately included in the study. Three randomized cases were excluded due to primary technical failure (graft rupture and bail-out stenting (N=2), aborted procedure (N=1)). Baseline homogeneity characteristics are listed in table 2. There was a baseline difference in toe pressure and rate of diabetes; otherwise the groups were homogenous with regard to general health, medication and bypass anatomy and technique. Technical details of the interventions are given in table 3. Six patients died during follow-up (DCB 4, BA 2). There was one major amputation in the BA-group. The overall TLR-rate at one year was 34.5 % and 46.4 % in the DCB and BA groups, respectively (P= .33). Relative risk for DCB was 0.81 (95% CI 0.40-1.63, P= .596). Five (8.8 %) grafts occluded during the follow-up, 1/29 (3.4 %) and 4/28 (14.3 %) in the DCB and BA groups respectively (P=0.36). There was a trend towards benefit from DCB: assisted primary patency was 93.1% (DCB) vs. 85.7% (BA) (P= .362) while secondary patency was 100 % in the DCB group compared to 89.3% in the BA group (P= .076). Figures 3-5 show the Kaplan-Meier plots for patency. There was no difference between the groups in clinical findings at any stage of the trial (table 4).

In an *ad hoc* subanalysis, TLR-rate was significantly lower in *de novo* lesions that were treated with DCB compared to BA (15.0 % compared to 18.9 %, P= .03).

4. Discussion

As vein graft stenoses are often the result of NIH rather than calcified lesions as seen in arterial stenoses, we hypothesized that this model would be ideal to demonstrate

clinical effect from NIH suppression by paclitaxel. Our study did not show significant overall benefit from use of paclitaxel-coated balloons. There was, however, a trend toward better overall secondary patency rates in the DCB group, and this was clinically significant in *de novo* stenoses. In further subgroup analysis, the baseline difference in diabetes did not impact outcome.

Drug coated and drug-eluting devices have in recent years claimed their place in the treatment of peripheral arterial disease, and the trend in clinical practice is increasingly shifting towards balloon angioplasty combined with DCB or stent rather than BA alone. Many studies show clinical benefit particularly in femoropopliteal native artery lesions, with recent trials suggesting benefit several years postoperatively.[10] Kayssi *et al* published a Cochrane review of DCB *vs.* BA in 2016. This review showed better patency rates, longer freedom-from-TLR, and less binary restenosis after DCB angioplasty. Importantly, however, there was no statistical significance in outcomes such as death, freedom-from-amputation, change in Rutherford, or change in ABI. Furthermore, there was no benefit from DCB in a subgroup analysis of patients with CLI, and another subgroup of tibial vessel lesions.[11] In the current study we compared the DCB with BA in patients who underwent treatment for a bypass stenosis. Mid-term results of DCB so far have been controversial; good results are seen in the SFA, while the outcomes of randomized trials are less clear for below-the-knee arteries. [12-15] With the exception of cell migration, the pathological mechanisms of in-stent restenosis (ISR) are comparable to NIH in grafts. However, during 3 years' follow-up, there was no difference in outcome between DCBs and BA for femoropopliteal ISR in a recent randomized trial. [16] Another prospective trial showed superior clinical outcomes after DCB for ISR at 24 months. [17] Two small studies have demonstrated promising results for use of DCB

in failing dialysis accesses.[18,19]. The biomechanical and anatomical properties of vein grafts differ greatly from native arteries, and less is known about the potential of drug-coated devices in this field. One small, randomized trial did not demonstrate benefit from use of DCB over BA in bypass vein grafts.[20] This study included synthetic grafts and anastomotic stenosis, and is thus not directly comparable to our design. Similar results were observed in a Danish registry review comparing bare metal stents to drug-eluting stents in vein grafts in coronary bypass surgery[21], and another retrospective study comparing BA to DCB in peripheral grafts.[22] The latter included 83 patients and has a follow-up of >2 years. The results are quite reminiscent of ours with regard to patencies. In a recent small retrospective analysis, 39 patients with failing autologous grafts were analyzed for primary, assisted primary, and secondary patency after DCB or BA.[23] There was no difference between the groups and, on financial grounds, use of DCB was discouraged.

The indications for use of DCBs in peripheral graft restenosis are, as of yet, not firmly established. Interventions for bypass graft stenosis are relatively common. Usually the stenosis is asymptomatic and is found by the ultrasound follow-up. The indication for PTA is to maintain graft patency, as occlusion usually means loss of the vein graft, and the availability of good vein material for bypass is limited. In our earlier retrospective study we found that there might be some benefit from DCB compared to BA in the treatment of graft stenosis.[24] Our current study does not provide conclusive evidence in favor of DCBs as a routine solution for vein graft stenoses. However, it suggests that when a lesion is treated for the first time, there may be benefit from using a DCB. The difference in outcome rates between *de novo* stenosis and restenosis is interesting. Several factors may contribute to this result. By definition, stenoses treated with primary PTA include lesions caused by all underlying etiologies.

