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Paclitaxel density and clinical efficacy of drug-coated balloon angioplasty for femoropopliteal artery disease: meta-analysis and adjusted indirect comparison of 20 randomised trials

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Introduction

Multiple endovascular technologies have been evaluated as stand-alone or combined therapies for atherosclerotic disease of the femoropopliteal arteries[1]. Amongst others, balloon catheters coated with the taxol derivative paclitaxel, a highly lipophilic antiproliferative drug, have been associated with superior efficacy compared to plain balloons in the treatment of *de novo* and restenotic lesions of the femoropopliteal arteries[2].

Despite the large number of DCB platforms currently available on the market, little is known regarding their comparative effectiveness in preventing the risk of repeat revascularisation. Against this background, we performed a meta-analysis of randomised trials comparing DCB versus plain balloon angioplasty, and an indirect comparison of DCB platforms grouped by paclitaxel density.

Methods

We updated the literature search from a previous systematic review[2]. The final search was performed in May 2018. Randomised trials comparing DCB versus plain balloon angioplasty as intended stand-alone therapies for *de novo* or restenotic disease of the femoropopliteal arteries were included, without restriction of language or publication status. Aggregated data from selected studies were analysed according to the intention-to-treat principle. The primary outcome was target lesion revascularisation (TLR) at 12-month follow-up. For the pairwise meta-analysis, the risk ratio (RR) with 95% confidence intervals (95% CI) was obtained using the Mantel-Haenszel fixed-effects model and the Hartung-Knapp random-effects model, by grouping DCB platforms according to paclitaxel density (2, 3 and 3.5 µg per mm^2 of balloon surface, respectively). We accounted for the dependency of the subgroups of trials in the total effect by calculating the risk for TLR with the robust variance estimation method (package robumeta). A χ^2 test for subgroup by treatment interaction was used to evaluate the difference in treatment effect across subgroups. The I^2 statistic[3] was used to quantify the heterogeneity between trials: values around 25%, 50% and 75% were suggested to indicate low, moderate or high heterogeneity, respectively. In addition, we estimated the between-study variance (τ^2) and the 95% prediction interval of the pooled estimate[4]. Publication bias was investigated according to Peters et al[5]. For the adjusted indirect comparison, subgroups of DCB platforms were compared assuming the plain balloon angioplasty arm as the common (adjusted) comparator. According to the method proposed by Song[6] and Bucher[7] we generated RRs (95% CI) and z scores for DCB with lower versus higher paclitaxel densities, finally providing the relative p-values. A requirement of adjusted indirect comparison is that compared trials are similar: for this reason, a random-effects meta-regression analysis tested the interaction of relevant baseline features of DCB-treated patients (proportion of diabetes, critical limb ischaemia and occluded vessels, lesion length and vessel size) and DCB generation (early or "PACCOCATH-like"[8] versus new) with the observed

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treatment effect. All analyses were performed using R, version 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 20 randomised trials with 3,038 participants were studied. Follow-up data up to 12 months were available for 1,723 patients allocated to DCB and 1,158 patients allocated to plain balloon angioplasty. A summary of trials, main characteristics of participants and description of DCB platforms are reported in **Supplementary Table 1**.

TLR occurred in 498 patients (17.2%) **(Figure 1A)**. The risk for TLR was significantly reduced in patients treated with DCB versus plain balloon angioplasty (9.1% versus 29.4%; RR [95% CI]: 0.33 [0.25; 0.45], p<0.01). The results did not change after

