EuroIntervention 2017;13:483-489 published online 1 February 2017

Drug-coated balloon angioplasty for in-stent restenosis of femoropopliteal arteries: a meta-analysis

Salvatore Cassese[1]*, MD, PhD; Gjin Ndrepepa[1], MD; Sebastian Kufner[1], MD; Robert A. Byrne[1], MB, BCh, PhD; Daniele Giacoppo[1], MD; Ilka Ott[1], MD; Karl-Ludwig Laugwitz[2,3], MD; Heribert Schunkert[1,3], MD; Adnan Kastrati[1,3], MD; Massimiliano Fusaro[1], MD

1. Deutsches Herzzentrum München, Technische Universität München, Munich, Germany; 2. 1. Medizinische Klinik und Poliklinik, Klinikum rechts der Isar, Technische Universität München, Munich, Germany; 3. DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany

This paper also includes supplementary data published online at: http://www.pcronline.com/eurointervention/119th_issue/73

KEYWORDS

- drug-eluting balloon
- femoropopliteal disease
- in-stent restenosis

Abstract

Aims: Our aim was to perform a meta-analysis to investigate the outcomes of patients undergoing percutaneous revascularisation with drug-coated balloon (DCB) angioplasty because of femoropopliteal in-stent restenosis (ISR).

Methods and results: We searched scientific databases for studies of DCB angioplasty for femoropopliteal ISR. The primary outcome was target lesion revascularisation (TLR). The main secondary outcome was recurrent ISR. Other outcomes of interest were Rutherford class (RC) improvement, ankle-brachial index (ABI) and death. A total of 367 patients enrolled in four studies received DCB (n=188) or plain balloon angioplasty (n=179). Median follow-up was 12 months. Patients treated with DCB angioplasty displayed a lower risk for TLR (odds ratio [OR] 0.20, 95% confidence interval [CI]: 0.07-0.55, p=0.002) and recurrent ISR (OR 0.24, 95% CI: 0.09-0.61, p=0.003), and a sustained RC improvement (OR 2.57, 95% CI: 1.40-4.72, p=0.002) with similar ABI and mortality as compared to those patients treated with plain balloon angioplasty.

Conclusions: In comparison to plain balloon angioplasty, DCB therapy for femoropopliteal ISR is associated with superior clinical and antirestenotic efficacy. Further randomised trials comparing DCB with therapies alternative to plain balloon, in a larger number of patients, and with extended follow-up are needed to address definitively the role of DCB for femoropopliteal ISR.

Corresponding author: Deutsches Herzzentrum München, Technische Universität München, Lazarettstrasse, 36, 80636 Munich, Germany. E-mail: cassese@dhm.mhn.de

SUBMITTED ON 08/09/2016 - REVISION RECEIVED ON 11/01/2017 - ACCEPTED ON 02/02/2017

DOI: 10.4244/EIJ-D-16-00735

Abbreviations

ABI ankle-brachial index
DCB drug-coated balloon
ISR in-stent restenosis
RC Rutherford class
TLR target lesion revascularisation

Introduction

The percutaneous treatment of patients suffering from clinically relevant atherosclerotic disease of femoropopliteal arteries has a first-line recommendation due to the high percentage of acute success[1,2]. Despite the fact that the widespread use of new-generation self-expanding nitinol stents has reduced the technical shortcomings associated with plain balloon angioplasty in this vascular bed, lumen re-narrowing at the stented level continues to occur and represents a challenging clinical problem[3].

Multiple endovascular technologies including balloon catheters, stents and debulking devices have been evaluated as stand-alone or combined therapies for in-stent restenosis (ISR) of femoropopliteal arteries[4]. Amongst others, balloon catheters coated with the Taxol derivative paclitaxel, a highly lipophilic antiproliferative drug, have attracted considerable interest[5]. The drug-coated balloon (DCB) has been associated with favourable angiographic and clinical efficacy in the treatment of *de novo* lesions of femoropopliteal arteries[6]. However, despite initially promising results observed in single-arm registries[7,8], modestly sized investigations of DCB angioplasty for femoropopliteal ISR displayed an inconsistent clinical performance[9,10]. As a consequence, the clinical impact of DCB in this setting remains controversial.

Against this background, we performed a meta-analysis of studies to investigate the outcomes associated with a DCB-based revascularisation in patients with femoropopliteal ISR.

Editorial, see page 386

Methods

SEARCH STRATEGY AND SELECTION CRITERIA

We searched Medline, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), abstracts from scientific sessions and relevant websites (www.cardiosource.com, www.clinicaltrialresults.org, www.escardio.org, www.tctmd.com, www.theheart.org) without restricting language or publication status. The references listed in all eligible studies were checked to identify further citations. The final search was performed in July 2016. Search terms included the keywords and the corresponding Medical Subject Headings for: "femoropopliteal (femoral) artery", "in-stent restenosis", "drug-coated (-eluting) balloon", "trial" and "randomised trial". Inclusion criteria were: (1) percutaneous revascularisation with DCB angioplasty because of femoropopliteal ISR, and (2) a minimum of six-month follow-up. Exclusion criteria were: (1) vessels treated with DCB angioplasty other than femoropopliteal arteries; (2) per-protocol use of endovascular devices other than DCB in the experimental group, and (3) duplicated data.

DATA COLLECTION AND ASSESSMENT OF RISK OF BIAS

Two investigators (S. Cassese and G. Ndrepepa) independently assessed publications for eligibility at title and/or abstract level, with divergences resolved by consensus. Studies that met inclusion criteria were selected for further analysis. The same investigators independently evaluated freedom from bias for each study, in accordance with The Cochrane Collaboration method[11]. No formal quality score adjudication was performed[12].

OUTCOME VARIABLES

The primary outcome of the current report was target lesion revascularisation (TLR). The main secondary outcome was recurrent ISR. Other outcomes of interest were Rutherford class (RC) improvement, ankle-brachial index (ABI) and death. All endpoints were evaluated according to definitions of original protocols.

STATISTICAL ANALYSIS

Odds ratio (OR) and weighted mean difference with 95% confidence interval (95% CI) were used as summary statistics. The Mantel-Haenszel random effects model (DerSimonian and Laird) was used to calculate pooled OR for categorical variables, whilst the inverse variance random effects model served to calculate pooled mean difference for continuous variables. The Breslow-Day chi^2 test and the I^2 statistic were used to test heterogeneity across the studies: I^2 values of <25%, 25-50% or >50% indicated low, moderate or high heterogeneity, respectively[11]. The restricted maximum likelihood method (Tau^2) took into account the occurrence of residual heterogeneity.

For the primary outcome we performed: (i) a visual estimation of funnel plot, as well as statistical tests to evaluate the possibility of publication bias[13-15]; (ii) an influence analysis, in which meta-analysis estimates are computed omitting one study at a time; and (iii) a trial sequential analysis, in which meta-analysis sample size calculations are combined with the threshold of statistical significance[16]. A sensitivity analysis evaluated the extent to which the randomised design or the funded nature of the study might have influenced the risk estimation for the primary outcome. Additionally, a random effects meta-regression analysis assessed the relation between the risk calculation for the primary outcome and relevant patients (age, proportion of males, proportion of individuals with diabetes or with a critical limb ischaemia [CLI] complaint at presentation, length of available follow-up) and lesion features (length, baseline percentage diameter stenosis, proportion of ISR class III, according to Tosaka et al[3]).