On the contrary, recurrent stenosis may hypothetically more often be due to other reasons than NIH, such as technical errors in anastomoses, inadequate valvulectomy, an erroneously placed clip or ligature in a graft branch *et cetera*. These stenoses of course do not benefit from the use of drug-coated devices, which can explain this difference in outcome. Furthermore, paclitaxel is an antiproliferative agent that is widely used in cancer treatment. Its potential toxic and inflammatory effect on arterial walls has been studied in animal models, with inconclusive results and unpredictable uptake patterns.[25,26]

In our institution, the practice has so far been to use DCBs in grafts with a history of one or more balloon angioplasties. However, our results indicate that this practice may need to be revised: there seems to be no benefit from use of DCB in the recurrent lesions, but rather when the vein graft stenosis is treated for the first time.

Our trial is limited and underpowered by its sample size. The primary reason for exclusion after assessment for eligibility was perianastomotic stenosis; inclusion of these would have yielded a much bigger sample size. However, this way the histology and pathogenesis of the included lesions probably are more homogenous, and confounding from surgical trauma to the graft is minimized. Furthermore, as the annual number of bypass operations has decreased due to the revolution in endovascular techniques, the number of vein grafts at risk has decreased equally. As a consequence of the limited number of patients, there is a high probability of type II error in the results. The main strength of the study is that it is to date the largest prospective controlled trial, with comprehensive follow-up as no patient was lost to follow-up. Furthermore, two dedicated and experienced research nurses, with training in graft surveillance with duplex ultrasound, did the follow-up

5. Conclusions

Our results are in line with the earlier retrospective studies. In our trial, no significant benefit was seen from DCBs for all graft stenoses, although a type II error is likely in our underpowered trial and no definitive conclusions can be made. For financial reasons, there has been hesitation towards using drug-coated balloons as a first choice in the treatment of graft stenosis. Our results suggest that this hesitation might be unfounded, and that these lesions could benefit more than recurrent stenoses. More data is needed to, in clinical practice, accurately select which lesions will benefit most from DCB. Furthermore, future trials should not only address patency and freedom from TLR, but also assess cost-efficiency. Also, histological studies on paclitaxel uptake and response in the arterialized venous wall are warranted.

Acknowledgements

The authors would like to thank research nurses Anita Mäkela and Anne Blumen for conducting the inclusion of patients and ultrasonographical follow-up.

Fig 1 Study setup

Fig 2 CONSORT flow diagram

Fig 3 Kaplan-Meier for 1-year primary patency with numbers-at-risk (BA=solid line, DCB=dashed line)

Fig 4 Kaplan-Meier for 1- year assisted primary patency with numbers-at-risk (BA=solid line, DCB=dashed line)

Fig 5 Kaplan-Meier for 1-year secondary patency with numbers-at-risk (BA=solid line, DCB=dashed line)

References

1. Owens CD, Gasper WJ, Rahman AS, Conte MS. Vein graft failure. J Vasc Surg 2015;61:203-16.

2. Saarinen E, Kauhanen P, Söderström M, Albäck A, Venermo M. Long-term Results of Inframalleolar Bypass for Critical Limb Ischaemia. Eur J Vasc Endovasc Surg 2016;52:815-22.

3. Muto A, Model L, Ziegler K, Eghbalieh SDD, Dardik A. Mechanisms of Vein Graft Adaptation to the Arterial Circulation; – Insights Into the Neointimal Algorithm and Management Strategies –. Circulation 2010;74:1501-12.

4. Varty K, Allen KE, Bell PRF, London NJM. Infrainguinal vein graft stenosis. Br J Surg 1993;80:825-33.

5. Tigerstedt NM, Savolainen-Peltonen H, Lehti S, Hayry P. Vascular cell kinetics in response to intimal injury ex vivo. J Vasc Res 2010;47:35-44.

6. Inderbitzin DT, Bremerich J, Matt P, Grapow MT, Eckstein FS, Reuthebuch O. One-year patency control and risk analysis of eSVS(R)-mesh-supported coronary saphenous vein grafts. J Cardiothorac Surg 2015;10:108,015-0293-y.

7. Garg K, Kaszubski PA, Moridzadeh R, Rockman CB, Adelman MA, Maldonado TS, Veith FJ, Mussa FF. Endovascular-first approach is not associated with worse amputation-free survival in appropriately selected patients with critical limb ischemia. J Vasc Surg 2014;59:392-9.

8. Windecker S, Remondino A, Eberli FR, Juni P, Raber L, Wenaweser P, Togni M, Billinger M, Tuller D, Seiler C, Roffi M, Corti R, Sutsch G, Maier W, Luscher T, Hess OM, Egger M, Meier B. Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization. N Engl J Med 2005;353:653-62.

9. Schmidt A, Piorkowski M, Werner M, Ulrich M, Bausback Y, Braunlich S, Ick H, Schuster J, Botsios S, Kruse HJ, Varcoe RL, Scheinert D. First experience with drug-eluting balloons in infrapopliteal arteries: restenosis rate and clinical outcome. J Am Coll Cardiol 2011;58:1105-9.

10. Micari A, Nerla R, Vadalà G, Castriota F, Grattoni C, Liso A, Russo P, Pantaleo P, Roscitano G, Cremonesi A. 2-Year Results of Paclitaxel-Coated Balloons for Long Femoropopliteal Artery Disease: Evidence From the SFA-Long Study. JACC: Cardiovasc Interv 2017;10:728-34.

