Eur J Vasc Endovasc Surg (xxxx) xxx, xxx

EJVES Open Access

SYSTEMATIC REVIEW

Risk of Major Amputation Following Application of Paclitaxel Coated Balloons in the Lower Limb Arteries: A Systematic Review and Meta-Analysis of Randomised Controlled Trials

Konstantinos Katsanos [a,*], Stavros Spiliopoulos [b], Ulf Teichgräber [c], Panagiotis Kitrou [a], Costantino Del Giudice [d], Patrick Björkman [e], Theodosios Bisdas [f], Sanne de Boer [g], Miltiadis Krokidis [h,i], Dimitrios Karnabatidis [a]

[a] Patras University Hospital, Rion, Greece
[b] Attikon University Hospital, Athens, Greece
[c] University Hospital Jena, Friedrich-Schiller-University, Jena, Germany
[d] Institut Mutualiste Montsouris, Paris, France
[e] Helsinki University Hospital, Helsinki, Finland
[f] Westphalian Wilhelms University, Munster, Germany
[g] Maastricht University Medical Centre+, Maastricht, the Netherlands
[h] Areteion Hospital, National and Kapodistrian University of Athens, Greece
[i] Inselspital Bern University Hospital, University of Bern, Switzerland

WHAT THIS PAPER ADDS

Previous meta-analyses have identified a higher risk of all cause death using paclitaxel coated devices in the femoropopliteal arteries, and of the composite of all cause death and major amputation in the infrapopliteal arteries. A systematic review and meta-analysis was performed of randomised controlled trials to investigate the long term risk of major amputation alone associated using paclitaxel drug coated balloons (DCB) in the lower limbs. A significantly higher long term risk of major limb loss using DCB in the femoropopliteal and/or infrapopliteal arteries was documented. There was also evidence of a significant non-linear dose response relationship.

Objective: There have been concerns about the long term safety of paclitaxel coated devices in the lower limbs. A formal systematic review and meta-analysis of randomised controlled trials (RCTs) was performed to examine the long term risk of major amputation using paclitaxel coated balloons in peripheral arterial disease (PAD).

Method: This systematic review was registered with PROSPERO (ID 227761). A broad bibliographic search was performed for RCTs investigating paclitaxel coated balloons in the peripheral arteries (femoropopliteal and infrapopliteal) for treatment of intermittent claudication or critical limb ischaemia (CLI). The literature search was last updated on 20 February 2021 without any restrictions on publication language, date, or status. Major amputations were analysed with time to event methods employing one and two stage models. Sensitivity and subgroup analyses, combinatorial meta-analysis, and a multivariable dose response meta-analysis to examine presence of a biological gradient were also performed.

Results: In all, 21 RCTs with 3 760 lower limbs were analysed (52% intermittent claudication and 48% CLI; median follow up two years). There were 87 major amputations of 2 216 limbs in the paclitaxel arms (4.0% crude risk) compared with 41 major amputations in 1 544 limbs in the control arms (2.7% crude risk). The risk of major amputation was significantly higher for paclitaxel coated balloons with a hazard ratio (HR) of 1.66 (95% CI 1.14 − 2.42; $p = .008$, one stage stratified Cox model). The prediction interval was 95% CI 1.10 − 2.46 (two stage model). The observed amputation risk was consistent for both femoropopliteal ($p = .055$) and infrapopliteal ($p = .055$) vessels. Number needed to harm was 35 for CLI. There was good evidence of a significant non-linear dose response relationship with accelerated risk per cumulative paclitaxel dose (chi square model $p = .007$). There was no evidence of publication bias ($p = .80$) and no significant statistical heterogeneity between studies ($I^2 = 0\%$, $p = .77$). Results were stable across sensitivity analyses (different models and subgroups based on anatomy and clinical indication and excluding unpublished trials). There were no influential single trials. Level of certainty in evidence was downrated from high to moderate because of sparse events in some studies.

Conclusion: There appears to be heightened risk of major amputation after use of paclitaxel coated balloons in the peripheral arteries. Further investigations are warranted urgently.

* Corresponding author. Department of Interventional Radiology, Patras University Hospital, Rion, 26504, Greece.
E-mail address: katsanos@med.upatras.gr (Konstantinos Katsanos).

 https://doi.org/10.1016/j.ejvs.2021.05.027

Please cite this article as: Katsanos K et al., Risk of Major Amputation Following Application of Paclitaxel Coated Balloons in the Lower Limb Arteries: A Systematic Review and Meta-Analysis of Randomised Controlled Trials, European Journal of Vascular and Endovascular Surgery, https://doi.org/10.1016/j.ejvs.2021.05.027

Keywords: Amputation, Balloon, Dose, Meta-analysis, Paclitaxel-coated, Randomised
Article history: Received 5 March 2021, Accepted 23 May 2021, Available online XXX

INTRODUCTION

Several randomised controlled trials (RCTs) have already shown that paclitaxel coated balloons significantly reduce the rates of vessel re-stenosis and target lesion revascularisation of the femoropopliteal artery in patients with symptomatic peripheral arterial disease (PAD).[1] Recently, concerns have been raised about the long term risk of death using paclitaxel coated devices in the femoropopliteal artery.[2,3] However, inconsistencies between randomised and real world evidence,[4,5] coupled with the absence of a plausible biological mechanism have fuelled an ongoing unresolved controversy on the role of paclitaxel in peripheral endovascular procedures. An interim mortality analysis of the SWEDEPAD randomised trial did not confirm a heightened mortality risk in cases of paclitaxel treatment.[6] Another more recent meta-analysis has claimed a significant detriment to amputation free survival using paclitaxel coated balloons in the infrapopliteal arteries for critical limb ischaemia (CLI) and has further intensified the debate around safety and effectiveness of paclitaxel coated balloons in the periphery.[7] Non-target embolisation of cytotoxic paclitaxel particulate material with long lasting tissue residence has been put forward as a possible mechanism for potential adverse limb events.[7] An updated systematic review and meta-analysis of RCTs was performed to investigate the risk of major amputation associated using paclitaxel coated balloons in the lower limbs.

MATERIALS AND METHODS

PICO tool and selection criteria

The design of the present systematic review and meta-analysis complied with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement.[8] The focus was on major amputations only, because other measures of safety and clinical effectiveness have already been thoroughly reported.[1] The PICO tool (Patient, Intervention, Comparison, Outcome)[9] was used to define the scientific question as follows: "*In patients suffering from peripheral arterial disease, is treatment of the peripheral (femoropopliteal and infrapopliteal) arteries with paclitaxel coated balloons, compared with control treatment, safe and effective in preventing major amputation in PAD?*". Each study was assessed for potential inclusion in the current meta-analysis on the basis of the following eligibility criteria: (1) only RCTs were considered for inclusion, (2) all types of paclitaxel coated balloon catheters were eligible provided that they were applied in the lower limb arteries, (3) selection allowed for both femoropopliteal and infrapopliteal arteries of the lower limbs, (4) the target population included patients presenting with symptoms of peripheral arterial disease (intermittent claudication or CLI documented by digital subtraction angiography, (4) follow up of at least six months was available, and (5) the studies reported counts of major amputations as part of their primary or secondary endpoints.

Search methods

This systematic review was registered in the PROSPERO public database (http://www.crd.york.ac.uk/PROSPERO; ID 227761). The authors searched for RCTs that investigated any type of paclitaxel coated or paclitaxel eluting balloon catheter in the peripheral arteries for the treatment of intermittent claudication or critical limb ischaemia. Electronic searches were conducted of PubMed (Medline), EMBASE (Ovid), AMED, Scopus, CENTRAL, the PROSPERO, and DARE databases. A broad bibliographic search was performed using the search string "(drug-coated OR paclitaxel-coated OR paclitaxel-eluting OR drug-eluting) AND (randomized)". Additional searches of the United States Food and Drug Administration (FDA), European Medicines Agency (EMA), United Kingdom Medicines and Healthcare products Regulatory Agency (MHRA), Japanese Pharmaceuticals and Medical Devices Agency (PMDA), Japanese University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR), Chinese Clinical Trials Registry (ChiCTR), and United States National Library of Medicine clinical trials database, and online archives of international cardiovascular conferences were performed including the terms "femoral", "popliteal", "femoropopliteal", "restenosis", "target lesion revascularization", "peripheral", "angioplasty", "stent", "tibial", "infrapopliteal", "below knee", "balloon", "paclitaxel-coated", "paclitaxel-eluting", "drug-coated", "drug-eluting", "peripheral arterial disease", "peripheral vascular disease", "intermittent claudication", "critical limb ischaemia", "plain balloon angioplasty", "percutaneous transluminal angioplasty", "clinical trial", "multi-center", "randomized", "controlled trial", and various pertinent terms with the corresponding Medical Subjects Headings (MeSH) using Boolean syntax. The literature search was last updated on 20 February 2021. There were no restrictions on publication language, publication date, or publication status.