Statistical analysis was performed using Review Manager (RevMan), Version 5.3 (The Cochrane Collaboration, Copenhagen, Denmark), Stata 11.4 (StataCorp, College Station, TX, USA) and TSA version 0.9 Beta software packages. This study was conducted in compliance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement[17].

Results

ELIGIBLE STUDIES

The process of study selection is summarised in **Online Figure 1**. A total of four studies comparing DCB versus plain balloon angioplasty

were included (three as full-length manuscripts presenting the FAIR[9], PACUBA I[10] and DEBATE ISR[18] studies, plus the COPACABANA trial[19], presented at the Leipzig Interventional Course 2015).

The risk of bias among studies included is reported in **Online Table 1**. Finally, a total of 367 participants (188 treated with DCB and 179 with plain balloon angioplasty) were included.

The main characteristics of the studies included are described in **Online Table 2**. Three out of four studies had a multicentre, randomised design (FAIR[9], PACUBA I[10] and COPACABANA[19]). In the remaining study (DEBATE ISR[18]), consecutive diabetic patients presenting with ISR of femoropopliteal arteries treated with DCB angioplasty were compared with an historical cohort of consecutive diabetic patients receiving plain balloon angioplasty because of femoropopliteal ISR. The main inclusion criterion in the original studies was the evidence of ISR of the femoropopliteal artery (≥50% in diameter and ≥30 mm in length), with at least one run-off vessel to the foot and symptoms ranging from claudication to ischaemic ulcerations. The main exclusion criterion was known or suspected allergy/intolerance to contrast medium, paclitaxel or dual antiplatelet therapy (DAPT). The balloon catheters used were coated with paclitaxel (at a dose of 3 μg/mm^2 [10,20] or 3.5 μg/mm^2 [9,18] of balloon surface) or uncoated. The antiproliferative drug was delivered directly from the balloon surface to the vessel wall with a vehicle consisting of an organic (urea[9,18] or shellac[10]) or inorganic (contrast medium[20]) excipient. Device descriptions are summarised in **Online Table 3**. In all studies, bail-out stenting after angioplasty was allowed in case of a suboptimal result after dilation in both treatment groups.

An overview of the main clinical endpoint definitions among studies included is reported in **Online Table 4**. In three out of four studies the primary endpoint consisted of the incidence of recurrent ISR at six- or 12-month follow-up[9,10,18]. In the remaining study the primary endpoint was late lumen loss after six months[20]. For one study, three-year follow-up data were available[18]. However, the current analysis relies on aggregate data up to 12 months in order to provide a homogenous follow-up among studies included.

The clinical characteristics of participants included in the original studies are reported in **Table 1**. Patients had a median age of 68.1 years (67.9-71.6), were predominantly male, with a high frequency of diabetes mellitus, and nearly 10% of cases involved a CLI complaint. Overall, lesions treated were intermediate in length (124.0 mm [98.1-156.5]) and the diameter stenosis was 89.5% (79.4-92.5). Patients treated with DCB angioplasty had a lesion length of 125.9 mm (101.1-152.5) and a diameter stenosis of 89.0% (77.7-91.3). Patients treated with plain balloon angioplasty had a lesion length of 123.2 mm (95.2-160.5) and a diameter stenosis of 89.9% (81.2-93.8). Roughly one third of lesions treated presented as complete occlusion (ISR class III) at baseline angiography. The median percentage of bail-out stenting was 9.1% among patients treated with DCB angioplasty and 7.0% among those treated with plain balloon angioplasty. Standard medical therapy was prescribed to all patients irrespective of the treatment received. The duration of DAPT after revascularisation ranged between one and six months, with a median DAPT duration of three months (1-6).

CLINICAL OUTCOMES

Of those included, 318 patients (86.6%) were available for assessment of outcomes of interest. Median follow-up was 12 months (9-12).

TLR, the primary outcome of the present report, occurred in 92 patients (28.9%) **(Figure 1)**. The risk of TLR was significantly reduced in patients treated with DCB versus plain balloon angioplasty (14.9% versus 44.3%; OR 0.20, 95% CI: 0.07-0.55, p=0.002). There was a high heterogeneity for this risk estimate (I^2=68%, p for heterogeneity [p_{het}]=0.03).

Recurrent ISR occurred in 118 patients (49.5%, data available for 238 patients [74.8%] enrolled in three studies[9,10,18]) **(Figure 2)**. The risk of recurrent ISR was significantly reduced in patients treated with DCB versus plain balloon angioplasty (32.5% versus 66.9%; OR 0.24, 95% CI: 0.09-0.61], p=0.003). There was a high heterogeneity for this risk estimate (I^2=65%, p_{het}=0.03).

RC improvement was reported in 134 patients (66.3%, data available for 202 patients [63.5%] enrolled in three studies: FAIR[9], PACUBA I[10] and DEBATE ISR[18]) **(Online Figure 2A)**. Patients treated with DCB angioplasty displayed a sustained RC

Table 1. Main characteristics of patients enrolled and lesions treated among studies included.

Study	Patients, n	Age, yrs	Males, %	Diabetes, %	CLI, %	Lesion length, mm	Diameter stenosis, %	ISR class III, %	Bail-out stenting, n (%)*
COPACABANA[19]	88	67.9	59.3	44.5	9.7	114.5	79.4	26.9	N/R
DEBATE ISR[18]	86	75.0	63.7	100	70.8	134.5	92.5	58.0	DCB: 7/44 (15.9%); plain balloon angioplasty: 11/42 (26.2%)
FAIR[9]	119	68.0	61.7	37.5	7.6	81.7	89.5	28.7	DCB: 1/62 (1.6%); plain balloon angioplasty: 4/57 (7.0%)
PACUBA I[10]	74	68.2	58.0	45.0	N/R	178.5	N/R	29.5	DCB: 5/35 (14.2%); plain balloon angioplasty: 2/39 (5.1%)

Overall mean values are reported. *Data are presented as number of events/total number of patients (proportion) for each treatment group. CLI: critical limb ischaemia; DCB: drug-coated balloon; ISR: in-stent restenosis; N/R: not reported. Study acronyms: COPACABANA: Cotavance™ Paclitaxel-Coated Balloon Versus Uncoated Balloon Angioplasty for Treatment of In-stent Restenosis in SFA and Popliteal Arteries; DEBATE ISR: Drug Eluting Balloon in peripherAl inTErvention for In-Stent Restenosis; FAIR: Femoral Artery In-Stent Restenosis; PACUBA I: A Randomised Clinical Trial of PAClitaxel drUg-eluting BAlloon Versus Standard Percutaneous Transluminal Angioplasty to Reduce Restenosis in Patients With In-stent Stenoses in the Superficial Femoral and Proximal Popliteal Artery