11. Kayssi A, Al-Atassi T, Oreopoulos G, Roche-Nagle G, Teng Tan K, Rajan D. Drug-eluting balloon angioplasty versus uncoated for peripheral arterial disease of the lower limbs. Cochrane Database of Systematic Reviews 2016

12. Liistro F, Porto I, Angioli P, Grotti S, Ricci L, Ducci K, Falsini G, Ventoruzzo G, Turini F, Bellandi G, Bolognese L. Drug-eluting balloon in peripheral intervention for below the knee angioplasty evaluation (DEBATE-BTK): a randomized trial in diabetic patients with critical limb ischemia. Circulation 2013;128:615-21.

13. Liistro F, Grotti S, Porto I, Angioli P, Ricci L, Ducci K, Falsini G, Ventoruzzo G, Turini F, Bellandi G, Bolognese L. Drug-eluting balloon in peripheral intervention for the superficial femoral artery: the DEBATE-SFA randomized trial (drug eluting

balloon in peripheral intervention for the superficial femoral artery). JACC Cardiovasc Interv 2013;6:1295-302.

14. Zeller T, Baumgartner I, Scheinert D, Brodmann M, Bosiers M, Micari A, Peeters P, Vermassen F, Landini M, Snead DB, Kent KC, Rocha-Singh KJ. Drug-eluting balloon versus standard balloon angioplasty for infrapopliteal arterial revascularization in critical limb ischemia: 12-month results from the IN.PACT DEEP randomized trial. J Am Coll Cardiol 2014;64:1568-76.

15. Laird JR, Schneider PA, Tepe G, Brodmann M, Zeller T, Metzger C, Krishnan P, Scheinert D, Micari A, Cohen DJ, Wang H, Hasenbank MS, Jaff MR. Durability of Treatment Effect Using a Drug-Coated Balloon for Femoropopliteal Lesions: 24-Month Results of IN.PACT SFA. J Am Coll Cardiol. 2015;66(21):2329-2338

16. Grotti S, Liistro F, Angioli P, Ducci K, Falsini G, Porto I, Ricci L, Ventoruzzo G, Turini F, Bellandi G, Bolognese L. Paclitaxel-Eluting Balloon vs Standard Angioplasty to Reduce Restenosis in Diabetic Patients With In-Stent Restenosis of the Superficial Femoral and Proximal Popliteal Arteries: Three-Year Results of the DEBATE-ISR Study. J Endovasc Ther. 2016;23(1):52-7.

17. Ott I, Cassese S, Groha P, Steppich B, Voll F, Hadamitzky M, Ibrahim T, Kufner S, Dewitz K, Wittmann T, Kasel AM, Laugwitz KL, Schunkert H, Kastrati A, Fusaro M. ISAR□PEBIS (Paclitaxel□Eluting Balloon Versus Conventional Balloon Angioplasty for In□Stent Restenosis of Superficial Femoral Artery): A Randomized Trial. J Am Heart Assoc 2017; 6.

18. Kitrou PM, Spiliopoulos S, Katsanos K, Papachristou E, Siablis D, Karnabatidis D. Paclitaxel-coated versus plain balloon angioplasty for dysfunctional arteriovenous

fistulae: one-year results of a prospective randomized controlled trial. J Vasc Interv Radiol 2015;26:348-54.

19. Patane D, Giuffrida S, Morale W, L'Anfusa G, Puliatti D, Bisceglie P, Seminara G, Calcara G, Di Landro D, Malfa P. Drug-eluting balloon for the treatment of failing hemodialytic radiocephalic arteriovenous fistulas: our experience in the treatment of juxta-anastomotic stenoses. J Vasc Access 2014;15:338-43.

20. Kitrou P, Parthipun A, Diamantopoulos A, Padayachee S, Karunanithy N, Ahmed I, Zayed H, Katsanos K. Paclitaxel-coated balloons for failing peripheral bypass grafts: the BYPACS study. J Cardiovasc Surg (Torino) 2014;55:217-24.

21. Hougaard M, Thayssen P, Kaltoft A, Tilsted H, Maeng M, Flensted Lassen J, Thuesen L, Okkels Jensen L. Long-term outcome following percutaneous coronary intervention with drug-eluting stents compared with bare-metal stents in saphenous vein graft lesions: From Western Denmark heart registry. Catheter Cardiovasc Interv 2014; 83:1035-42.

22. Linni K, Ugurluoglu A, Aspalter M, Hitzl W, Holzenbein T. Paclitaxel-coated versus plain balloon angioplasty in the treatment of infrainguinal vein bypass stenosis. J Vasc Surg 2016;63(2):391-8

23. Jongsma H, Akkersdijk G, de Smet A, Vroegindeweij D, de Vries JPM, Fioole B. Drug-eluting balloons and uncoated balloons perform equally to rescue infrainguinal autologous bypasses at risk. J Vasc Surg. 2017;66:454-460.