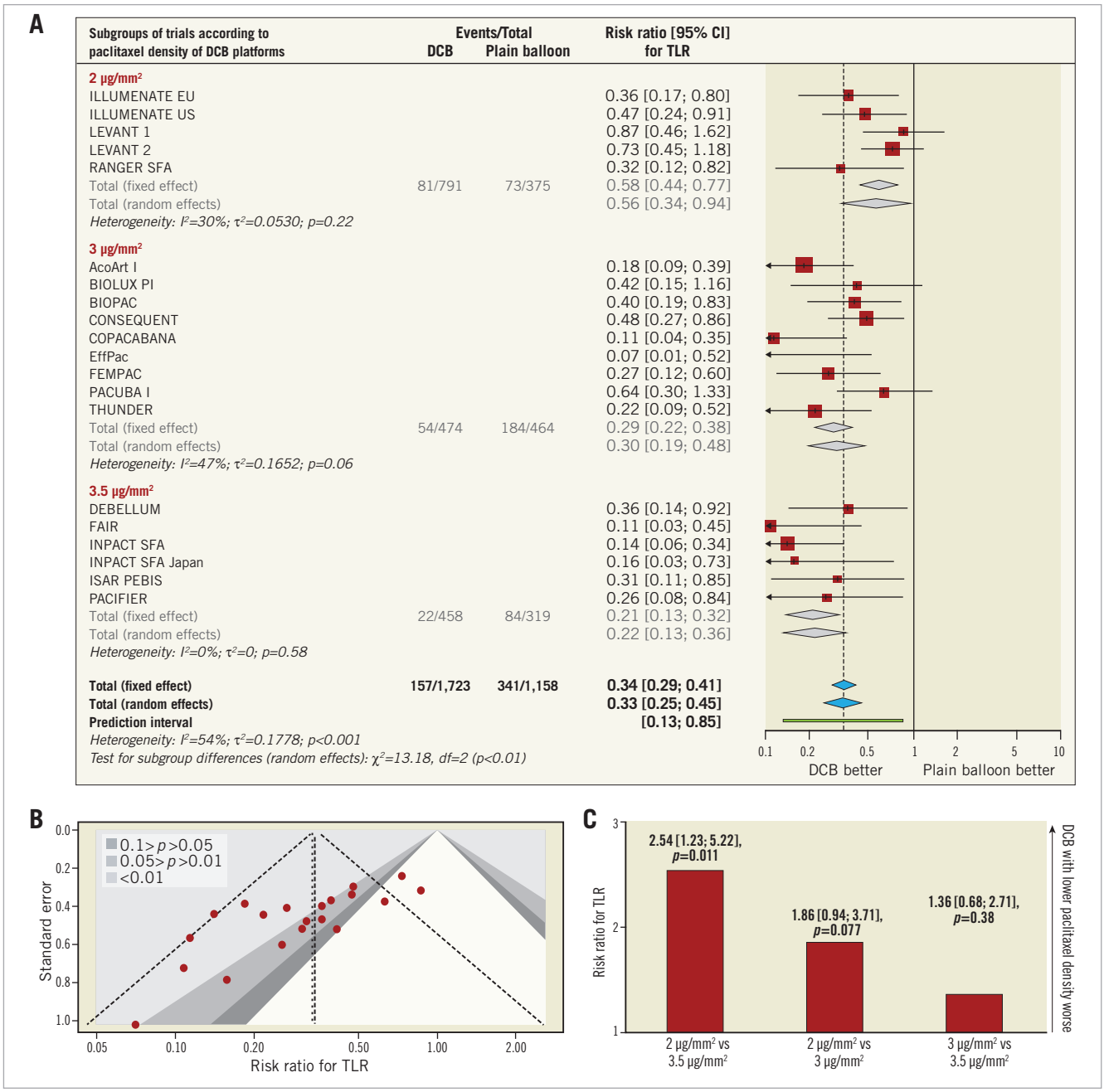

Figure 1. *Plots of target lesion revascularisation with DCB versus plain balloon angioplasty. A) Risk estimates for target lesion revascularisation (TLR) with DCB versus plain balloon angioplasty. Forest plots of risk ratios for TLR associated with DCB versus plain balloon angioplasty. The squares and the diamonds indicate the point estimates and the left and the right ends of the line the 95% confidence intervals. B) Contour-enhanced funnel plot for TLR with DCB versus plain balloon angioplasty. Contours are plotted for a range of significance levels defined by p-values of 0.01, 0.05, and 0.1. C) Risk estimates for TLR at adjusted indirect comparison of DCB platforms with different paclitaxel density. Risk ratios (bar graphs display the point estimate) for TLR associated with DCB platforms grouped by paclitaxel density.*