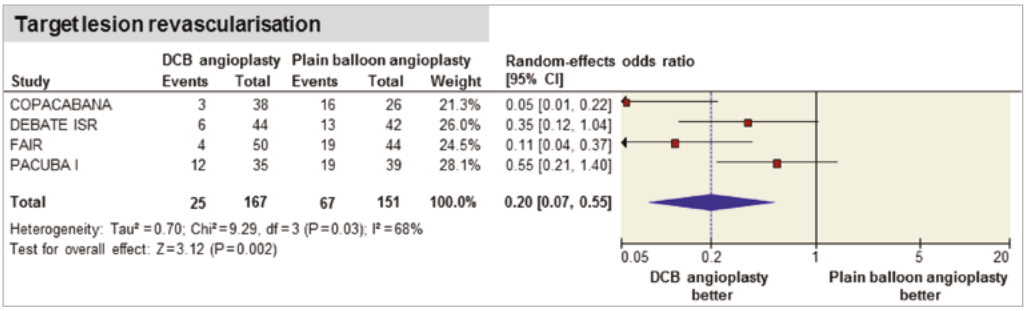


Figure 1. *Risk estimate for target lesion revascularisation with DCB versus plain balloon angioplasty. Plots of odds ratio for target lesion revascularisation associated with DCB versus plain balloon angioplasty. The diamond indicates the point estimate and the left and the right ends of the line the 95% confidence interval (CI). DCB: drug-coated balloon. Study acronyms are explained in Table 1.*

improvement as compared to those treated with plain balloon angioplasty (76.3% versus 55.6%; OR 2.57, 95% CI: 1.40-4.72, p=0.002; I^2=0%, p_{het}=0.80).

ABI was obtained in 206 patients enrolled in three studies: FAIR[9], PACUBA I [10] and COPACABANA[19] (64.7%) **(Online Figure 2B)**. No significant difference in terms of ABI was found after DCB in comparison to plain balloon angioplasty (range in mm 0.79 to 0.3 versus 0.84 to 1.60; –0.28 [-0.59, 0.03]; p=0.08). There was a high heterogeneity for this risk estimate (I^2=90%, p_{het}<0.0001).

Death occurred in 11 patients (6.2%; data available for 177 patients [55.6%] enrolled in two studies: FAIR[9] and DEBATE ISR[18]) **(Online Figure 2C)**. No significant difference in terms of risk for death was found in patients treated with DCB in comparison to plain balloon angioplasty (5.5% versus 6.9%; OR 0.78, 95% CI: 0.23-2.67, p=0.69; I^2=0%, p_{het}=0.72).

SMALL STUDY EFFECTS, INFLUENCE AND SENSITIVITY ANALYSES

Funnel plot distribution of the primary outcome was derived from the standard error of the logarithm OR plotted against the OR for TLR **(Online Figure 3A)**. In addition to visual estimation of the funnel plot, statistical tests excluded a publication bias for the primary outcome.

According to the influence analysis, no single study significantly altered the summary OR for TLR, though the heterogeneity remained high **(Online Figure 3B)**. However, when the analysis for the primary outcome was restricted to those studies evaluating the identical DCB platform[9,18], the risk estimate for TLR favoured the investigational device without high heterogeneity (OR 0.21, 95% CI: 0.07-0.62, p=0.005; I^2=47%, p_{het}=0.17). The trial sequential analysis revealed that the sample size accumulated provided robust evidence for TLR **(Online Figure 4)**.

There was no modification of the risk estimate for TLR according to the randomised design (p for interaction, [p_{int}]=0.39) or the funded nature of the studies (p_{int}=0.40). Moreover, the risk estimation for TLR had no statistical relation with the age of participants (p=0.60), the proportion of males (p=0.99), the proportion of patients with diabetes (p=0.60), or CLI complaint (p=0.26), lesion length (p=0.20), the baseline percentage of diameter stenosis (p=0.26), the proportion of ISR class III at baseline angiography (p=0.57) or the length of available follow-up (p=0.22) **(Online Table 5)**.

Discussion

This meta-analysis investigated the performance of DCB in patients suffering from ISR of femoropopliteal arteries. In all studies the control group consisted of patients treated with plain balloon angioplasty. The main findings are that: (i) DCB has superior efficacy in comparison to plain balloon angioplasty at one-year follow-up, irrespective of the baseline clinical and angiographic complexity; (ii) the available evidence is sufficient to confirm the superiority of DCB as compared to plain balloon angioplasty in this setting.

Multiple treatment options such as balloon angioplasty, repeat stenting and debulking have been investigated in patients with

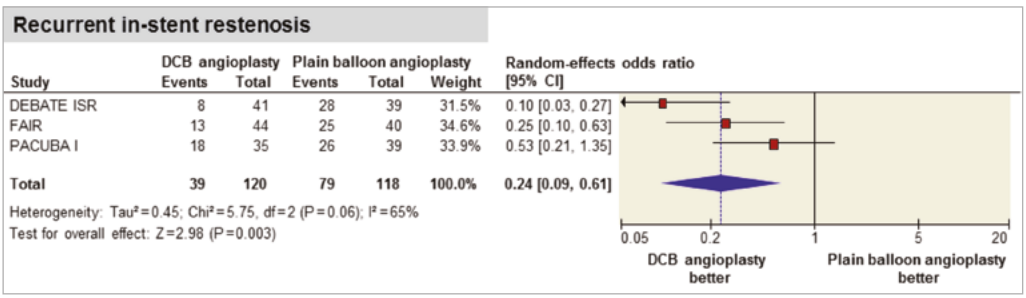


Figure 2. *Risk estimate for recurrent in-stent restenosis with DCB versus plain balloon angioplasty. Plots of odds ratio for recurrent in-stent restenosis associated with DCB versus plain balloon angioplasty. The diamond indicates the point estimate and the left and the right ends of the line the 95% confidence interval (CI). DCB: drug-coated balloon. Study acronyms are explained in Table 1.*

femoropopliteal ISR[4]. However, as there is no single therapy which is particularly effective or superior to any other, there is no established best treatment strategy for these cases.

Comparisons of DCB versus plain balloon angioplasty for femoropopliteal ISR included a limited number of patients and displayed inconsistent results[20]. For this reason, we conducted this meta-analysis to study the performance of DCB angioplasty in patients presenting with ISR of femoropopliteal arteries. This report highlights a number of important issues.

REDUCED RISK FOR TLR AFTER DCB ANGIOPLASTY

In the present analysis, DCB versus plain balloon angioplasty for femoropopliteal ISR showed a significantly lower risk for TLR at one-year follow-up. There was no significant relation between this risk estimate and the clinical and angiographic complexity at baseline. Interestingly, each of the individual studies included in this report contained only sufficient power for surrogate outcomes, thus supporting the necessity of a meta-analysis to investigate the clinical impact of DCB angioplasty in this scenario. By pooling >300 patients with femoropopliteal ISR, this study lends support to the lower risk for TLR of DCB versus plain balloon angioplasty, since the available sample size accounts for >90% of that required to address a measurable effect of DCB for this endpoint. In this respect, the objective of future studies of DCB therapy in patients with femoropopliteal ISR remains twofold: first, to disclose whether the performance of DCB should be regarded as a "class effect"; second, to assess the relative efficacy of DCB angioplasty versus revascularisation strategies other than plain balloon angioplasty. Indeed, we cannot fully ascertain whether the high heterogeneity observed in the risk calculations for main outcomes is due to different antirestenotic potency among DCB catheters studied; however, here we provide robust evidence against the use of plain balloon angioplasty as a comparative therapy in studies of femoropopliteal ISR.