Data extraction and primary outcome

A standardised data extraction form was used to collect the following information from all selected studies: (1) characteristics of the study design methods (randomisation, blinding, concealment of allocation, dropouts, outcome reporting, risk of bias); (2) patient and limb sample size and baseline clinical characteristics; (3) Rutherford classification of peripheral vascular disease; (4) description of active drug

Please cite this article as: Katsanos K et al., Risk of Major Amputation Following Application of Paclitaxel Coated Balloons in the Lower Limb Arteries: A Systematic Review and Meta-Analysis of Randomised Controlled Trials, European Journal of Vascular and Endovascular Surgery, https://doi.org/10.1016/j.ejvs.2021.05.027

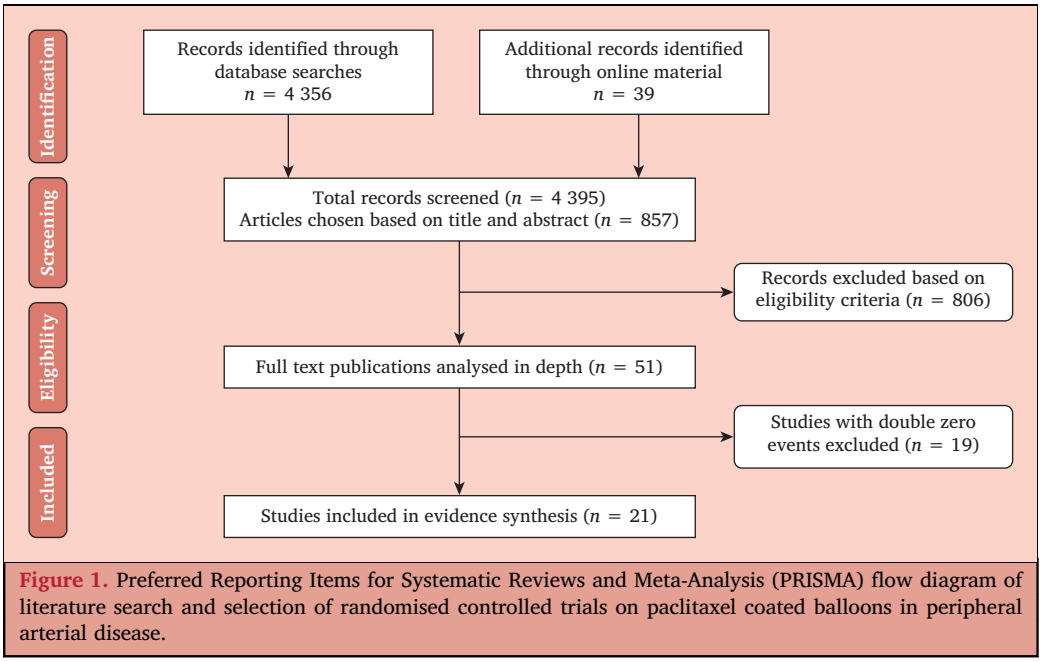

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram of literature search and selection of randomised controlled trials on paclitaxel coated balloons in peripheral arterial disease.

coated balloon (DCB) device and control endovascular treatment; and (5) major amputation counts at different follow up time intervals. The primary outcome measure was set at major amputation defined as any reported limb loss of the index limb above the ankle. Major amputations were analysed on an intention to treat approach. Minor amputations were excluded from the present analysis.

Risk of bias and certainty of evidence

Risk of bias assessment employed the revised Cochrane Collaboration's tool for assessing risk of bias (RoB 2 tool).[10,11] The latter tool evaluates potential risk of bias for five domains: (1) randomisation process, (2) deviation from intended interventions, (3) missing outcome data, (4) measurement of outcomes, and (5) selection of the reported results. Certainty of evidence was assessed with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, which considers risk of bias, imprecision, indirectness, inconsistency, and publication bias of the observed treatment effect as potential reasons for downgrading the level of confidence. Conversely, certainty about the quality of the evidence can be upgraded for large effect size or presence of a dose response gradient.[12]

Sensitivity and subgroup analyses

Heterogeneity was evaluated with the Cochran's Q (chi square) and the I^2 statistical test, while small study effects and publication bias were assessed by visual inspection of funnel plots asymmetry and quantitatively with the Egger's linear regression test.[13] Several sensitivity and subgroup analyses of the primary endpoint were performed to assess consistency and robustness of the summary treatment effect. Subgroups of different paclitaxel coated balloons based on paclitaxel concentration (2.0 μg/mm^2 *vs.* 3.0 *vs.* 3.5 μg/mm^2) were analysed. Leave one out meta-analysis and combinatorial meta-analysis were applied to test for influential studies (single cases or clusters of studies), interrogate between study heterogeneity, and better visualise the distribution of the pooled effect estimate after examining all possible study combinations (2^{k-1}, where k is the number of selected RCTs).[14] Attrition bias was assessed first by comparing dropouts rates and consent withdrawals between treatment arms, and second by multiple imputation of right censored cases assuming departure from independent censoring.[15,16]

Dose response meta-analysis

In the search for epidemiological evidence of causation, a quantitative multivariable dose response meta-analysis was undertaken to investigate the potential presence of a biological gradient using the methods of Crippa *et al.*[17] Cumulative intraprocedural paclitaxel dose was extracted from published material or inferred from the product of the paclitaxel coated balloon concentration [*C*] and treated vessel surface area (surface area of a cylinder based on reported lesion length [*L*] and vessel diameter [*D*]). It is widely recommended (and explicitly stated in most RCT protocols) that DCB application is performed with a longer balloon compared with the target lesion length to avoid geographic miss. Hence, lesion length *L* was corrected for routine practice of longer DCB sizing based on a validation model of six RCTs that reported actual paclitaxel dose delivered (Supplementary material). Linear and non-linear dose response models were explored.

Statistical methods

Studies with zero events in both study arms were excluded from numerical synthesis according to Cochrane guidance (Cochrane handbook *chapter 16.9.3*). Quantitative synthesis of the included RCTs was performed with the "*meta*", "*dmetar*", "*metafor*", "*survival*", "*coxme*", "*Informative-Censoring*", and *"dosresmeta"* packages in R language

Please cite this article as: Katsanos K et al., Risk of Major Amputation Following Application of Paclitaxel Coated Balloons in the Lower Limb Arteries: A Systematic Review and Meta-Analysis of Randomised Controlled Trials, European Journal of Vascular and Endovascular Surgery, https://doi.org/10.1016/j.ejvs.2021.05.027

Table 1. Design characteristics of included randomised controlled trials on paclitaxel coated balloons in peripheral arterial disease for claudication or critical limb ischaemia (CLI)