24. Björkman P, Peltola E, Albäck A, Venermo M. Peripheral Vascular Restenosis: A Retrospective Study on the Use of Drug-Eluting Balloons in Native Arteries, Vein Grafts and Dialysis Accesses. Scand J Surg. 2017;106:158-164

386 25. Kelsch B, Scheller B, Biedermann M, Clever YP, Schaffner S, Mahnkopf D,
387 Speck U, Cremers B. Dose response to Paclitaxel-coated balloon catheters in the
388 porcine coronary overstretch and stent implantation model. Invest Radiol
389 2011;46:255-63.

390 26. Radeleff B, Lopez-Benitez R, Stampfl U, Stampfl S, Sommer C, Thierjung H,
391 Berger I, Kauffmann G, Richter GM. Paclitaxel-induced arterial wall toxicity and
392 inflammation: tissue uptake in various dose densities in a minipig model. J Vasc
393 Interv Radiol 2010;21:1262-70.

394

395

Inclusion criteria	**Exclusion criteria**
US documented stenosis (PSVR >2.5)	Any previous DCB-treatment
Eligible for angioplasty	Perianastomotic stenosis (<15 mm)
Adequate inflow to graft	Any known coagulopathy
Age >18	Occluded graft
Signed and dated consent	Apparent need for stenting or surgical repair
Negative pregnancy test when applicable	Life expectancy <1 year

Table 1. Inclusion and exclusion criteria

		DCB		BA		*p*-value
		Mean	**Range**	**Mean**	**Range**	
Age		70.4	45-88	72.3	55-89	*.970*
		N	***%***	***N***	***%***	
Sex	Female	14	48.3	11	39.3	*.639*
	Male	15	51.7	17	60.7	
Diabetes	None	18	62.1	11	39.3	*.012*
	Type 1	0	0	2	7.1	
	Type 2, drug controlled	6	20.7	5	35.7	
	Type 2, insulin controlled	5	17.2	10	17.9	
Hyperlipidemia	None	3	10.3	1	3.6	*.409*
	Diet controlled	1	3.4	0	0	
	Statin	25	86.2	27	96.4	
Cerebrovascular	None	25	86.2	26	92.9	*.381*
	Asymptomatic, evidence of disease	2	6.9	0	0	
	TIA, resolved stroke	2	6.9	1	3.6	
	Stroke with permanent deficit	0	0	1	3.6	
Hypertension	None	6	20.7	8	28.6	*.366*
	1 drug	12	41.4	10	35.7	
	2 drugs	9	31	10	35.7	
	>2 drugs	2	6.9	0	0	
Cardiac	None	15	51.7	17	60.7	*.394*
	AMI >6 mo, asymptomatic CHF	9	31	5	17.9	
	Stable AP, asymp. arrhythmia	5	17.2	6	21.4	
	Unstable AP, symp. arrhythmia, severe CHF	0	0	0	0	
Pulmonary	Normal X-ray, pulmonary function tests 80% of predicted	24	82.8	24	85.7	*.990*
	Asymptomatic, mild changes on X-ray, PFT 65-80%	4	13.8	2	7.1	
	Dyspnea, changes on X-ray, PFT 35-65%	1	3.4	2	7.1	
Renal failure	No	23	79.3	24	85.7	*.345*
	S-creatinine 114-229 µmol/l	2	6.9	1	3.6	
	S-creatinine 230-458 µmol/l	1	3.4	1	3.6	
	S-creatinine >458 µmol/l or on dialysis/transplanted	1	3.4	1	3.6	
Smoking	None	12	41.4	14	50	*.579*
	No, quit within 10 years	5	17.2	6	21.4	
	Yes, <20/day	9	31	7	25	
	Yes, >20/day	2	6.9	1	3.6	
Medication	ASA	26	89.7	23	82.1	*.273*

	Clopidogrel	18	62.1	16	42.9	*1.000*
	Low molecular weight heparin	6	20.7	2	7.1	*.079*
	Warfarin	5	17.2	5	17.9	*.782*
Rutherford classification	0 (asymptomatic)	13	44.8	13	46.4	*.434*
	I, II and III (any claudication)	0	0	5	17.9	
	IV (rest pain)	6	20.7	2	7.1	
	V (ulcers)	7	24.1	3	10.7	
	VI (gangrene)	3	10.3	5	17.9	
Toe pressure (mmHg)		53.1	(5-100)	71.4	(15-148)	*.034*
Anke-brachial index		0.6	(0-1)	0.74	(0-1,24)	*.112*
Bypass anatomy	Fem-pop above knee	4	13.8	4	14.3	*1.000*
	Fem-pop below knee	11	37.9	13	46.4	
	Fem-crural	14	48.3	7	25	
	Fem-pedal	0	0	4	14.3	
Graft	Single-segment GSV-graft	20	69	19	67.9	*.185*
	Spliced vein and/or arm vein	9	31	9	32.1	
Graft age (days, median)		200	(30 - 2570)	340	(50 - 6840)	*.445*
Lesion length (mm)		11.5	(2 - 40)	14.4	(2 - 100)	*.595*
PSV-ratio		6.86	2.9 - 18.8	6.10	2.2 - 17.0	*.619*
Prior PTA (same lesion)		9	31	11	39.3	*.496*