REDUCED RISK FOR RECURRENT ISR AFTER DCB ANGIOPLASTY

In this analysis, we observed a reduced risk for recurrent ISR at one-year follow-up with DCB versus plain balloon angioplasty for femoropopliteal ISR. The favourable outcome associated with DCB is probably due to inhibition of neointimal hyperplasia, a common finding of restenotic lesions of stented segments[21]. The complex interplay between biomechanical forces, shear stress of the vessel wall and proliferation of neointima observed in the femoropopliteal arteries constrained from a permanent scaffold are regarded as responsible for the pathophysiological process which leads to restenosis[22]. Thus, in this setting, DCB-based therapies should be preferred over other available strategies, such as plaque removal devices and stents **(Online Table 6)**. Regarding the first of these, the use of debulking devices as a stand-alone therapy has been associated with inconsistent midterm results[23-25]. Regarding the second, drug-coated[26] or covered stents[27] showed acceptable patency up to one-year follow-up, though the shrinkage of the vessel lumen by multiple stent layers (the so-called "onion skin" phenomenon) may potentially impair the vascular compliance and increase the risk of recurrent ISR[20,28].

FEMOROPOPLITEAL ISR IS A LONG-LASTING PROCESS

In the current study, patients treated with DCB angioplasty because of femoropopliteal ISR reported a sustained improvement of clinical status at one-year follow-up as compared to those patients treated with plain balloon angioplasty. However, a follow-up longer than one year remains important to rule out definitively a time-dependent efficacy of DCB in this particular setting. In fact, Schmidt and co-workers have recently demonstrated a drop-off of vessel patency two years after DCB therapy for femoropopliteal ISR[8]. Consistent with this, Grotti and co-workers found that, three years after the index procedure, DCB and plain balloon angioplasty led to a similar risk of reintervention of the affected limb[29]. In contrast with the coronary vasculature, preclinical models of restenosis after peripheral artery stenting have demonstrated that metallic implants permanently overstretch the arterial wall and provoke a persistent neointimal growth, which may be responsible for the exaggerated "catch-up" phenomenon observed after DCB therapy because of femoropopliteal ISR[30]. According to results of preliminary investigations, the synergy of different endovascular technologies for femoropopliteal ISR holds promise[31], though a more proper evaluation requires further studies with a successful retention of patients enrolled throughout the study period.

Study limitations

The current study presents a number of limitations. First, this meta-analysis was based on aggregate data from both randomised and observational studies. However, there was no interaction between study design and primary outcome. Second, the assessment of publication bias was based on a small number of trials, a fact that limits a definitive conclusion regarding the existence of potential bias due to small study effects. Third, the risk estimation for death relies on aggregate data from two out of four studies, a fact which limits a definitive conclusion regarding this outcome. Fourth, we observed a considerable drop-out of patients during follow-up among the original studies, a fact which may somewhat limit the conclusiveness of this report. Fifth, DAPT duration varied among studies included in this report, and the possible effect of a prolonged or more potent platelet inhibition cannot be defined in this context. Finally, although the potential need for multiple DCB catheters to treat long lesions should be acknowledged, we did not perform a cost-effectiveness analysis evaluating the economic impact of DCB as compared to plain balloon angioplasty for treating femoropopliteal ISR.

Conclusions

The results of our meta-analysis suggest that, in patients presenting with ISR of femoropopliteal arteries, a percutaneous intervention with DCB as compared to plain balloon angioplasty offers superior clinical and antirestenotic efficacy at one-year follow-up. These

findings should be interpreted with caution in view of the limited number and the different design of the included studies. Future randomised trials should compare DCB with therapies other than plain balloon angioplasty in a larger number of patients with follow-up longer than one year, in order to address definitively the role of DCB in this complex patient population.

Impact on daily practice

In patients with atherosclerotic disease of femoropopliteal arteries, new-generation stents reduced the mechanical shortcomings associated with plain balloon angioplasty. Notwithstanding this, lumen re-narrowing at the stented level still represents a challenging clinical problem. This analysis found that, at one-year follow-up, drug-coated balloons are associated with superior efficacy as compared to plain balloon angioplasty in patients with restenosis after femoropopliteal stenting. The evidence provided in this report is sufficient to discourage the use of plain balloon angioplasty as comparative therapy in future studies of restenosis after stenting of femoropopliteal arteries.

Conflict of interest statement

A. Kastrati reports patent applications related to drug-eluting stent technologies. R. Byrne reports receiving lecture fees from B. Braun Melsungen AG, Biotronik and Boston Scientific and scientific support from Boston Scientific and HeartFlow. D. Giacoppo is the recipient of a research fellowship grant funded by the European Association of Percutaneous Cardiovascular Interventions (EAPCI). The other authors have no conflicts of interest to declare.

References

1. European Stroke Organization, Tendera M, Aboyans V, Bartelink ML, Baumgartner I, Clement D, Collet JP, Cremonesi A, De Carlo M, Erbel R, Fowkes FG, Heras M, Kownator S, Minar E, Ostergren J, Poldermans D, Riambau V, Roffi M, Rother J, Sievert H, van Sambeek M, Zeller T; ESC Committee for Practice Guidelines. ESC Guidelines on the diagnosis and treatment of peripheral artery diseases: Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries: the Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology (ESC). *Eur Heart J.* 2011;32:2851-906.

2. Anderson JL, Halperin JL, Albert N, Bozkurt B, Brindis RG, Curtis LH, Demets D, Guyton RA, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK. 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. *Circulation.* 2013;127:1425-43.

3. Tosaka A, Soga Y, Iida O, Ishihara T, Hirano K, Suzuki K, Yokoi H, Nanto S, Nobuyoshi M. Classification and clinical impact of restenosis after femoropopliteal stenting. *J Am Coll Cardiol.* 2012;59:16-23.

4. Singh GD, Armstrong EJ, Laird JR. Femoropopliteal in-stent restenosis: current treatment strategies. *J Cardiovasc Surg (Torino).* 2014;55:325-33.

5. Cortese B, Granada JF, Scheller B, Schneider PA, Tepe G, Scheinert D, Garcia L, Stabile E, Alfonso F, Ansel G, Zeller T. Drug-coated balloon treatment for lower extremity vascular disease intervention: an international positioning document. *Eur Heart J.* 2016;37:1096-103.

6. Cassese S, Byrne RA, Ott I, Ndrepepa G, Nerad M, Kastrati A, Fusaro M. Paclitaxel-coated versus uncoated balloon angioplasty reduces target lesion revascularization in patients with femoropopliteal arterial disease: a meta-analysis of randomized trials. *Circ Cardiovasc Interv.* 2012;5:582-9.

7. Stabile E, Virga V, Salemme L, Cioppa A, Ambrosini V, Sorropago G, Tesorio T, Cota L, Popusoi G, Pucciarelli A, Biamino G, Rubino P. Drug-eluting balloon for treatment of superficial femoral artery in-stent restenosis. *J Am Coll Cardiol.* 2012;60:1739-42.

8. Schmidt A, Piorkowski M, Gorner H, Steiner S, Bausback Y, Scheinert S, Banning-Eichenseer U, Staab H, Branzan D, Varcoe RL, Scheinert D. Drug-Coated Balloons for Complex Femoropopliteal Lesions: 2-Year Results of a Real-World Registry. *JACC Cardiovasc Interv.* 2016;9:715-24.