accounting for the dependency of the subgroups of trials in the total effect (0.33 [0.24; 0.43], p<0.01). Although the 95% prediction interval remained below the null (0.13; 0.85), there was evidence of high heterogeneity (I^2=54%, p<0.01) due to a significant difference in treatment effect within subgroups, unrelated to publication bias (p=0.69) **(Figure 1B)**. Similarly, there was no modification of the risk estimate for TLR according to the proportion of diabetes (p=0.79), critical limb ischaemia (p=0.83), occlusive lesions (p=0.74), lesion length (p=0.83), vessel size (p=0.97) or DCB generation (p=0.14) across treated patients. In contrast, at indirect comparison **(Figure 1C)**, the risk for TLR related to DCB platforms with a paclitaxel density of 2 µg/mm^2 was significantly higher as compared to platforms with 3.5 µg/mm^2 (2.54 [1.23; 5.22], p=0.011) and trended higher as compared to platforms with 3 µg/mm^2 (1.86 [0.94; 3.71], p=0.077). There was no difference in treatment effect across DCB platforms with a paclitaxel density of 2 µg/mm^2 (p=0.14). DCB platforms with paclitaxel density of 3 µg/mm^2 or 3.5 µg/mm^2 displayed a comparable risk for TLR (1.36 [0.68; 2.71], p=0.38).

Discussion

This is the largest meta-analysis of randomised trials comparing DCB and plain balloon angioplasty for femoropopliteal artery disease performed so far. In addition, this study presents the first indirect comparison of DCB platforms grouped by paclitaxel density.

The comparative clinical efficacy of DCB platforms available on the market has yet to be investigated. On the one hand, this meta-analysis lends support to a gradient in the magnitude of clinical efficacy of DCB angioplasty in patients with femoropopliteal artery disease. In fact, DCB versus plain balloon angioplasty was associated with a relative reduction in the risk of TLR of between 78% and 44%. At indirect comparison, DCB platforms with lower paclitaxel density had up to a 2.5-fold increase in the risk of TLR as compared to DCB with higher paclitaxel densities. On the other hand, this analysis remains hypothesis-generating. Indeed, despite the lack of statistical interaction between the observed treatment effect and baselines features of participants, some heterogeneity persisted within DCB groups, suggesting that factors other than paclitaxel density affect the risk for TLR.

However, the results of this study have important clinical implications for the design of future trials. Indeed, it has become evident that plain balloon angioplasty represents a weak comparator to provide a reliable measure of effectiveness of DCB therapy. In this respect, head-to-head comparisons powered for clinical outcomes between different DCBs are urgently needed to obtain a better insight into the clinical performance of these devices.

Study limitations

First, this meta-analysis relies on aggregate data. A meta-analysis based on individual participant data would provide better evidence for the comparative efficacy of different DCB platforms in specific subgroups of patients. Second, we cannot exclude that unmeasured confounders are responsible for the gradient of efficacy of DCB platforms observed in the present study. Finally, a 12-month follow-up is certainly inadequate to address the durability of treatment effect associated with the different DCB platforms included in this report.

Conclusions

In patients with femoropopliteal artery disease, DCB angioplasty reduces the risk of repeat revascularisation at one year as compared to plain balloon angioplasty, with evidence of a gradient of clinical efficacy across DCB platforms depending on paclitaxel density.

Impact on daily practice

In patients with femoropopliteal artery disease, drug-coated balloon angioplasty reduces the risk of repeat revascularisation at one year as compared to plain balloon angioplasty. Our study lends support to a gradient of clinical efficacy across DCB platforms depending on paclitaxel density. The comparative efficacy of different DCB platforms should be tested in head-to-head comparisons powered for clinical outcomes.