Table 2. Baseline characteristics

	DCB		**BA**		
	median	range	median	range	p-value
Balloon diameter (mm)	4.2	2.5 - 6	5.0	3 - 5.5	*.888*
	mean		mean		
Inflation (sec.)	223.5	60 - 510	182.7	60 - 360	*.200*

Table 3. Intraoperative characteristics

	DCB		**BA**		
Rutherford class	median	range	median	range	*p*-value
1 months	1	1 - 6	1	1 - 6	*.839*
6 months	1	1 - 6	1	1 - 5	*.464*
12 months	1	1 - 4	1	1 - 4	*.851*
ABI	mean		mean		
1 months	.99	.69 - 1.14	.88	.41 - 1.16	*.118*
6 months	.94	.55 - 1.15	.88	.41 - 1.30	*.430*
12 months	.95	.77 - 1.22	.96	.69 - 1.34	*.789*

Table 4. Clinical follow-up

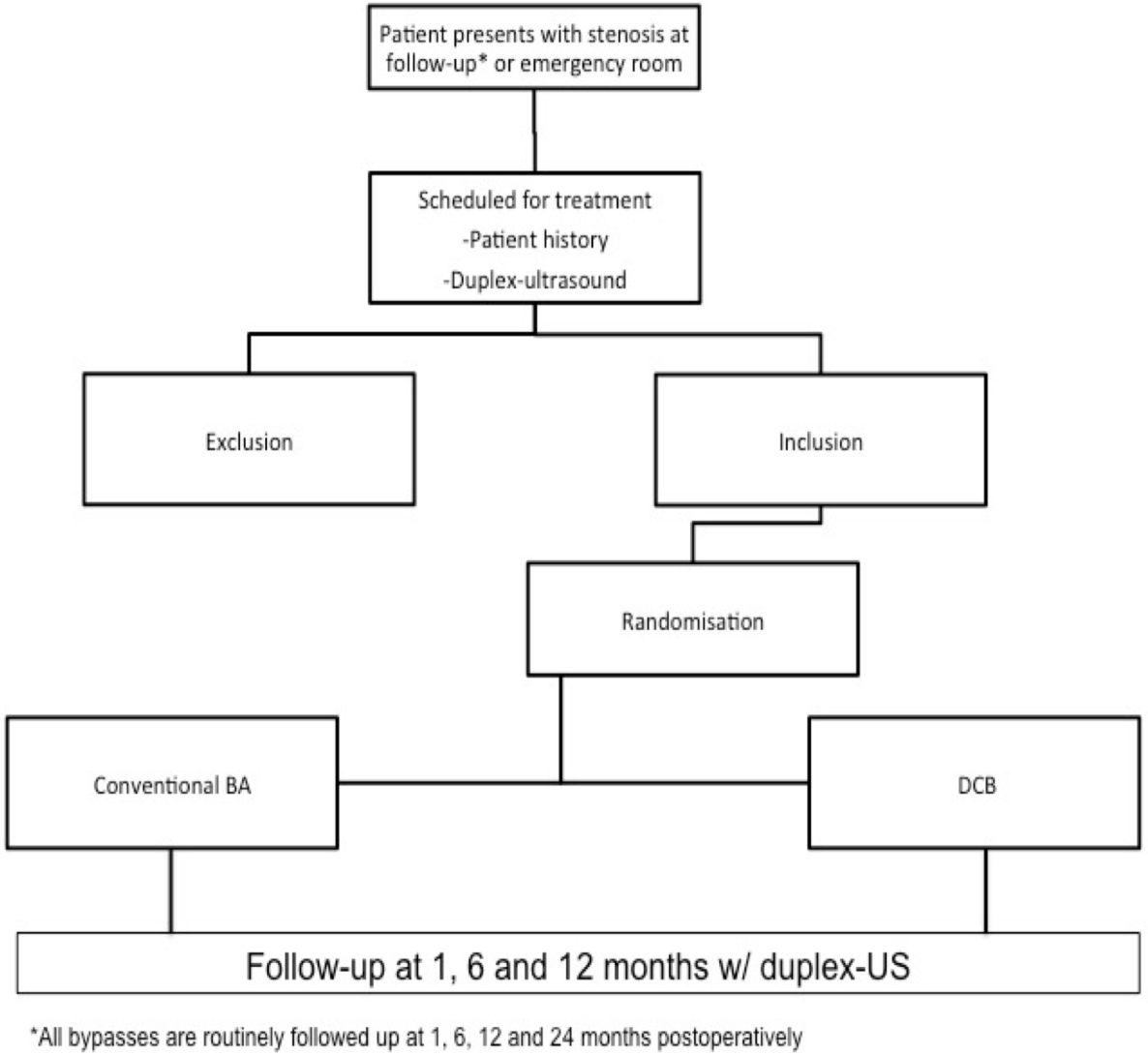
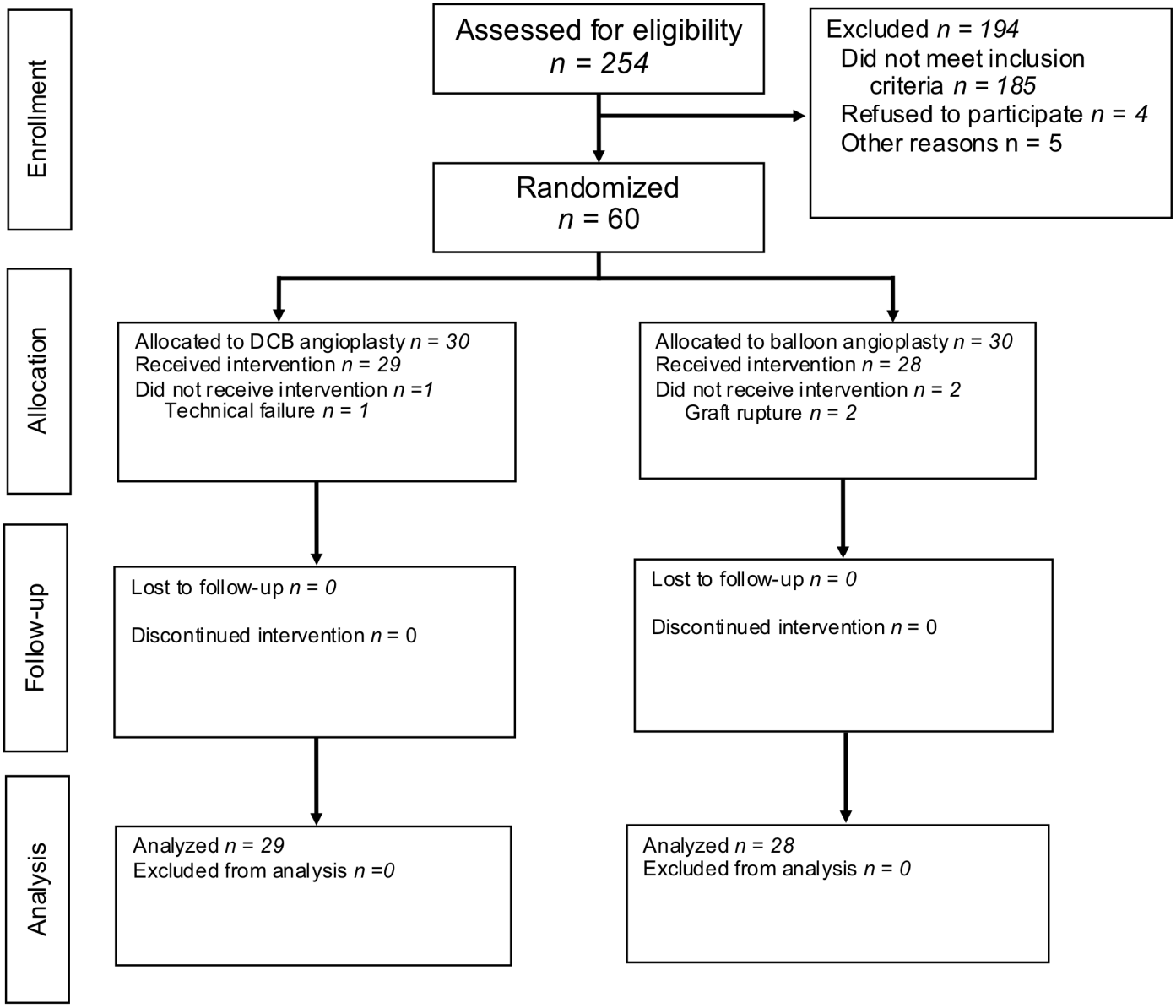
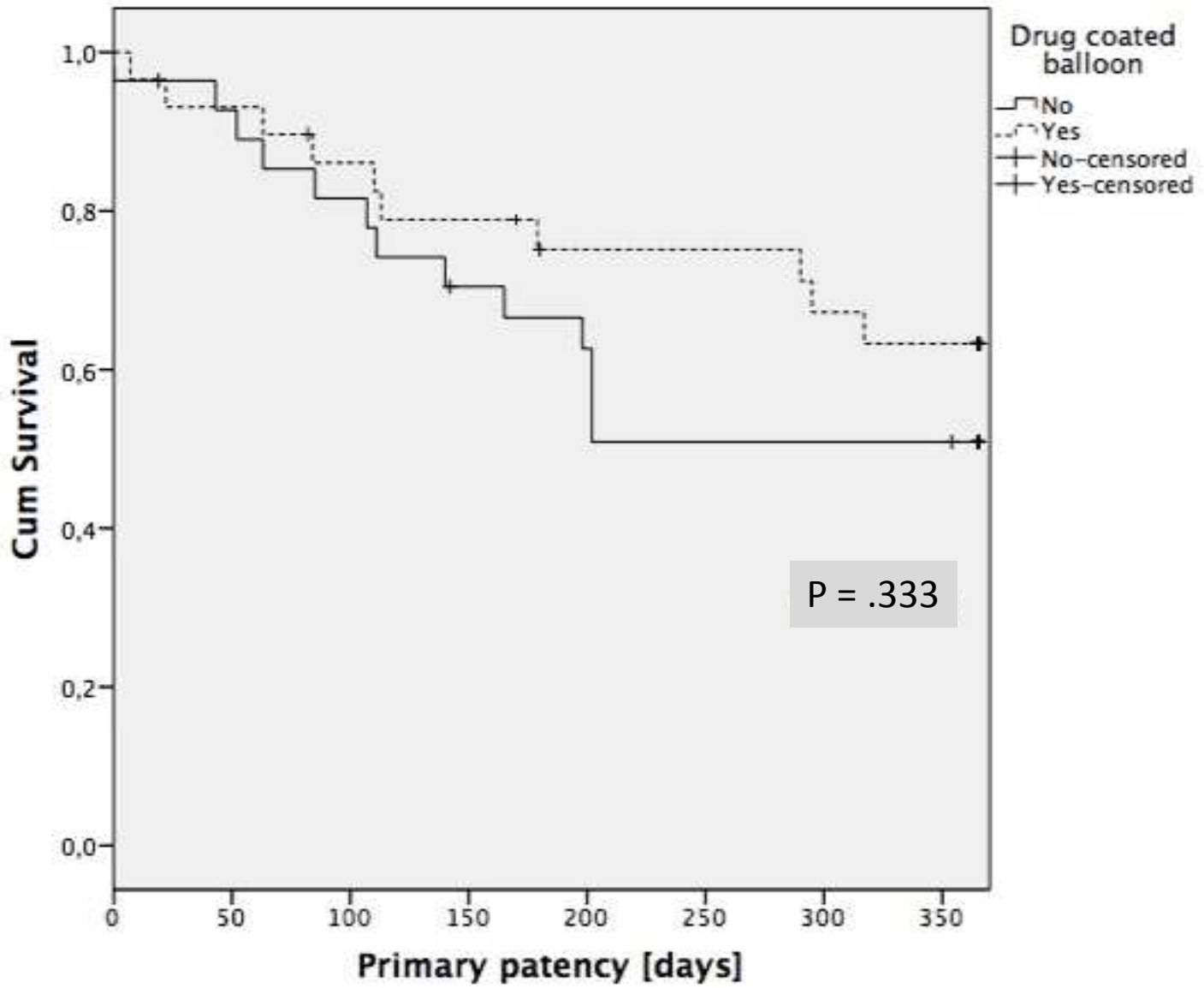