9. Krankenberg H, Tubler T, Ingwersen M, Schluter M, Scheinert D, Blessing E, Sixt S, Kieback A, Beschorner U, Zeller T. Drug-Coated Balloon Versus Standard Balloon for Superficial Femoral Artery In-Stent Restenosis: The Randomized Femoral Artery In-Stent Restenosis (FAIR) Trial. *Circulation.* 2015;132:2230-6.

10. Kinstner CM, Lammer J, Willfort-Ehringer A, Matzek W, Gschwandtner M, Javor D, Funovics M, Schoder M, Koppensteiner R, Loewe C, Ristl R, Wolf F. Paclitaxel-Eluting Balloon Versus Standard Balloon Angioplasty in In-Stent Restenosis of the Superficial Femoral and Proximal Popliteal Artery: 1-Year Results of the PACUBA Trial. *JACC Cardiovasc Interv.* 2016;9:1386-92.

11. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* 2003;327:557-60.

12. Jüni P, Witschi A, Bloch R, Egger M. The hazards of scoring the quality of clinical trials for meta-analysis. *JAMA.* 1999;282:1054-60.

13. Sterne JA, Egger M, Smith GD. Systematic reviews in health care: Investigating and dealing with publication and other biases in meta-analysis. *BMJ.* 2001;323:101-5.

14. Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Stat Med.* 2006;25:3443-57.

15. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Comparison of two methods to detect publication bias in meta-analysis. *JAMA.* 2006;295:676-80.

16. Wetterslev J, Thorlund K, Brok J, Gluud C. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. *J Clin Epidemiol.* 2008;61:64-75.

17. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med.* 2009;151:264-9, W64.

18. Liistro F, Angioli P, Porto I, Ricci L, Ducci K, Grotti S, Falsini G, Ventoruzzo G, Turini F, Bellandi G, Bolognese L. Paclitaxel-eluting balloon vs. standard angioplasty to reduce recurrent restenosis in diabetic patients with in-stent restenosis of the superficial femoral and proximal popliteal arteries: the DEBATE-ISR study. *J Endovasc Ther.* 2014;21:1-8.

19. Tepe G. Cotavance paclitaxel-coated balloon vs. uncoated balloon angioplasty for treatment of in-stent restenosis in SFA and the popliteal arteries: the COPACABANA trial. Oral presentation at Leipzig Interventional Course (LINC) 2015, January 27-30, 2015. Leipzig, Germany.

20. Gray BH, Buchan JA. The Treatment of Superficial Femoral Artery In-Stent Restenosis: The Jury Is Still Out. *JACC Cardiovasc Interv.* 2016;9:1393-6.

21. Gongora CA, Shibuya M, Wessler JD, McGregor J, Tellez A, Cheng Y, Conditt GB, Kaluza GL, Granada JF. Impact of Paclitaxel Dose on Tissue Pharmacokinetics and Vascular Healing: A Comparative Drug-Coated Balloon Study in the Familial Hypercholesterolemic Swine Model of Superficial Femoral In-Stent Restenosis. *JACC Cardiovasc Interv.* 2015;8:1115-23.

22. Yahagi K, Otsuka F, Sakakura K, Sanchez OD, Kutys R, Ladich E, Kolodgie FD, Virmani R, Joner M. Pathophysiology of superficial femoral artery in-stent restenosis. *J Cardiovasc Surg (Torino).* 2014;55:307-23.

23. Brodmann M, Rief P, Froehlich H, Dorr A, Gary T, Eller P, Hafner F, Deutschmann H, Seinost G, Pilger E. Neointimal hyperplasia after silverhawk atherectomy versus percutaneous transluminal angioplasty (PTA) in femoropopliteal stent reobstructions: a controlled, randomized pilot trial. *Cardiovasc Intervent Radiol.* 2013;36:69-74.

24. Dippel EJ, Makam P, Kovach R, George JC, Patlola R, Metzger DC, Mena-Hurtado C, Beasley R, Soukas P, Colon-Hernandez PJ, Stark MA, Walker C; EXCITE ISR Investigators. Randomized controlled study of excimer laser atherectomy for treatment of femoropopliteal in-stent restenosis: initial results from the EXCITE ISR trial (EXCImer Laser Randomized Controlled Study for Treatment of FemoropopliTEal In-Stent Restenosis). *JACC Cardiovasc Interv.* 2015;8:92-101.

25. Laird JR Jr, Yeo KK, Rocha-Singh K, Das T, Joye J, Dippel E, Reddy B, Botti C, Jaff MR. Excimer laser with adjunctive balloon angioplasty and heparin-coated self-expanding stent grafts for the treatment of femoropopliteal artery in-stent restenosis: twelve-month results from the SALVAGE study. *Catheter Cardiovasc Interv.* 2012;80:852-9.

26. Zeller T, Dake MD, Tepe G, Brechtel K, Noory E, Beschorner U, Kultgen PL, Rastan A. Treatment of femoropopliteal in-stent restenosis with paclitaxel-eluting stents. *JACC Cardiovasc Interv.* 2013;6:274-81.

27. Bosiers M, Deloose K, Callaert J, Verbist J, Hendriks J, Lauwers P, Schroe H, Lansink W, Scheinert D, Schmidt A, Zeller T, Beschorner U, Noory E, Torsello G, Austermann M, Peeters P. Superiority of stent-grafts for in-stent restenosis in the superficial femoral artery: twelve-month results from a multicenter randomized trial. *J Endovasc Ther.* 2015;22:1-10.

28. Iida O, Takahara M, Soga Y, Hirano K, Yamauchi Y, Zen K, Kawasaki D, Nanto S, Yokoi H, Uematsu M; ZEPHYR Investigators. The Characteristics of In-Stent Restenosis After Drug-Eluting Stent Implantation in Femoropopliteal Lesions and 1-Year Prognosis After Repeat Endovascular Therapy for These Lesions. *JACC Cardiovasc Interv.* 2016;9:828-34.

29. 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;23:52-7.

30. Joner M, Nakazawa G, Bonsignore C, Acampado E, Steigerwald K, Merl S, Vallbracht T, Kolodgie FD, Virmani R. Histopathologic evaluation of nitinol self-expanding stents in an animal model of advanced atherosclerotic lesions. *EuroIntervention.* 2010;5:737-44.

31. Gandini R, Del Giudice C, Merolla S, Morosetti D, Pampana E, Simonetti G. Treatment of chronic SFA in-stent occlusion with combined laser atherectomy and drug-eluting balloon angioplasty in patients with critical limb ischemia: a single-center, prospective, randomized study. *J Endovasc Ther.* 2013;20:805-14.

32. Dick P, Sabeti S, Mlekusch W, Schlager O, Amighi J, Haumer M, Cejna M, Minar E, Schillinger M. Conventional balloon angioplasty versus peripheral cutting balloon angioplasty for treatment of femoropopliteal artery in-stent restenosis: initial experience. *Radiology.* 2008;248:297-302.

Supplementary data

Online Table 1. Assessment of risk of bias for studies included.

Online Table 2. Main characteristics of studies included.

Online Table 3. Description of DCB catheters used among studies included.

Online Table 4. Definitions of endpoints among studies included.

Online Table 5. Meta-regression analysis for the primary outcome.

Online Table 6. Published randomised studies investigating endovascular therapies other than DCB angioplasty for femoropopliteal ISR.

Online Figure 1. Flow diagram of study selection process.

Online Figure 2. Forest plots of risk estimates for the secondary outcomes.