Study*, authors and year	Design and patients (limbs) sample	Paclitaxel coated balloon tested	Paclitaxel dosage and excipient	Baseline CLI diagnosis − %	Lesion anatomy and length − cm	Available follow up period − y
THUNDER[29,31] Tepe *et al.* 2008	Multicentre 102 (48 *vs.* 54)	Cotavance Bavaria Medizin (MedRad)	3.0 μg / mm^2 Paccocath (Iopromide)	19.6	Femoropopliteal 7.5 ± 6.2	5
FEMPAC[32] Werk *et al.* 2008	Multicentre 87 (45 *vs.* 42)	Cotavance Bavaria Medizin (MedRad)	3.0 μg / mm^2 Paccocath (Iopromide)	5.7	Femoropopliteal 5.7 ± 5.5	2
IN.PACT SFA[42,62–64] Schneider *et al.* 2015	Multicentre 331 (220 *vs.* 111)	IN.PACT Admiral Medtronic	3.5 μg / mm^2 Urea	5.4	Femoropopliteal 8.9 ± 4.9	5
LEVANT I[26,65] Scheinert *et al.* 2014	Multicentre 101 (49 *vs.* 52)	Lutonix (Bard) BD	2.0 μg / mm^2 Polysorbate and Sorbitol	6.9	Femoropopliteal 8.8 ± 3.7	2
LEVANT II[25,65] Rosenfield *et al.* 2015 (incl. roll-in)	Multicentre 532 (372 *vs.* 160)	Lutonix (Bard) BD	2.0 μg / mm^2 Polysorbate and Sorbitol	8.0	Femoropopliteal 6.2 ± 4.2	1
ACOART I[28,66] Jia *et al.* 2016	Multicentre 200 (100 *vs.* 100)	Orchid Acotec Scientific	3.0 μg / mm^2 Magnesium stearate	42.0	Femoropopliteal 14.7 ± 11.0	2
ILLUMENATE Pivotal[24] Krishnan *et al.* 2017	Multicentre 300 (200 *vs.* 100)	Stellarex by Spectranetics	2.0 μg / mm^2 Polyethylene-glycol	4.3	Femoropopliteal 8.0 ± 4.5	4
DRECOREST I[40] Bjorkman *et al.* 2018	Single centre 60 (30 *vs.* 30)	IN.PACT Admiral Medtronic	3.5 μg / mm^2 Urea	43.3 (failing bypass)	Femoropopliteal 1.2 ± 1.0	5
COPA CABANA[30] Tepe *et al.* 2020	Multicentre 87 (47 *vs.* 41)	Cotavance Bavaria Medizin (MedRad)	3.0 μg / mm^2 Paccocath (Iopromide)	9.2	Femoropopliteal 15.2 ± 8.5	2
PACUS[44] Giudice *et al* 2017	Single centre 56 (28 *vs.* 28)	IN.PACT Admiral Medtronic	3.5 μg / mm^2 Urea	100.0	Femoropopliteal 16.4 ± 1.4	2
RAPID[38,39] De Boer *et al.* 2017	Multicentre 160 (80 *vs.* 80)	Legflow and stent Cardionovum	3.0 μg / mm^2 Ammonium salt	17.0	Femoropopliteal 15.8 ± 7.4	2
BELGIAN IN.PACT [41] Debing *et al.* 2017	Multicentre 106 (52 *vs.* 54)	IN.PACT Admiral Medtronic	3.5 μg / mm^2 Urea	52.8	Femoropopliteal 7.7 ± 5.8	6 mo
REEWARM[36] Ye *et al.* 2020	Multicentre 200 (100 *vs.* 100)	Reewarm Endovastec China	3.0 μg / mm^2 Iopromide	27.0	Femoropopliteal 9.6 ± 4.8	1
DEBELLUM[43,67] Fanelli *et al.* 2014	Single centre 50 (33 *vs.* 38)	IN.PACT Admiral Medtronic	3.5 μg / mm^2 Urea	38.0	Femoropopliteal and infrapopliteal 7.6 ± 0.6	1
DEBATE-BTK[45] Liistro *et al.* 2013	Single centre 132 (71 *vs.* 72)	IN.PACT Amphirion Medtronic	3.5 μg / mm^2 Urea	100.0	Infrapopliteal 12.9 ± 8.3	2
IN.PACT DEEP[46,68] Zeller *et al.* 2014	Multicentre 358 (239 *vs.* 119)	IN.PACT Amphirion Medtronic	3.5 μg / mm^2 Urea	99.7	Infrapopliteal 10.2 ± 9.1	5
BIOLUX P-II[37] Zeller *et al.* 2015	Multicentre 72 (36 *vs.* 36)	Passeo-18 Lux Biotronik	3.0 μg / mm^2 BTHC	77.8	Infrapopliteal 11.3 ± 8.8	1
Haddad *et al.*[33] 2017	Single centre 93 (45 *vs.* 48)	Luminor 14 iVascular Spain	3.0 μg / mm^2 Organic ester	100.0	Infrapopliteal NA	1
SINGA-PACLI[35] Tan *et al.* 2019	Multicentre 138 (70 *vs.* 68)	Passeo-18 Lux Biotronik	3.0 μg / mm^2 BTHC	100.0	Infrapopliteal 9.0 ± 7.4	1

Please cite this article as: Katsanos K et al., Risk of Major Amputation Following Application of Paclitaxel Coated Balloons in the Lower Limb Arteries: A Systematic Review and Meta-Analysis of Randomised Controlled Trials, European Journal of Vascular and Endovascular Surgery, https://doi.org/10.1016/j.ejvs.2021.05.027

Table 1-*continued*

Study*, authors and year	Design and patients (limbs) sample	Paclitaxel coated balloon tested	Paclitaxel dosage and excipient	Baseline CLI diagnosis − %	Lesion anatomy and length − cm	Available follow up period − y
ACOART-II[34] Jia *et al.* 2020	Multicentre 120 (61 *vs.* 59)	Litos AcoTec Scientific	3.0 μg / mm^2 Magnesium stearate	99.0	Infrapopliteal 17.0 ± 8.6	1
LUTONIX-BTK[27,69] Mustapha *et al.* 2019	Multicentre 442 (287 *vs.* 155)	Lutonix (Bard) BD	2.0 μg / mm^2 Polysorbate and sorbitol	90.5	Infrapopliteal 11.2 ± 9.3	2

BTHC = butyryl-trihexyl-citrate.

* All included randomised controlled trials tested paclitaxel coated balloons for treatment of peripheral arterial disease. In the DRECOREST-I trial, paclitaxel drug coated balloons (DCB) were randomised *vs.* plain balloon angioplasty for failing bypass surgery. In the COPA-CABANA randomised study, DCB were investigated for treatment of in stent restenosis and the non-randomised double dose cohort for recurrent in stent restenosis was excluded. The DEBELLUM study randomised both femoropopliteal and infrapopliteal lesions. In the PACUS trial, DCB were randomised *vs.* a combination of high frequency low intensity intravascular ultrasound therapy and contrast dissolved liquid paclitaxel (1.0 μg / mm^3) delivered in the femoropopliteal treatment area under distal balloon occlusion and aspirated with a 50 mL syringe after 60 sec. Total dose of liquid paclitaxel in the control arm was accounted for in the multivariable dose response meta-analysis. In the RAPID study, DCB was combined with a biomimetic stent (SUPERA) and randomised *vs.* the stent (SUPERA) alone.

environment (version 3.6.3). Categorical variables were expressed as counts and percentages, and continuous variables as means ± standard deviation. To address differences in follow up period and number of participants who either died or were lost to follow up (LTFU), the primary endpoint was summarised on the log hazard scale as recommended for time to event outcomes.[18] Study specific hazard ratios (HR) and respective variances were sourced from individual publications or calculated from published Kaplan—Meier curves and survival tables by applying the methods of Tierney *et al.*[19] and Guyot *et al.*[20] for extraction of individual time to event patient outcomes. The latter have shown high reproducibility and excellent accuracy for calculation of survival probabilities and HRs. For missing or incomplete data, the principal investigators were contacted, and individual patient time to event data were requested. Examples of time to event analyses are given in the Supplementary material (Fig. S1).

Summary statistics were expressed as HRs and the associated 95% confidence intervals (CI). One and two stage models were employed for the current meta-analysis.[21] Number needed to harm (NNH) was calculated in case of significant findings at the end of the reported follow up period. Hazard functions of major amputations were pooled with a fixed effects model in the absence of significant statistical heterogeneity. A stratified Cox model with a random effect for each trial was applied in case of the one stage patient level model,[22] whereas an inverse variance weighting method was used for the two stage trial level model.[18] To address the risk of informative censoring, bootstrap multiple imputation methods were used to impute censored failure times from the predictive distribution of the observed failure times.[15] A total of $n = 100$ datasets were imputed and Rubin's rules were applied to pool parameter estimates after fitting a one stage stratified Cox model in each of the imputed datasets. For the dose response meta-analysis, a one stage random effects model was applied with restricted maximum likelihood using trial level summary effects on the log hazard scale.[17] In case of the dose response model, a restricted cubic spline model with three knots located at the 10th, 50th, and 90th percentiles was fitted because splines are more advantageous over conventional non-linear models.[23] The level of statistical significance was set at $\alpha = .05$.

RESULTS

The literature search yielded 4 395 articles eligible for further analysis. Of those, 857 publications were considered for inclusion based on their title and abstract. Finally, 51 items reporting the results of 40 RCTs in total were included for further in depth full text analysis after excluding studies that did not meet the predefined inclusion criteria (PRISMA selection process in Fig. 1). Design characteristics of tested

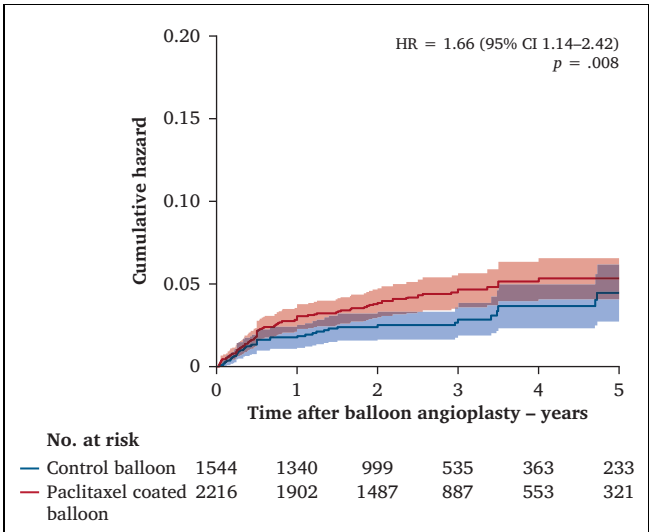

Figure 2. Cumulative hazard functions (time to event) of major amputations in the two treatment arms of paclitaxel coated balloon and of control balloon in patients with peripheral arterial disease. A one stage proportional hazards Cox model stratified at trial level (random effect) was applied.

Please cite this article as: Katsanos K et al., Risk of Major Amputation Following Application of Paclitaxel Coated Balloons in the Lower Limb Arteries: A Systematic Review and Meta-Analysis of Randomised Controlled Trials, European Journal of Vascular and Endovascular Surgery, https://doi.org/10.1016/j.ejvs.2021.05.027

devices are outlined in Table S1. Nineteen RCTs reported zero events of major amputations in both study arms and were excluded from further numerical analysis (Table S2). In all, 21 RCTs with 3 760 lower limbs were eventually included in the quantitative evidence synthesis. The primary characteristics of the 21 selected RCTs are outlined in Table 1.