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

The complete list of references can be found in the online version of this paper.

Supplementary data

Supplementary Table 1. Summary of trials and main features of DCB-treated patients/lesions across the included studies.

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Supplementary data

Supplementary Table 1. Summary of trials and main features of DCB-treated patients/lesions across the included studies.

Trial	Patients enrolled, n	DCB type, brand name (manufacturer)	Paclitaxel density, μg/mm^2	Excipient	ISR only	Diabetes, %	CLI, %	Total occlusions, %	Lesion length, mm	RVD, mm
ILLUMENATE EU[9]	294	Stellarex, (Spectranetics)	2	Polyethylene glycol	No	37	2	19	72	5
ILLUMENATE US[10]	300	Stellarex, (Spectranetics)	2	Polyethylene glycol	No	49.5	4	19	80	4.9
LEVANT I[11]	101	Lutonix (Bard)	2	Polysorbate/sorbitol	No	45	6	41	80.8	4.1
LEVANT 2[12]	476	Lutonix (Bard)	2	Polysorbate/sorbitol	No	43.4	8	20.6	62.7	4.8
RANGER SFA[13]	105	Ranger (Boston Scientific)	2	Citrate ester	No	39	N/A	34	68	5
AcoArt I[14]	200	Orchid (Acotec Scientific)	3	Magnesium stearate	No	54	40	57	147	3.83
BIOLUX P-I[15]	60	Passeo-18 Lux (Biotronik)	3	Butyryl-tri-hexyl citrate	No	36.7	20	N/A	51.4	4.6
BIOPAC[16]	66	mcPCB PAK (Balton)	3	Biodegradable polymer	No	33.3	N/A	44	84.6	4.47
CONSEQUENT[17]	153	SeQuent Please OTW (B. Braun Melsungen)	3	Resveratrol	No	34.6	N/A	23.1	137	5.06
COPACABANA[§]	88	Cotavance (Medrad, Medtronic)	3	Iopromide	Yes	42.6	8	25.5	152	N/A
EffPac[ǂ]	171	Luminor (iVascular)	3	Organic ester	No	36.5	4	20.2	59	5.4
FEMPAC[18]	87	Paccocath (Bavaria Medizin Technologie)	3	Iopromide	No	40	4	13	40	5.2
PACUBA[19]	74	FREEWAY 0.035 (Eurocor)	3	Shellac	Yes	52	N/A	31	173	5.7

THUNDER[8]	154 (102)*	Paccocath (Bavaria Medizin Technologie)	3	Iopromide	No	50	N/A	27	75	5
DEBELLUM[20]	50	In.Pact (Medtronic)	3.5	Urea	No	52	36	21	76	4
FAIR[21]	119	In.Pact (Medtronic)	3.5	Urea	Yes	28	5	15	82.3	5.1
INPACT SFA[22]	331	In.Pact (Medtronic)	3.5	Urea	No	40.5	5	25.8	89	4.64
INPACT SFA Japan[23]	100	In.Pact (Medtronic)	3.5	Urea	No	59	4	16	91	4.84
ISAR PEBIS[24]	70	In.Pact (Medtronic)	3.5	Urea	Yes	33	3	36	132	4.8
PACIFIER[25]	85 (91)¶	In.Pact (Medtronic)	3.5	Urea	No	43.2	5	22.7	70	4.92

CLI: critical limb ischaemia; DCB: drug-coated balloon; ISR: in-stent restenosis; N/A: not available; RVD: reference vessel diameter.

* with (without) the arm randomly assigned to receive paclitaxel diluted in the contrast medium (arm excluded since not pertinent to the study research question); ¶ total number of cases, since 6 patients were treated twice. § Tepe G. Cotavance paclitaxel-coated balloon vs. uncoated balloon angioplasty for treatment of in-stent restenosis in SFA and the popliteal arteries: 2-year results of the COPACABANA trial. Oral presentation at Leipzig Interventional Course 2017; January 25, 2017; ǂ Teichgräber U. EffPac Trial: Effectiveness of LUMINOR DCB versus POBA in the SFA: 12 months results. Oral presentation at Charing Cross International Symposium 2018; April 25, 2018.