Online Figure 3. Funnel plot and influence analysis according to primary outcome.

Online Figure 4. Trial sequential analysis for the primary outcome.

The supplementary data are published online at: http://www.pcronline.com/eurointervention/119th_issue/73

Supplementary data

Online Table 1. Assessment of risk of bias for studies included.

Study	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome assessors	Description of incomplete outcome data	Selective outcome reporting	Sample size calculation	Industry funding
COPACABANA[19]	Yes (computer-generated)	N/R	Yes	Yes (independent core laboratory)	N/R	No	N/R	No
DEBATE ISR[18]	N/A	N/A	No	Yes	No	No	No	No
FAIR[9]	Yes (computer-generated, blocks)	No	No	Yes (independent core laboratory)	Yes (flow diagram)	No	Yes (superiority design)	Yes
PACUBA I[10]	Yes (computer-generated)	N/R	Yes	Yes (independent core laboratory)	Yes (flow diagram)	No	Yes (superiority design)	No

N/A: not applicable; N/R: not reported. Study acronyms: COPACABANA: Cotavance™ Paclitaxel-Coated Balloon Versus Uncoated Balloon Angioplasty for Treatment of In-stent Restenosis in SFA and Popliteal Arteries; DEBATE ISR: Drug Eluting Balloon in peripherAl inTErvention for In-Stent Restenosis; FAIR: Femoral Artery In-Stent Restenosis; PACUBA I: A Randomised Clinical Trial of PAClitaxel drUg-eluting BAlloon Versus Standard Percutaneous Transluminal Angioplasty to Reduce Restenosis in Patients With In-stent Stenoses in the Superficial Femoral and Proximal Popliteal Artery.

Online Table 2. Main characteristics of studies included.

Study	Year	Main inclusion criteria	Main exclusion criteria	Primary endpoint	DAPT prescription	Registration no.
COPACABANA[19]	2012-2014	Age ≥18 years; Rutherford class 2-5; in-stent occlusion or restenosis of femoropopliteal artery ≥70% vessel diameter; ≥30 and ≤270 mm in length; ≥3.0 and ≤7.0 mm reference vessel diameter; inflow free from flow-limiting lesions; successful guidewire passage; outflow free from flow-limiting lesions	Angiographic evidence of thrombus; stent fracture type 2-4; untreated significant inflow or outflow lesions; no patent distal run-off vessel; allergy, hypersensitivity or contraindication to one of the study drugs; ≤1-year life expectancy	6-month LLL	N/R	NCT01594684
DEBATE ISR[18]	2010-2011	Age ≥18 years; diabetes mellitus; Rutherford class 4-6; in-stent occlusion or restenosis of femoropopliteal artery ≥50% vessel diameter (at DUS and/or angiography); ≥40 mm in length; ≥1 run-off vessel to the foot	Planned major amputation of the target limb; allergy, hypersensitivity or contraindication to one of the study drugs; ≤1-year life expectancy	12-month binary restenosis	ASS+clopidogrel ≥1 month	NCT01558531
FAIR[9]	2010-2012	Age ≥21 years; Rutherford class 2-4; in-stent occlusion or restenosis of superficial femoral artery ≥70% vessel diameter (at DUS); ≥100 and ≤200 mm in length; ≥1 run-off vessel to the foot	Untreated significant inflow lesions; treatment with oral anticoagulants; chronic renal insufficiency requiring dialysis; ≤1-year life expectancy	6-month binary restenosis	ASS+clopidogrel ≥6 months	NCT01305070
PACUBA I[10]	2010-2012	Age >50 years; Rutherford class 2-3; in-stent occlusion or restenosis of femoropopliteal artery ≥70% vessel diameter (at DUS and/or CTA); ≥1 run-off vessel to the foot	Planned major amputation of the target limb; major surgical procedures (not including minor amputations) <30 days prior to enrolment or planned <30 days from enrolment; ≤1-year life expectancy	12-month binary restenosis	ASS+clopidogrel ≥3 months	NCT01247402

CTA: computed tomographic angiography; DAPT: dual antiplatelet therapy; DUS: duplex ultrasonography; LLL: late lumen loss. Study acronyms: COPACABANA: Cotavance™ Paclitaxel-Coated Balloon Versus Uncoated Balloon Angioplasty for Treatment of In-stent Restenosis in SFA and Popliteal Arteries; DEBATE ISR: Drug Eluting Balloon in peripherAl inTErvention for In-Stent Restenosis; FAIR: Femoral Artery In-Stent Restenosis; PACUBA I: A Randomised Clinical Trial of PAClitaxel drUg-eluting BAlloon Versus Standard Percutaneous Transluminal Angioplasty to Reduce Restenosis in Patients With In-stent Stenoses in the Superficial Femoral and Proximal Popliteal Artery.

Online Table 3. Description of DCB catheters used among studies included.

Study	Brand name (manufacturer)	Paclitaxel dose/DCB surface	Excipient (hydrophilicity)	Proprietary technology
COPACABANA[19]	Cotavance (Bavaria Medizin Technologie/Bayer AG, Berlin, Germany; Medrad, Inc., Warrendale, PA, USA)	3 µg/mm^2	Iopromide* (+)	PACCOCATH
DEBATE ISR[18]	IN.PACT Admiral (Medtronic, Minneapolis, MN, USA)	3.5 µg/mm^2	Urea† (+++)	FreePAC
FAIR[9]	IN.PACT Admiral (Medtronic, Minneapolis, MN, USA)	3.5 µg/mm^2	Urea† (+++)	FreePAC
PACUBA I[10]	FREEWAY 035 (Eurocor, Bonn, Germany)	3 µg/mm^2	Shellac¶ (++)	Bioshell

*contrast medium, Ultravist 370 (Bayer Pharma AG, Berlin, Germany); †dosage 0.5 µg/mm^2; ¶natural resin composed of shellolic and alleuritic acid. DCB: drug-coated balloon. Study acronyms: COPACABANA: Cotavance™ Paclitaxel-Coated Balloon Versus Uncoated Balloon Angioplasty for Treatment of In-stent Restenosis in SFA and Popliteal Arteries; DEBATE ISR: Drug Eluting Balloon in peripherAl inTErvention for In-Stent Restenosis; FAIR: Femoral Artery In-Stent Restenosis; PACUBA I: A Randomised Clinical Trial of PAClitaxel drUg-eluting BAlloon Versus Standard Percutaneous Transluminal Angioplasty to Reduce Restenosis in Patients With In-stent Stenoses in the Superficial Femoral and Proximal Popliteal Artery.

Online Table 4. Definitions of endpoints among studies included.