Out of the 21 RCTs, four studies with 1 375 cases tested a 2.0 μg/mm^2 paclitaxel coated balloon,[24–27] 10 studies with 1 260 patients tested a variety of 3.0 μg/mm^2 paclitaxel coated balloon catheters,[18,28–39] and seven studies with 1 125 patients investigated the highest 3.5 μg/mm^2 paclitaxel coating technology.[40–46] Paclitaxel coated balloons were used in the femoropopliteal arteries in 13 studies with 2 323 lower limbs, in the infrapopliteal arteries in seven studies with 1 366 limbs, whereas one study with 71 limbs enrolled both the femoropopliteal and infrapopliteal segments.[43] There was a largely balanced distribution of baseline patient and lesion characteristics across all studies as described in detail in previously published meta-analyses. Overall, mean patient age ranged between 67 and 76 years, randomised subjects were predominantly males, and the most prevalent risk factors included smoking, diabetes, hypertension, and hyperlipidaemia.[2,7,47]

The enrolled patient population encompassed 1 972 lower limbs (52%) suffering from short distance intermittent claudication and 1 788 limbs presenting with CLI (48%). A wide range of lesions was treated with a weighted average lesion length of 10 cm (Table 1). The median RCT follow up period was two years (range 0.5—5 years). Of 21 RCTs, 16 studies were designed as randomised multicentre trials and five as single centre trials.[33,40,43–45] Overall risk of bias was mostly low to moderate for all included trials. Randomisation and allocation concealment were performed adequately in most cases and there was low risk of outcome data missingness or selective data reporting. There were some concerns about performance bias in all studies because none of them was executed in a double blind fashion. This was reflected accordingly in the second domain of the RoB-2 tool (Fig. S2; revised Cochrane Risk of Bias tool).

Major amputations

In all, 21 RCTs reported 128 events in 3 760 lower limbs after a median individual patient follow up period of two years (max. five years). There were 87 major amputations of 2 216 limbs in the paclitaxel arms (4.0% crude risk) compared with 41 major amputations in 1 544 limbs in the

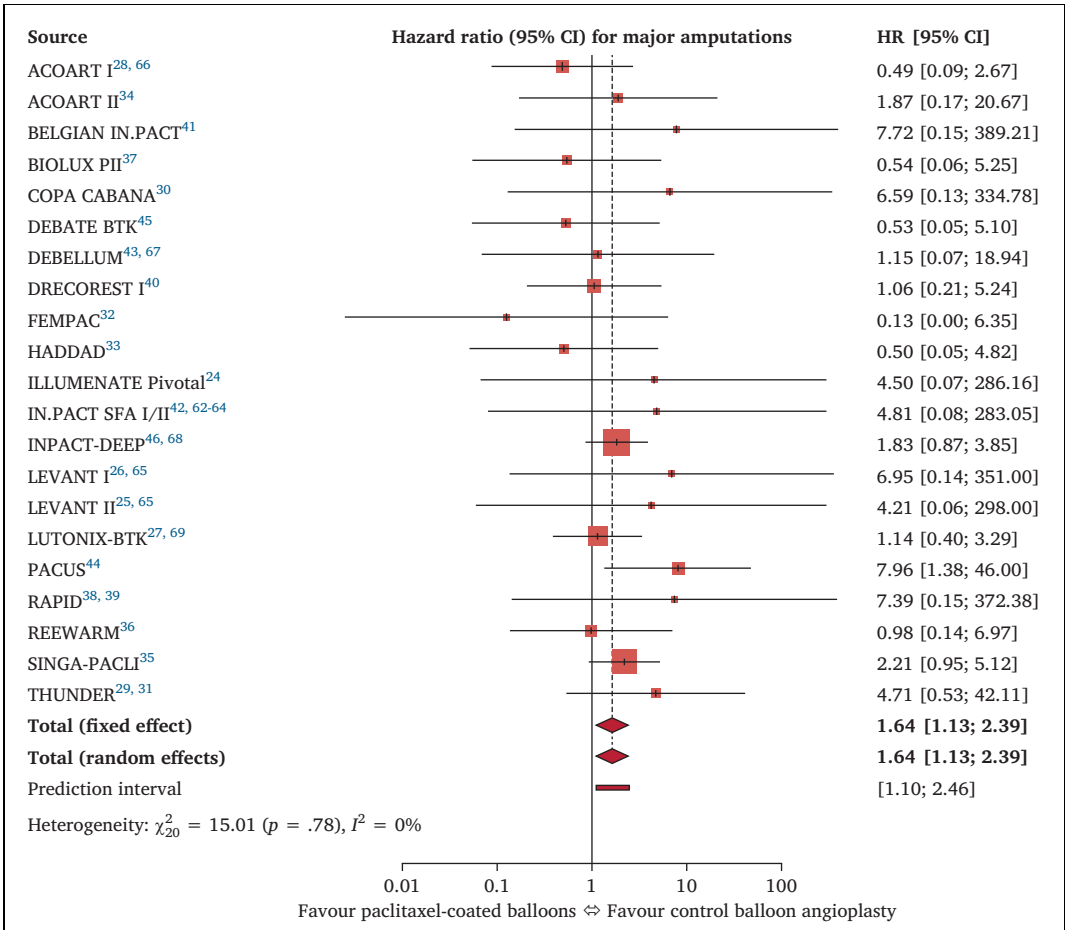

Figure 3. Forest plot of the two stage meta-analysis of trial level hazard ratios (HR) for major amputations of paclitaxel coated balloon *versus* control balloon angioplasty in patients with peripheral arterial disease. HRs were pooled with inverse variance weighting. There was no significant heterogeneity. Fixed effect and random effects models are shown. CI = confidence interval.

Please cite this article as: Katsanos K et al., Risk of Major Amputation Following Application of Paclitaxel Coated Balloons in the Lower Limb Arteries: A Systematic Review and Meta-Analysis of Randomised Controlled Trials, European Journal of Vascular and Endovascular Surgery, https://doi.org/10.1016/j.ejvs.2021.05.027

control arms (2.7% crude risk). Application of paclitaxel coated balloons was associated with a significantly higher risk of major amputation with a pooled HR of 1.66 (95% CI 1.14 — 2.42; $p = .008$, one stage stratified Cox model). Cumulative hazard functions in the two treatment arms are shown in Fig. 2. The prediction interval for the two stage model was 95% CI 1.10 — 2.46 (Fig. 3). There was no significant statistical heterogeneity between studies ($I^2 = 0\%$, $p = .77$). In subgroup analyses, the observed amputation risk was consistent for both femoropopliteal ($p = .055$) and infrapopliteal ($p = .055$) vessels (Fig. 4). Eleven of the 21 RCTs enrolled predominantly CLI patients. The crude amputation risk in CLI trials was 7.2% (74 events of 1 022 limbs) in case of paclitaxel coated treatment *vs.* 4.7% (36 events of 766 limbs) in controls. The risk of major amputation was significant in trials including mostly CLI patients (HR 1.56, 95% CI 1.04 — 2.33; $p = .03$), but not in trials enlisting intermittent claudication patients (HR 2.47, 95% CI 0.87 — 6.97; $p = .088$) (Fig. 5). The corresponding NNH for CLI was 35.

In the dose response meta-analysis, a significant dose dependent association between peri-procedural paclitaxel coated balloon exposure and risk of major amputation was detected (Fig. 6). In the log linear model, there was a significantly higher relative risk of major amputation by 1.12 times per every paclitaxel milligram delivered (95% CI 1.04 — 1.21, $p = .003$) without any significant heterogeneity across studies ($I^2 = 0\%$, $p = .87$). Because of evidence of departure from linearity (Wald test $p = .007$ of regression coefficients) and improved goodness of fit, a non-linear restricted cubic spline model is presented instead (Fig. 6). Amputation risk was accelerated over increasing paclitaxel dose. Predicted amputation risk was 1.7 times higher (95% CI 1.09 — 2.53) at the 5 mg paclitaxel exposure level and 4.4 times higher (95% CI 1.59 — 12.1) at the 10 mg exposure level (chi-square model $p = .007$). Findings of the accelerated dose response gradient were very similar with and without the treated lesion length correction factor (Dose response section, Supplementary material).

In the sensitivity tests, the pooled HR was congruent across leave one out meta-analysis without any influential studies (Table S3). Combinatorial meta-analysis showed a homogeneous set of studies without any outliers or influential clusters, and absence of between study statistical heterogeneity. The pooled estimate demonstrated a symmetric, unimodal distribution indicative of treatment effect homogeneity (Fig. 7). Different statistical models produced similar results with little variation in the magnitude and precision of the observed effect size (Table S4). For multicentre trials only, the calculated HR was 1.71 (95% CI 1.13 — 2.59; $p = .011$). Reported rates of dropout and consent withdrawal were low and similar between the paclitaxel and control groups (7.6 *vs.* 7.3%, $p = .71$; Table S5). Pooled multiple imputed HR was 1.69 (95% CI 1.18 — 2.41, $p = .004$).