Trial acronyms: ILLUMENATE EU: Prospective, Randomized, Multi-center, Single-blinded Study for the Treatment of Subjects Presenting With De Novo Occluded/Stenotic or Re-occluded/Restenotic Lesions of the Superficial Femoral or Popliteal Arteries Using Paclitaxel or Bare Percutaneous Transluminal Angioplasty Balloon Catheter; ILLUMENATE US: ProspectIve, Randomized, SingLe-Blind, U.S. MuLti-Center Study to EvalUate TreatMent of Obstructive SupErficial Femoral Artery or Popliteal LesioNs With A Novel PacliTaxel-CoatEd Percutaneous Angioplasty Balloon; LEVANT I: A Prospective, Multicenter, Single Blind, Randomized, Controlled Trial Comparing the Lutonix Catheter vs. Standard Balloon Angioplasty for Treatment of Femoropopliteal Arteries With and Without Stenting; LEVANT 2: A Prospective, Multicenter, Single Blind, Randomized, Controlled Trial Comparing the Moxy Drug Coated Balloon vs. Standard Balloon Angioplasty for Treatment of Femoropopliteal Arteries; RANGER SFA: Prospective, Randomized, Multicentre Clinical Study of the Hemoteq

Ranger™ Paclitaxel-Coated PTA Balloon Catheter (Ranger DCB) in Comparison to Uncoated PTA Balloons in Femoropopliteal Lesions; AcoArt I: Prospective, Multi-center and Randomized Controlled Clinical Study to Verify Effectiveness and Safety of Drug-eluting Balloon in PTA Procedure; BIOLUX P-I: A Prospective, Multi-centre, Randomized Controlled, First in Man Study to Assess the Safety and Performance of the Passeo-18 Lux Paclitaxel Releasing PTA Balloon Catheter vs. the Uncoated Passeo 18 Balloon Catheter in Patients With Stenosis and Occlusion of the Femoropopliteal Arteries; BIOPAC: Prospective, controlled, clinical randomized trial evaluating novel, microcrystalline and biodegradable polymer paclitaxel coated balloon for the treatment of femoro-popliteal disease; CONSEQUENT: Clinical Trial on Peripheral Arteries Treated With SeQuent® Please P Paclitaxel Coated Balloon Catheter; COPACABANA: Cotavance™ Paclitaxel-Coated Balloon Versus Uncoated Balloon Angioplasty for Treatment of In-stent Restenosis in SFA and Popliteal Arteries; EffPac: Multicenter Randomized Controlled Trial to Assess the Effectiveness of Paclitaxel-coated Luminor® Balloon Catheter Versus Uncoated Balloon Catheter in the Superficial Femoral and Popliteal Arteries to Prevent Vessel Restenosis or Reocclusion; FEMPAC: Paclitaxel Coated Balloon Catheter for Inhibition of Restenosis in Femoropopliteal Arteries; PACUBA I: A Monocenter Randomized 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; THUNDER: Local Taxan With Short Time Contact for Reduction of Restenosis in Distal Arteries; DEBELLUM: Drug-Eluting Balloon Evaluation for Lower Limb MUltilevel TreatMent; FAIR: Femoral Artery In-Stent Restenosis Trial; INPACT SFA: Randomized Trial of IN.PACT Admiral(TM) Drug Coated Balloon vs Standard PTA for the Treatment of SFA and Proximal Popliteal Arterial Disease; ISAR PEBIS: Randomized Trial of Paclitaxel Eluting Balloon or Conventional Balloon for Treatment of In-Stent Restenosis of the Superficial Femoral Artery in Patients With Symptomatic Peripheral Artery Disease; PACIFIER: Paclitaxel-coated Balloons in Femoral Indication to Defeat Restenosis.

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