Trial	TLR	Recurrent ISR	RC improvement	Death
COPACABANA[19]	Any reintervention or artery bypass graft surgery involving the target lesion	>50% diameter stenosis at angiography or measured as a PVR ≥2.4 at duplex ultrasound*	≥1 Rutherford class improvement post index procedure and at follow-up as compared to baseline	N/A
DEBATE ISR[18]	Clinically driven repeat revascularisation of the target lesion	>50% diameter stenosis at angiography or measured as a PVR ≥2.5 at duplex ultrasound at any point within the stent(s), plus the 5-mm segments proximally and distally	≥1 Rutherford class improvement post index procedure and at follow-up as compared to baseline	Death of any cause
FAIR[9]	Any reintervention or artery bypass graft surgery involving the target lesion	>50% diameter stenosis measured as a PVR ≥2.4 at duplex ultrasound	≥1 Rutherford class improvement post index procedure and at follow-up as compared to baseline	Death of any cause
PACUBA I[10]	Any reintervention of the target lesion due to presence of a symptomatic >50% diameter stenosis	>50% diameter stenosis at angiography or measured as a PVR ≥2.4 at duplex ultrasound in the absence of clinically driven TLR	≥1 Rutherford class improvement post index procedure and at follow-up as compared to baseline	N/R

*In cases where results were available for both angiography and duplex ultrasound, angiographic results (if conducted within follow-up window) were used to determine binary restenosis. ISR: in-stent restenosis; N/A: not available; N/R: not reported; PVR: peak systolic velocity ratio; RC: Rutherford class; TLR: target lesion revascularisation. Study acronyms: COPACABANA: Cotavance™ Paclitaxel-Coated Balloon Versus Uncoated Balloon Angioplasty for Treatment of In-stent Restenosis in SFA and Popliteal Arteries; DEBATE ISR: Drug Eluting Balloon in peripherAl inTErvention for In-Stent Restenosis; FAIR: Femoral Artery In-Stent Restenosis; PACUBA I: A Randomised Clinical Trial of PAClitaxel drUg-eluting BAlloon Versus Standard Percutaneous Transluminal Angioplasty to Reduce Restenosis in Patients With In-stent Stenoses in the Superficial Femoral and Proximal Popliteal Artery.

Online Table 5. Meta-regression analysis for the primary outcome.

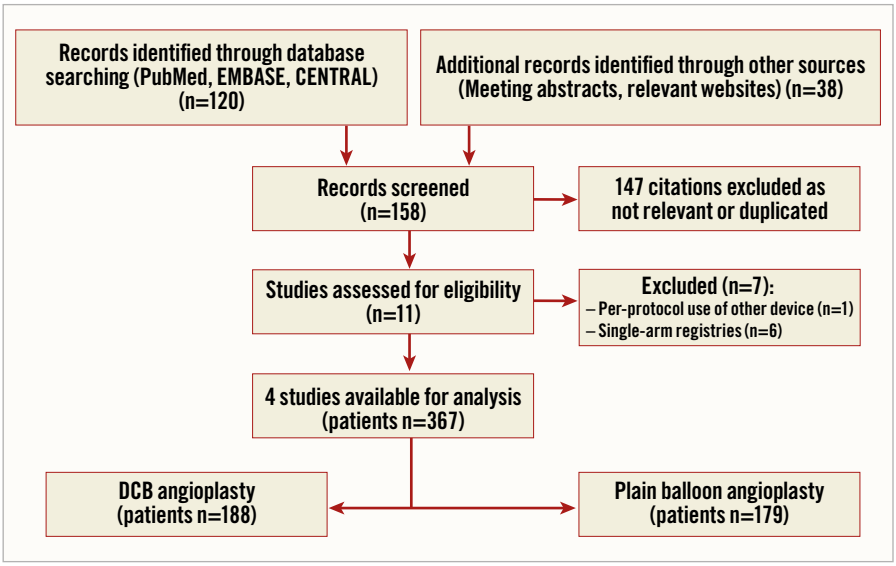
Variable	Exp(b) [95% CI]	Δ tau	*p*-value
Age, years	1.13 [0.48-2.68]	0.61	0.60
Males, %	0.99 [0.28-3.55]	–0.01	0.99
Diabetes, %	1.01 [0.91-1.12]	0.61	0.60
CLI, %	1.02 [0.89-1.16]	2.27	0.26
Lesion length, mm	1.02 [0.97-1.07]	1.85	0.20
Diameter stenosis, %	1.14 [0.55-2.36]	2.28	0.26
ISR class III, %	1.03 [0.84-1.26]	0.66	0.57
Follow-up duration, months	1.33 [0.66-2.70]	1.76	0.22

The mean values for lesion length and diameter stenosis in each included study are reported in Table 1. For baseline angiographic data, digital subtraction angiography was performed in two studies, FAIR[9] and PACUBA I[10], to assess, among other lesion features, the pattern of restenosis, the length (determined by means of a radiopaque ruler placed under the patient's upper thigh), and the percentage diameter stenosis. The remaining studies, DEBATE ISR[18] and COPACABANA[19], reported that a baseline angiography of the target vessel was performed to collect the same lesion features. In addition, in these latter studies an independent core lab, blinded to assigned treatment and clinical status, reviewed acquired angiograms and performed the quantitative angiographic analysis using a semi-automated edge contour detection computer analysis system. CLI: critical limb ischaemia; ISR: in-stent restenosis

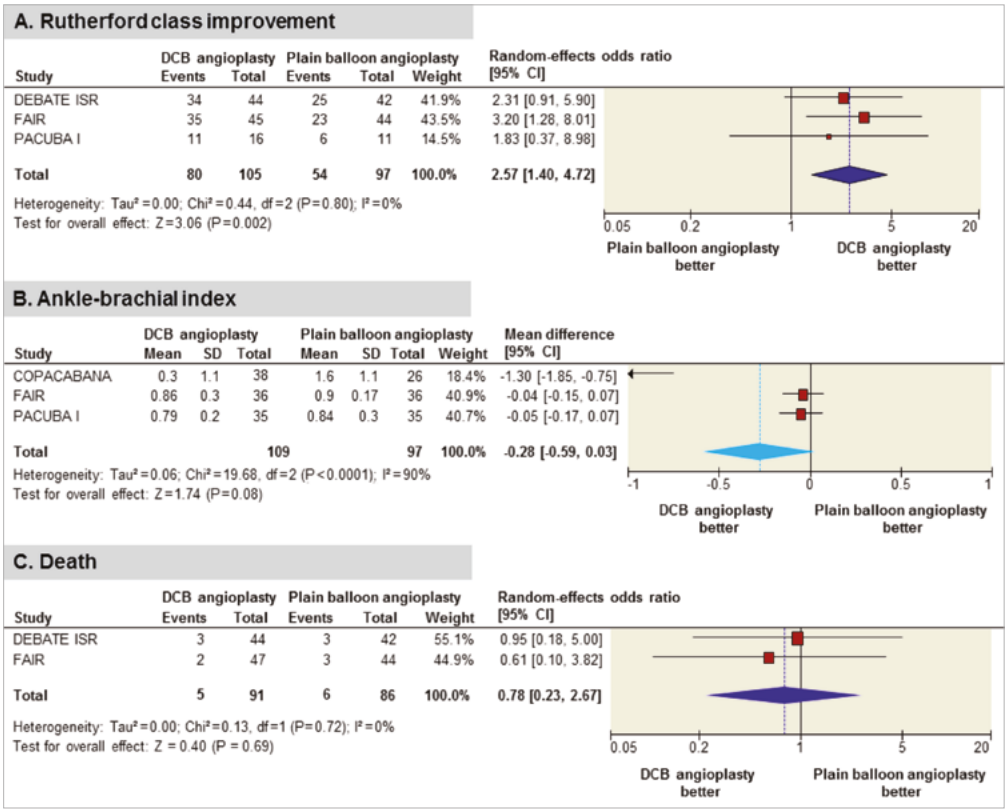
Online Table 6. Published randomised studies investigating endovascular therapies other than DCB angioplasty for femoropopliteal ISR.