Subanalyses of different paclitaxel dose densities were numerically consistent but exhibited wide confidence intervals and only the higher 3.5 μg/mm^2 dose platform

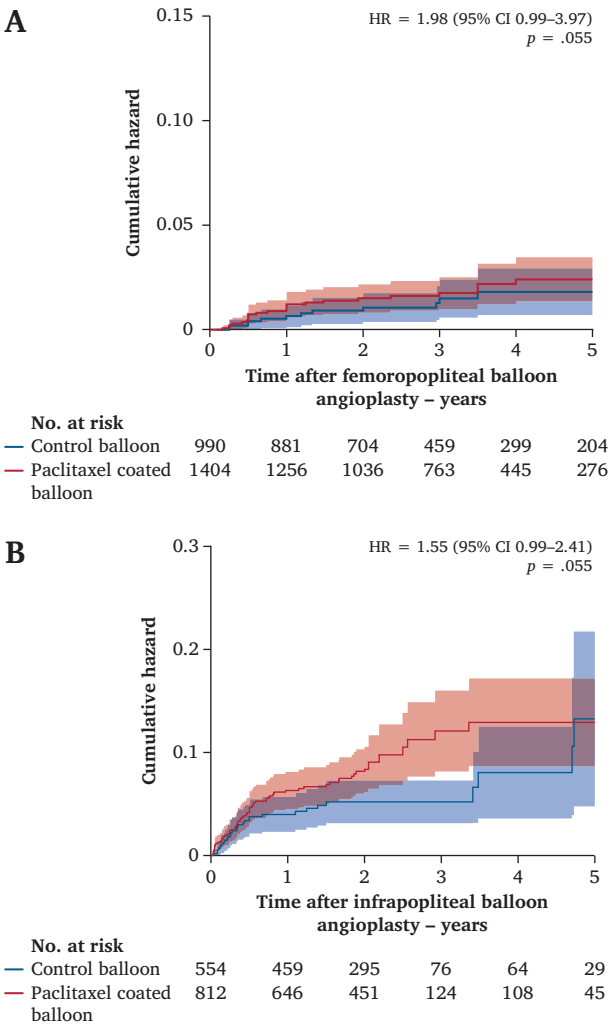

Figure 4. Cumulative hazard functions of major amputations in the two treatment arms of paclitaxel coated balloon and of control balloon for (A) femoropopliteal and (B) infrapopliteal arteries in patients with peripheral arterial disease. A one stage proportional hazards Cox model stratified at trial level (random effect) was applied.

reached the level of statistical significance with an HR of 1.92 (95% CI 1.06 — 3.48; $p = .033$, Fig. S3). Leaving one excipient out meta-analysis confirmed also that the observed effect was dominated by the higher 3.5 μg/mm^2 — Urea design (Table S4). There was no visual asymmetry of the funnel plot to suggest publication bias (Egger's test = 0.09; $p = .80$; Figs S4 and S5). Level of certainty in evidence was downrated from high to moderate because of sparse events in some studies implying imprecision. Complete numerical results are provided in detail in the Supplementary material (Table S6).

DISCUSSION

Concerns have been raised about the long term risk of all cause death using paclitaxel coated devices in the peripheral arteries. Study level meta-analyses have demonstrated a statistically significant higher long term risk of

Please cite this article as: Katsanos K et al., Risk of Major Amputation Following Application of Paclitaxel Coated Balloons in the Lower Limb Arteries: A Systematic Review and Meta-Analysis of Randomised Controlled Trials, European Journal of Vascular and Endovascular Surgery, https://doi.org/10.1016/j.ejvs.2021.05.027

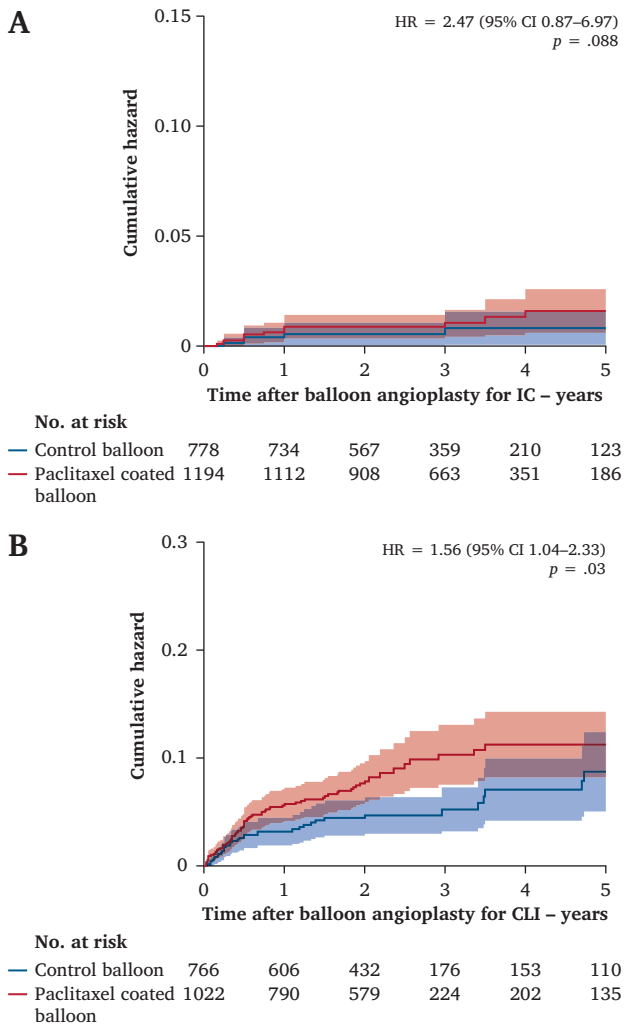

Figure 5. Cumulative hazard functions of major amputations in the two treatment arms of paclitaxel coated balloon and of control balloon for (A) intermittent claudication (IC) and (B) critical limb ischaemia (CLI) in patients with peripheral arterial disease. Selection of studies was based on dichotomy of trial level CLI rates (median proportion 42%). A one stage proportional hazards Cox model stratified at trial level (random effect) was applied.

death associated with the application of paclitaxel coated devices in the femoropopliteal artery.[2,47] The United States Federal Drug Agency (FDA) conducted internal meta-analyses of industry sponsored RCTs and corroborated the presence of an inexplicable late mortality signal.[48] Ultimately, an individual patient data meta-analysis of eight FDA approved paclitaxel coated devices (paclitaxel balloons and stents) observed a significant 4.6% absolute increased long term mortality risk associated with paclitaxel coated device use compared with balloon angioplasty.[3] In parallel, results of a multitude of observational real world studies, mostly in the form of retrospective analyses of administrative patient records and reimbursement claims in the United States and in Germany, have produced conflicting results claiming adequate safety and

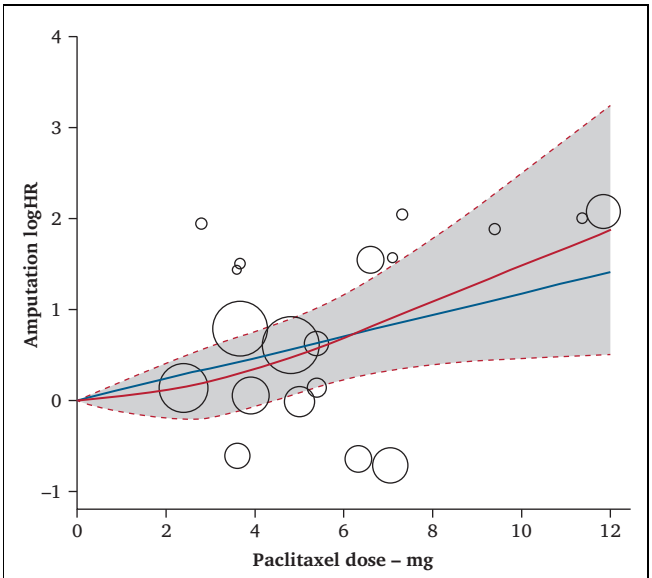

Figure 6. Dose response relationship between the amputation log hazard (logHR) point estimate and the cumulative paclitaxel coated balloon dose in milligrams delivered at index procedure of balloon angioplasty for peripheral arterial disease. The blue line denotes the log linear model and red line (with shaded 95% confidence bands) shows the non-linear spline model (three knots at the 10th, 50th, and 90th percentiles; Chi square model p = .007). A one stage random effects model with restricted maximum likelihood was applied.