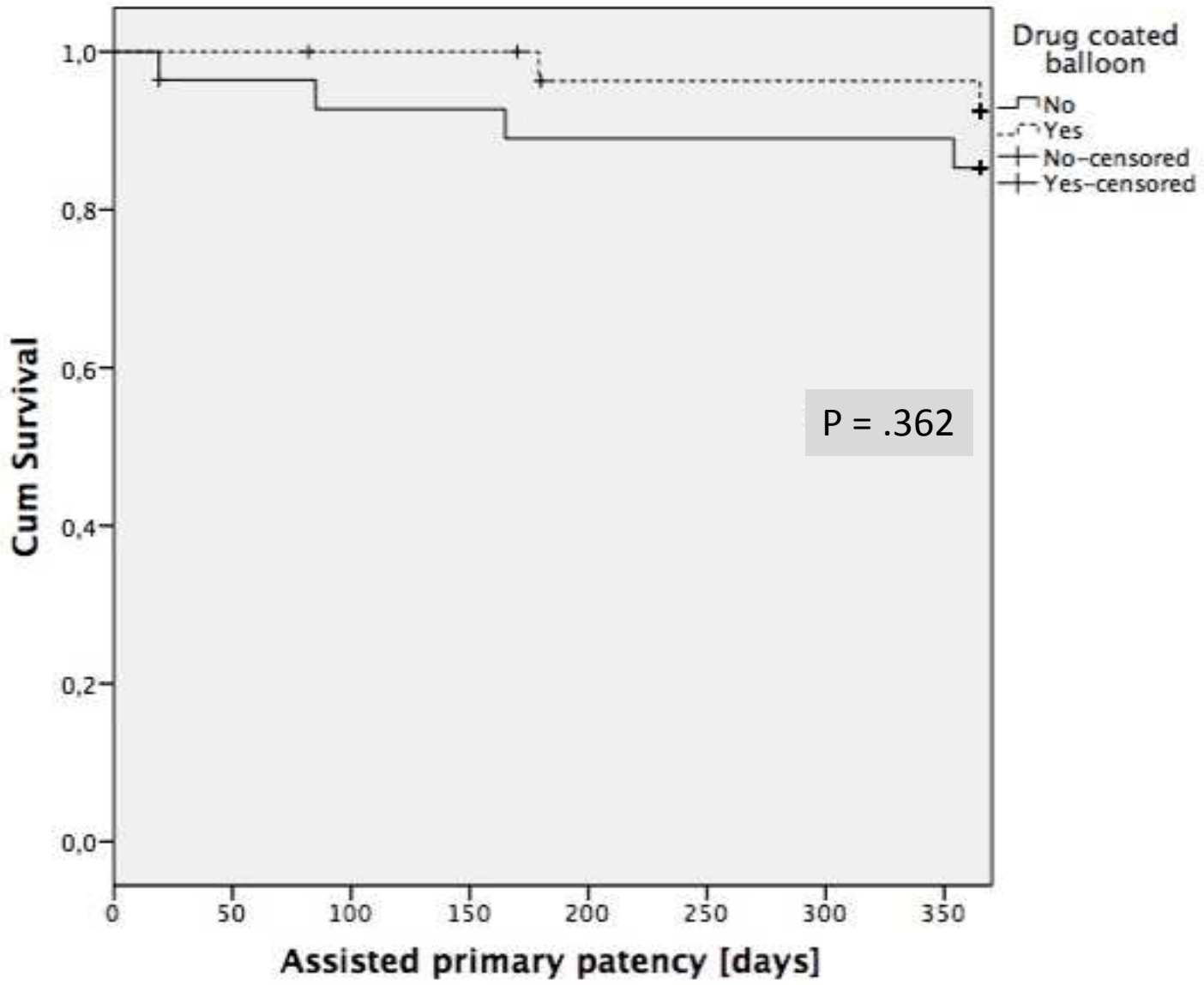
Figure 1. Study design

CONSORT diagram

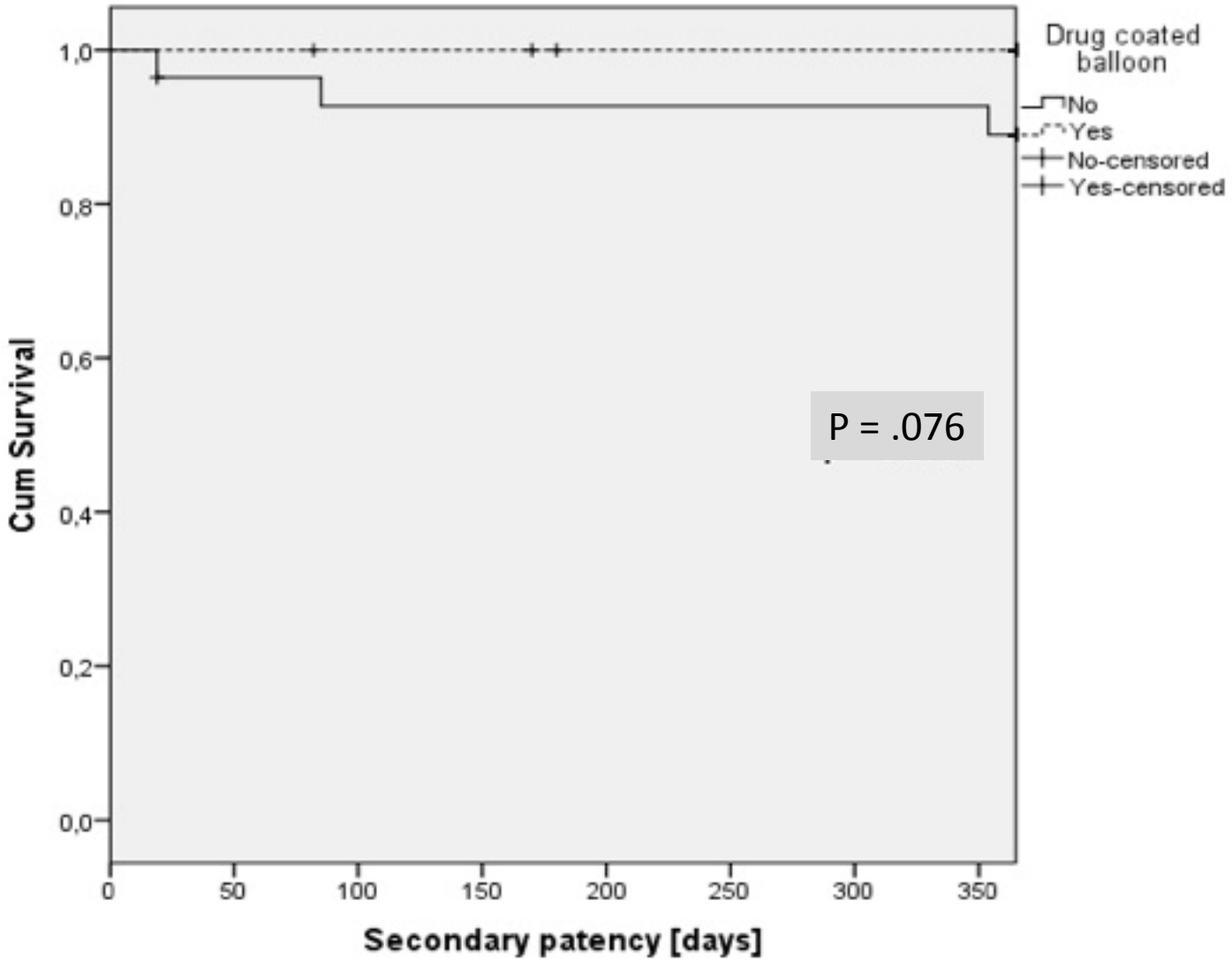




BA	28	25	22	18	15	13	13	13
DCB	29	26	23	21	18	18	16	15



BA	28	26	25	24	23	21	21	21
DCB	29	26	24	23	20	20	19	19



BA	28	27	27	27	26	26	26	26
DCB	29	29	28	28	26	26	26	26