Study	Comparison	Patients, n	Primary endpoint	TLR	Recurrent ISR	Follow-up, months
Brodmann et al[22]	Silverhawk atherectomy device (Covidien, ev3 Endovascular, Inc., Plymouth, MN, USA) versus plain balloon angioplasty	19	6-month reoccurrence of intimal hyperplasia within the treated segment	2.2% versus 1.0%; (p=0.48)	N/R	6
Dick et al[31]	Peripheral Cutting Balloon (Boston Scientific, Marlborough, MA, USA) versus plain balloon angioplasty	40	6-month occurrence of >50% diameter stenosis at angiography or measured as a PVR ≥2.4 at duplex ultrasound	41.2% versus 36.3%; (p=0.76)	64.7% versus 72.7%; (p=0.59)	6
EXCITE ISR[23]	Turbo-Elite/Turbo-Tandem laser catheter (Spectranetics Corp., Colorado Springs, CO, USA) plus plain balloon angioplasty versus plain balloon angioplasty	250	6-month freedom from TLR	22.2% versus 36.3%; (p=0.03)	33.3% versus 42.8%; (p=0.22)	6
RELINE[26]	VIABAHN Endoprosthesis with PROPATEN Bioactive Surface (W.L. Gore & Associates, Flagstaff, AZ, USA) versus plain balloon angioplasty	83	12-month primary patency	20.5% versus 56.8%; (p=0.003)	26.6% versus 63.6%; (p<0.001)	12

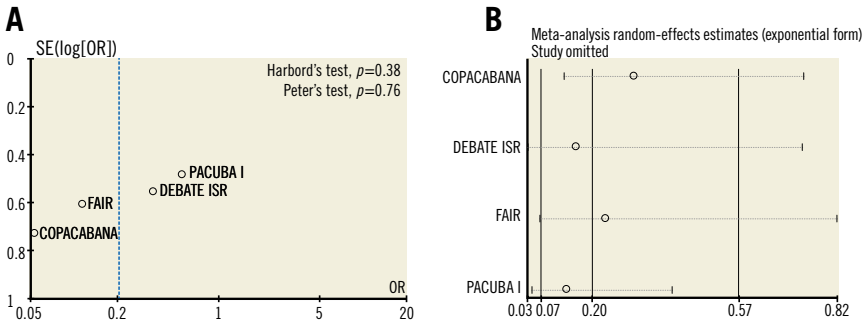
DCB: drug-coated balloon; ISR: in-stent restenosis; PVR: peak systolic velocity ratio; TLR: target lesion revascularisation. Study acronyms: EXCITE ISR: EXCImer Laser Randomised Controlled Study for Treatment of FemoropopliTEal In-Stent Restenosis; RELINE: The GORE VIABAHN® Endoprosthesis With PROPATEN Bioactive Surface Versus Plain Old Balloon Angioplasty (POBA) for the Treatment of Superficial Femoral Artery (SFA) In-Stent Restenosis



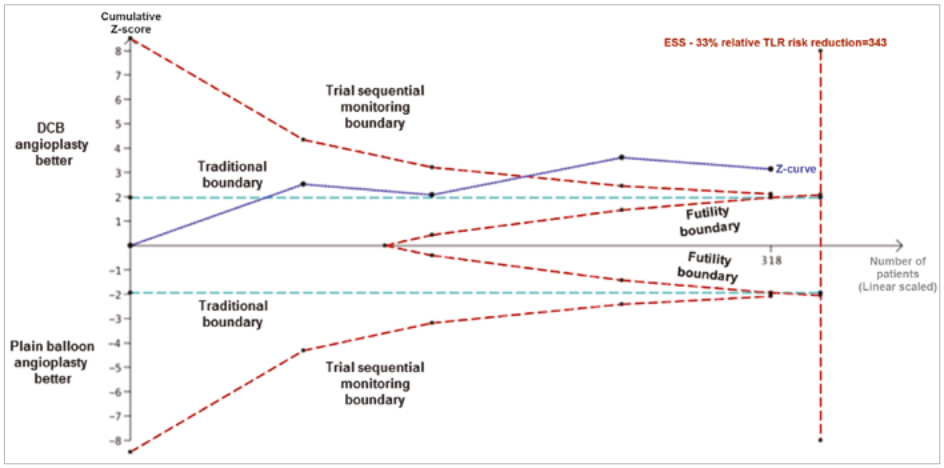
Online Figure 1. *Flow diagram of study selection process. Flow chart for the study selection process according to Preferred Reporting Items for Systematic reviews and Meta-Analyses. DCB: drug-coated balloon*



Online Figure 2. *Risk estimates for other secondary outcomes of DCB versus plain balloon angioplasty. Plots of odds ratio for A) Rutherford class improvement, B) ankle-brachial index, and C) death associated with DCB versus plain balloon angioplasty. The diamond indicates the point estimate and the left and the right ends of the line the 95% confidence interval (CI). DCB: drug-coated balloon. Study acronyms: COPACABANA: Cotavance Paclitaxel-Coated Balloon Versus Uncoated Balloon Angioplasty for Treatment of In-stent Restenosis in SFA and Popliteal Arteries; DEBATE ISR: Drug Eluting Balloon in peripherAl inTErvention for In-Stent Restenosis; FAIR: Femoral Artery In-Stent Restenosis; PACUBA I: A Randomised Clinical Trial of PAClitaxel drUg-eluting BAlloon Versus Standard Percutaneous Transluminal Angioplasty to Reduce Restenosis in Patients With In-stent Stenoses in the Superficial Femoral and Proximal Popliteal Artery.*



Online Figure 3. *Funnel plot and influence analysis according to primary outcome. A) Funnel plot distribution of trials according to primary outcome. The standard error (SE) of the logarithm of odds ratio – log(OR) – is plotted against the OR of target lesion revascularisation. B) Influence analysis according to primary outcome. Meta-analysis random-effects estimates for target lesion revascularisation are computed omitting one study at a time. Study acronyms: COPACABANA: Cotavance Paclitaxel-Coated Balloon Versus Uncoated Balloon Angioplasty for Treatment of In-stent Restenosis in SFA and Popliteal Arteries; DEBATE ISR: Drug Eluting Balloon in peripherAl inTErvention for In-Stent Restenosis; FAIR: Femoral Artery In-Stent Restenosis; PACUBA I: A Randomised Clinical Trial of PAClitaxel drUg-eluting BAlloon Versus Standard Percutaneous Transluminal Angioplasty to Reduce Restenosis in Patients With In-stent Stenoses in the Superficial Femoral and Proximal Popliteal Artery.*



Online Figure 4. *Trial sequential analysis for the primary outcome. Heterogeneity adjusted estimated sample size (ESS) of 343 participants calculated on the basis of odds ratio of target lesion revascularisation (TLR) of 44.3% in the control group, relative risk (RR) reduction=33%, alpha=5%, beta=20%, I^2=0%. Dashed blue cumulative Z-curve crossed the light green dashed traditional boundary, the dashed red information size boundary and the dashed red futility boundary, thereby suggesting firm evidence for the DCB angioplasty group as compared to the plain balloon angioplasty group with respect to this outcome. Horizontal dashed light green lines illustrate traditional level of statistical significance (p=0.05).*