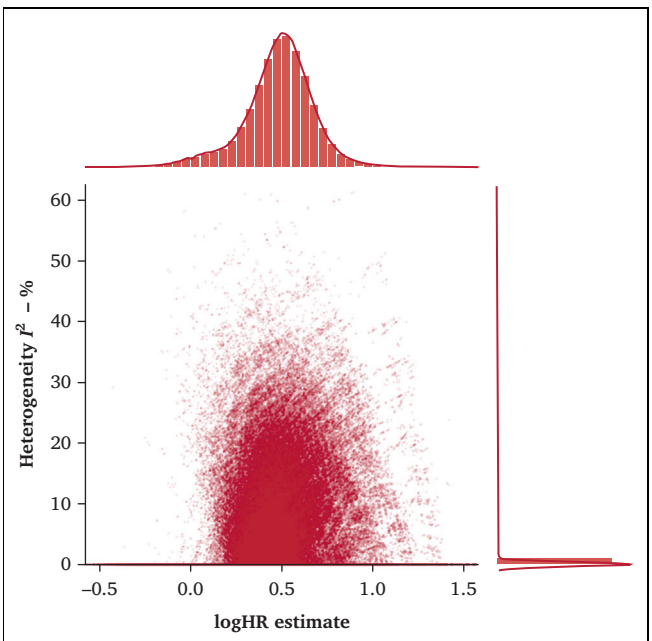

Figure 7. Combinatorial meta-analysis of study statistical heterogeneity. A random sample of 10^6 model fits was calculated of a total of 2^{20} study combinations. Scatterplot of heterogeneity I^2 against the log hazard (logHR) point estimate shows a homogeneous distribution of the summary effect without any influential subset of studies. Histograms with smoothed kernel densities of both effect size and I^2 estimates have been drawn and are juxtaposed on the respective axes.

Please cite this article as: Katsanos K et al., Risk of Major Amputation Following Application of Paclitaxel Coated Balloons in the Lower Limb Arteries: A Systematic Review and Meta-Analysis of Randomised Controlled Trials, European Journal of Vascular and Endovascular Surgery, https://doi.org/10.1016/j.ejvs.2021.05.027

occasionally some survival benefit associated with paclitaxel use in peripheral vascular disease.[4,5,49,50] A recent interim report from the SWEDEPAD registry RCT did not show an overall mortality difference, but 2.0 μg/mm^2 paclitaxel coated balloons were used in 41% of the cases. Long term HR was 1.18 (95% CI 0.72 — 1.93) for intermittent claudication, which is similar to the non-significant point estimate reported by Katsanos *et al.* for the low dose devices (RR 1.27, 95% CI 0.70 — 2.32).[2]

To the present authors' knowledge, this analysis is the first to document a statistically significant higher long term risk of major amputation associated with the application of paclitaxel coated balloons in the peripheral arteries. The summary effect demonstrated a 66% higher relative risk of major amputation in the paclitaxel coated treated limbs. In particular, the finding affected mostly the CLI population with a NNH of 35. In addition, there was good evidence of a significant non-linear dose response relationship with accelerated risk per cumulative paclitaxel dose. The results showed a consistent and homogeneous signal of potential harm for both femoropopliteal and infrapopliteal vessels. These findings are particularly worrisome considering that there is already widespread use of several paclitaxel coated balloon catheters, especially in higher risk peripheral vascular patients per the latest FDA guidance letter.[51] A previous meta-analysis also raised concerns about poorer amputation free survival (composite endpoint of death and major amputation) using paclitaxel coated balloons in the infrapopliteal arteries.[7] Interestingly, real world outcomes in the German population (Barmer Health Insurance claims) reported numerically higher five year rates of limb loss in the femoropopliteal segment for intermittent claudication (1.0 *vs.* 0.8%) and in the infrapopliteal segment for CLI treatment (7.6 *vs.* 6.5%) for paclitaxel devices (propensity matched comparisons) contrary to the claimed survival benefit.[49,50]

Certainly, all paclitaxel coated balloon catheters suffer from distal embolisation of significant amounts of paclitaxel particulate material when inflated in the circulatory system.[52] It has been long shown that less than 10% of the paclitaxel load is being transferred to the treated vessel wall in case of drug coated balloon catheters and as much as 90% escapes into the distal circulation.[53,54] Hence, downstream showers of cytotoxic solid state paclitaxel material combined with its long lasting tissue residence remains the most likely hypothesis for the herein noted increased risk of amputation. Tissue absorption of solid state paclitaxel is far lower than the rate of tissue metabolic clearance, resulting in local presence of the drug for several months. Consequently, long term tissue bioavailability of paclitaxel depends more on its low solubility (i.e., anhydrous and dihydrate less soluble than amorphous) and the total amount of paclitaxel delivered during the index procedure.[55] Furthermore, time scale numerical analyses support the notion that paclitaxel tissue retention is governed by an intricate interplay of paclitaxel crystallinity, coating/excipient dissolution kinetics, saturation levels of local tissue binding sites, and diffusion barriers potentially imposed by atherosclerosis.[56] For example, calcified plaque material may impede diffusion of paclitaxel up to 100 fold compared with preclinical observations in healthy animal experiments.[55]

Overall, paclitaxel pharmacokinetics appear to be multiphasic and non-linear leading to long lasting tissue residence with unknown long term biological effects. In the literature, there are scarce reports of vascular fibrinoid necrosis, aneurysmal degeneration, small vessel inflammation, and focal downstream skeletal muscle necrosis as the most likely result of local paclitaxel toxicity.[57,58] Hence, the present authors believe that systemic release and downstream embolisation of cytotoxic paclitaxel particles in combination with the underlying ischaemia and inflammation in the case of CLI is the most likely explanation for the noted risk of amputation. Of note, the present findings relate only to paclitaxel coated balloon catheters. On the contrary, in the PADI trial, use of coronary polymer coated paclitaxel eluting stents in the infrapopliteal arteries have been shown to be effective in reducing major amputations at five years and safe at 10 years of follow up.[59] Considerations of major differences in the total paclitaxel dose (more than an order of magnitude less in case of coronary paclitaxel eluting stents compared with DCBs) and release kinetics (polymer controlled sustained release *vs.* acute balloon burst) lend weight to the primary hypothesis of downstream paclitaxel particulate showers as the main reason of the observed higher risk of major amputations using paclitaxel coated balloons in the peripheral arteries.

Intersociety guidelines published in 2017 on the management of peripheral vascular disease have recommended paclitaxel coated balloons and stents for short femoropopliteal lesions (< 25 cm; recommendation class IIb);[60] however, the updated 2019 Global Vascular Guidelines (GVG) noted the identified mortality risk for intermittent claudication and the ongoing investigations of regulatory bodies and independent research teams to further clarify those concerns (Addendum).[61] Considering the present findings, the authors agree with the recommendation of the GVG steering committee that appropriately powered and controlled clinical studies need to continue investigating the risks and benefits of different paclitaxel coated devices for critical limb ischaemia treatments. However, caution and consideration of the potential mortality and herein presented amputation risks must be exercised outside the setting of clinical trials.[2,7]

The present work has several limitations. First, some RCTs did not report any major amputations in either arm (mostly claudicants with one year follow up), whereas some of the 21 analysed RCTs reported sparse events, and this may have given rise to imprecision. Therefore, certainty of evidence was downrated from high to moderate regardless of the positive dose response association. Patient level time to event data were extracted and analysed with a one stage model to increase power and precision and there was also consistent size and direction of the summary effect in the various subgroup and sensitivity tests (leave one out, multicentre, and different fitted models), but still, the reported amputation risk may be driven by sampling errors or even pure chance considering the overall low event rates. In addition, the low dose balloons appeared to be safe, but this

Please cite this article as: Katsanos K et al., Risk of Major Amputation Following Application of Paclitaxel Coated Balloons in the Lower Limb Arteries: A Systematic Review and Meta-Analysis of Randomised Controlled Trials, European Journal of Vascular and Endovascular Surgery, https://doi.org/10.1016/j.ejvs.2021.05.027

may be because of the small number of events and lack of adequate statistical power to detect a true effect. Second, good evidence was found of a biological gradient and the risk of amputation was potentiated in the 3.5 μg/mm^2 subset of studies using the IN.PACT technology with urea excipient that remains widely used in the femoropopliteal segment. Certainly, considering differences in paclitaxel crystallinity and excipient formulation across different balloon platforms, the presented dose response meta-analysis is probably rudimentary and could not account for variations of tissue bioavailability across different devices. Future trials should include larger sample sizes and be adequately powered to detect potential differences of major amputations between uncoated and coated balloons, or even between different paclitaxel coated balloon designs (dosages and/or excipients). Third, other sources of clinical heterogeneity and potential variable interactions could not be explored in the absence of individual patient covariates. It is likely that different dose and excipient combinations may produce different clinical results. Fourth, amputation rates constituted a secondary safety endpoint in all studies and the actual clinical indications to perform a major amputation were not reported in the studies to help distinguish between infectious, ischaemic, or neuropathic causes of major limb loss. Finally, included RCTs were published over a period of more than a decade, none of them was powered for limb salvage outcomes, and improvements in general medical management or in the design of newer paclitaxel coated balloon platforms over time could not be accounted for.

In conclusion, there appears to be heightened risk of major amputation after paclitaxel coated balloon application in the femoropopliteal and infrapopliteal arteries, especially in the setting of critical limb ischaemia. Downstream embolisation of cytotoxic paclitaxel particulate material would be the most likely explanation. Considering the widespread use of those devices in high risk vascular patients, this observation needs to be urgently refuted within the context of properly designed randomised studies.

CONFLICT OF INTEREST

All authors have completed the ICMJE uniform disclosure. KK reports research grants from Abbott, Rontis, and Medalliance, and personal fees from Concept Medical outside the submitted work. PK reports personal fees from BD outside the submitted work. CG reports grants from Boston Scientific and Penumbra Inc. outside the submitted work. UT reports grants from iVascular and Concept Medical outside the submitted work. DK reports grants from BD and RONTIS outside the submitted work. MK, SS, SB, PB, and TB have nothing to disclose.

FUNDING

None.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2021.05.027.

REFERENCES

1 Katsanos K, Spiliopoulos S, Paraskevopoulos I, Diamantopoulos A, Karnabatidis D. Systematic review and meta-analysis of randomized controlled trials of paclitaxel-coated balloon angioplasty in the femoropopliteal arteries: role of paclitaxel dose and bioavailability. *J Endovasc Ther* 2016;**23**:356–70.
2 Katsanos K, Spiliopoulos S, Kitrou P, Krokidis M, Karnabatidis D. Risk of death following application of paclitaxel-coated balloons and stents in the femoropopliteal artery of the leg: a systematic review and meta-analysis of randomized controlled trials. *J Am Heart Assoc* 2018;**7**:e011245.
3 Rocha-Singh KJ, Duval S, Jaff MR, Schneider PA, Ansel GM, Lyden SP, et al. Mortality and paclitaxel-coated devices: an individual patient data meta-analysis. *Circulation* 2020;**141**:1859–69.
4 Freisinger E, Koeppe J, Gerss J, Goerlich D, Malyar NM, Marschall U, et al. Mortality after use of paclitaxel-based devices in peripheral arteries: a real-world safety analysis. *Eur Heart J* 2020;**41**:3732–9.
5 Secemsky EA, Kundi H, Weinberg I, Jaff MR, Krawisz A, Parikh SA, et al. Association of survival with femoropopliteal artery revascularization with drug-coated devices. *JAMA Cardiol* 2019;**4**:332–40.
6 Nordanstig J, James S, Andersson M, Andersson M, Danielsson P, Gillgren P, et al. Mortality with paclitaxel-coated devices in peripheral artery disease. *N Engl J Med* 2020;**383**:2538–46.
7 Katsanos K, Spiliopoulos S, Kitrou P, Krokidis M, Paraskevopoulos I, Karnabatidis D. Risk of death and amputation with use of paclitaxel-coated balloons in the infrapopliteal arteries for treatment of critical limb ischaemia: a systematic review and meta-analysis of randomized controlled trials. *J Vasc Interv Radiol* 2020;**31**:202–12.
8 Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009;**62**:1006–12.
9 Schardt C, Adams MB, Owens T, Keitz S, Fontelo P. Utilization of the PICO framework to improve searching PubMed for clinical questions. *BMC Med Inform Decis Mak* 2007;**7**:16.
10 Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;**343**:d5928.
11 Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;**366**:l4898.
12 Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;**336**:924–6.
13 Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**:629–34.
14 Olkin I, Dahabreh IJ, Trikalinos TA. GOSH - a graphical display of study heterogeneity. *Res Synth Methods* 2012;**3**:214–23.
15 Jackson D, White IR, Seaman S, Evans H, Baisley K, Carpenter J. Relaxing the independent censoring assumption in the Cox proportional hazards model using multiple imputation. *Stat Med* 2014;**33**:4681–94.
16 Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009;**338**:b2393.
17 Crippa A, Discacciati A, Bottai M, Spiegelman D, Orsini N. One-stage dose-response meta-analysis for aggregated data. *Stat Methods Med Res* 2019;**28**:1579–96.
18 Debray TP, Moons KG, van Valkenhoef G, Efthimiou O, Hummel N, Groenwold RH, et al. Get real in individual participant data (IPD) meta-analysis: a review of the methodology. *Res Synth Methods* 2015;**6**:293–309.

Please cite this article as: Katsanos K et al., Risk of Major Amputation Following Application of Paclitaxel Coated Balloons in the Lower Limb Arteries: A Systematic Review and Meta-Analysis of Randomised Controlled Trials, European Journal of Vascular and Endovascular Surgery, https://doi.org/10.1016/j.ejvs.2021.05.027

19 Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007;**8**:16.
20 Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Med Res Methodol* 2012;**12**:9.
21 Burke DL, Ensor J, Riley RD. Meta-analysis using individual participant data: one-stage and two-stage approaches, and why they may differ. *Stat Med* 2017;**36**:855−75.
22 de Jong VMT, Moons KGM, Riley RD, Tudur Smith C, Marson AG, Eijkemans MJC, et al. Individual participant data meta-analysis of intervention studies with time-to-event outcomes: A review of the methodology and an applied example. *Res Synth Methods* 2020;**11**:148−68.
23 Zhang C, Jia P, Yu L, Xu C. Introduction to methodology of dose-response meta-analysis for binary outcome: With application on software. *J Evid Based Med* 2018;**11**:125−9.
24 Krishnan P, Faries P, Niazi K, Jain A, Sachar R, Bachinsky WB, et al. Stellarex drug-coated balloon for treatment of femoropopliteal disease: twelve-month outcomes from the randomized ILLUMENATE pivotal and pharmacokinetic studies. *Circulation* 2017;**136**:1102−13.
25 Rosenfield K, Jaff MR, White CJ, Rocha-Singh K, Mena-Hurtado C, Metzger DC, et al. Trial of a paclitaxel-coated balloon for femoropopliteal artery disease. *N Engl J Med* 2015;**373**:145−53.
26 Scheinert D, Duda S, Zeller T, Krankenberg H, Ricke J, Bosiers M, et al. The LEVANT I (Lutonix paclitaxel-coated balloon for the prevention of femoropopliteal restenosis) trial for femoropopliteal revascularization: first-in-human randomized trial of low-dose drug-coated balloon versus uncoated balloon angioplasty. *JACC Cardiovasc Interv* 2014;**7**:10−9.
27 Mustapha JA, Brodmann M, Geraghty PJ, Saab F, Settlage RA, Jaff MR, et al. Drug-coated vs uncoated percutaneous transluminal angioplasty in infrapopliteal arteries: six-month results of the Lutonix BTK trial. *J Invasive Cardiol* 2019;**31**:205−11.
28 Jia X, Zhang J, Zhuang B, Fu W, Wu D, Wang F, et al. Acotec drug-coated balloon catheter: randomized, multicenter, controlled clinical study in femoropopliteal arteries: evidence from the AcoArt I trial. *JACC Cardiovasc Interv* 2016;**9**:1941−9.
29 Tepe G, Schnorr B, Albrecht T, Brechtel K, Claussen CD, Scheller B, et al. Angioplasty of femoral-popliteal arteries with drug-coated balloons: 5-year follow up of the THUNDER trial. *JACC Cardiovasc Interv* 2015;**8**:102−8.
30 Tepe G, Schroeder H, Albrecht T, Reimer P, Diehm N, Baeriswyl JL, et al. Paclitaxel-coated balloon vs uncoated balloon angioplasty for treatment of in-stent restenosis in the superficial femoral and popliteal arteries: the COPA CABANA trial. *J Endovasc Ther* 2020;**27**:276−86.
31 Tepe G, Zeller T, Albrecht T, Heller S, Schwarzwalder U, Beregi JP, et al. Local delivery of paclitaxel to inhibit restenosis during angioplasty of the leg. *N Engl J Med* 2008;**358**:689−99.
32 Werk M, Langner S, Reinkensmeier B, Boettcher HF, Tepe G, Dietz U, et al. Inhibition of restenosis in femoropopliteal arteries: paclitaxel-coated versus uncoated balloon: femoral paclitaxel randomized pilot trial. *Circulation* 2008;**118**:1358−65.
33 Haddad SE, Shishani JM, Qtaish I, Rawashdeh MA, Qtaishat BS. One year primary patency of infrapopliteal angioplasty using drug- eluting balloons: single center experience at King Hussein Medical Center. *J Clin Imaging Sci* 2017;**7**:31.
34 Jia X, Zhuang B, Wang F, Gu Y, Zhang J, Lu X, et al. Drug-coated balloon angioplasty compared with uncoated balloons in the treatment of infrapopliteal artery lesions (AcoArt II-BTK). *J Endovasc Ther* 2021;**28**:215−21.
35 Tan B, Patel A, Irani F, et al. Prospective randomised controlled trial comparing DCB angioplasty vs. conventional balloon angioplasty for below-the-knee arteries in patients with critical limb ischaemia (NCT02129634). In: *Presented at: Cardiovascular Interventional Radiological Society Europe (CIRSE) Annual Meeting; September 2019*. Lisbon: Portugal; 2019.
36 Ye W, Zhang X, Dai X, Huang X, Liu Z, Jiang M, et al. Reewarm PTX drug-coated balloon in the treatment of femoropopliteal artery disease: A multi-center, randomized controlled trial in China. *Int J Cardiol* 2021;**326**:164−9.
37 Zeller T, Beschorner U, Pilger E, Bosiers M, Deloose K, Peeters P, et al. Paclitaxel-coated balloon in infrapopliteal arteries: 12-month results from the BIOLUX P-II randomized trial (BIOTRONIK'S-first in man study of the Passeo-18 LUX drug releasing PTA balloon catheter vs. the uncoated Passeo-18 PTA balloon catheter in subjects requiring revascularization of infrapopliteal arteries). *JACC Cardiovasc Interv* 2015;**8**:1614−22.
38 de Boer SW, de Vries J, Werson DA, Fioole B, Vroegindeweij D, Vos JA, et al. Drug coated balloon supported SUPERA stent versus SUPERA stent in intermediate and long-segment lesions of the superficial femoral artery: 2-year results of the RAPID Trial. *J Cardiovasc Surg (Torino)* 2019;**60**:679−85.
39 de Boer SW, van den Heuvel DAF, de Vries-Werson DAB, Vos JA, Fioole B, Vroegindeweij D, et al. Short-term results of the RAPID randomized trial of the legflow paclitaxel-eluting balloon with SUPERA stenting vs SUPERA stenting alone for the treatment of intermediate and long superficial femoral artery lesions. *J Endovasc Ther* 2017;**24**:783−92.
40 Bjorkman P, Kokkonen T, Alback A, Venermo M. Drug-coated versus plain balloon angioplasty in bypass vein grafts (the DRECOREST I-Study). *Ann Vasc Surg* 2019;**55**:36−44.
41 Debing E, Aerden D, Vanhulle A, Gallala S, von Kemp K. TRIAL Investigators. Paclitaxel-coated versus plain old balloon angioplasty for the treatment of infrainguinal arterial disease in diabetic patients: the Belgian diabetic IN.PACT Trial. *J Cardiovasc Surg (Torino)* 2017;**58**:528−34.
42 Schneider PA, Laird JR, Tepe G, Brodmann M, Zeller T, Scheinert D, et al. Treatment effect of drug-coated balloons is durable to 3 years in the femoropopliteal arteries: long term results of the IN.PACT SFA randomized trial. *Circ Cardiovasc Interv* 2018;**11**:e005891.
43 Fanelli F, Cannavale A, Corona M, Lucatelli P, Wlderk A, Salvatori FM. The "DEBELLUM"–lower limb multilevel treatment with drug eluting balloon–randomized trial: 1-year results (Torino) *J Cardiovasc Surg* 2014;**55**:207−16.
44 Gandini R, Del Giudice C. Local ultrasound to enhance paclitaxel delivery after femoral-popliteal treatment in critical limb ischaemia: the PACUS trial. *JACC Cardiovasc Interv* 2016;**9**:2147−53.
45 Liistro F, Porto I, Angioli P, Grotti S, Ricci L, Ducci K, et al. Drug-eluting balloon in peripheral intervention for below the knee angioplasty evaluation (DEBATE-BTK): a randomized trial in diabetic patients with critical limb ischaemia. *Circulation* 2013;**128**:615−21.
46 Zeller T, Micari A, Scheinert D, Baumgartner I, Bosiers M, Vermassen FEG, et al. The IN.PACT DEEP clinical drug-coated balloon trial: 5-year outcomes. *JACC Cardiovasc Interv* 2020;**13**:431−43.
47 Klumb C, Lehmann T, Aschenbach R, Eckardt N, Teichgraber U. Benefit and risk from paclitaxel-coated balloon angioplasty for the treatment of femoropopliteal artery disease: A systematic review and meta-analysis of randomised controlled trials. *EClinicalMedicine* 2019;**16**:42−50.
48 Altman DG, Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. *BMJ* 1999;**319**:1492−5.
49 Heidemann F, Peters F, Kuchenbecker J, Kreutzburg T, Sedrakyan A, Marschall U, et al. Long term outcomes after revascularisations below the knee with paclitaxel coated devices: a propensity score matched cohort analysis. *Eur J Vasc Endovasc Surg* 2020;**60**:549−58.
50 Behrendt CA, Sedrakyan A, Peters F, Kreutzburg T, Schermerhorn M, Bertges DJ, et al. Editor's Choice - Long term survival after femoropopliteal artery revascularisation with

Please cite this article as: Katsanos K et al., Risk of Major Amputation Following Application of Paclitaxel Coated Balloons in the Lower Limb Arteries: A Systematic Review and Meta-Analysis of Randomised Controlled Trials, European Journal of Vascular and Endovascular Surgery, https://doi.org/10.1016/j.ejvs.2021.05.027

paclitaxel coated devices: a propensity score matched cohort analysis. *Eur J Vasc Endovasc Surg* 2020;**59**:587–96.

51 U.S. Food and Drug Administration. UPDATE: Treatment of peripheral arterial disease with paclitaxel-coated balloons and paclitaxel-eluting stents potentially associated with increased mortality - letter to health care providers. Available at: https://www.fda.gov/medical-devices/letters-health-care-providers/update-treatment-peripheral-arterial-disease-paclitaxel-coated-balloons-and-paclitaxel-eluting. [Accessed 22 December 2020].

52 Gongora CA, Shibuya M, Wessler JD, McGregor J, Tellez A, Cheng Y, et al. 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.

53 Speck U, Cremers B, Kelsch B, Biedermann M, Clever YP, Schaffner S, et al. Do pharmacokinetics explain persistent restenosis inhibition by a single dose of paclitaxel? *Circ Cardiovasc Interv* 2012;**5**:392–400.

54 Stolzenburg N, Breinl J, Bienek S, Jaguszewski M, Lochel M, Taupitz M, et al. Paclitaxel-coated balloons: investigation of drug transfer in healthy and atherosclerotic arteries - first experimental results in rabbits at low inflation pressure. *Cardiovasc Drugs Ther* 2016;**30**:263–70.

55 Tzafriri AR, Vukmirovic N, Kolachalama VB, Astafieva I, Edelman ER. Lesion complexity determines arterial drug distribution after local drug delivery. *J Control Release* 2010;**142**:332–8.

56 Tzafriri AR, Parikh SA, Edelman ER. Taking paclitaxel coated balloons to a higher level: Predicting coating dissolution kinetics, tissue retention and dosing dynamics. *J Control Release* 2019;**310**:94–102.

57 Torii S, Jinnouchi H, Sakamoto A, Romero ME, Kolodgie FD, Virmani R, et al. Comparison of biologic effect and particulate embolization after femoral artery treatment with three drug-coated balloons in healthy swine model. *J Vasc Interv Radiol* 2019;**30**:103–9.

58 Kolodgie FD, Pacheco E, Yahagi K, Mori H, Ladich E, Virmani R. Comparison of particulate embolization after femoral artery treatment with IN.PACT Admiral versus Lutonix 035 paclitaxel-coated balloons in healthy swine. *J Vasc Interv Radiol* 2016;**27**:1676–85.

59 Konijn LCD, Wakkie T, Spreen MI, de Jong PA, van Dijk LC, Wever JJ, et al. 10-Year paclitaxel dose-related outcomes of drug-eluting stents treated below the knee in patients with chronic limb-threatening ischaemia (the PADI trial). *Cardiovasc Intervent Radiol* 2020;**43**:1881–8.

60 Aboyans V, Ricco JB, Bartelink MEL, Bjorck M, Brodmann M, Cohnert T, et al. Editor's Choice - 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS). *Eur J Vasc Endovasc Surg* 2018;**55**:305–68.

61 Conte MS, Bradbury AW, Kolh P, White JV, Dick F, Fitridge R, et al. Global Vascular Guidelines on the Management of Chronic Limb-Threatening Ischaemia. *Eur J Vasc Endovasc Surg* 2019;**58**:S1–109.

62 Laird JR, Schneider PA, Tepe G, Brodmann M, Zeller T, Metzger C, et al. 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**:2329–38.

63 Tepe G, Laird J, Schneider P, Brodmann M, Krishnan P, Micari A, et al. Drug-coated balloon versus standard percutaneous transluminal angioplasty for the treatment of superficial femoral and popliteal peripheral artery disease: 12-month results from the IN.PACT SFA randomized trial. *Circulation* 2015;**131**:495–502.

64 Laird JA, Schneider PA, Jaff MR, Brodmann M, Zeller T, Metzger DC, et al. Long term clinical effectiveness of a drug-coated balloon for the treatment of femoropopliteal lesions. *Circ* Cardiovasc Interv 2019;**12**:e007702.

65 Ouriel K, Adelman MA, Rosenfield K, Scheinert D, Brodmann M, Pena C, et al. Safety of paclitaxel-coated balloon angioplasty for femoropopliteal peripheral artery disease. *JACC Cardiovasc Interv* 2019;**12**:2515–24.

66 Xu Y, Jia X, Zhang J, Zhuang B, Fu W, Wu D, et al. Drug-coated balloon angioplasty compared with uncoated balloons in the treatment of 200 Chinese patients with severe femoropopliteal lesions: 24-month results of AcoArt I. *JACC Cardiovasc Interv* 2018;**11**:2347–53.

67 Fanelli F, Cannavale A, Boatta E, Corona M, Lucatelli P, Wlderk A, et al. Lower limb multilevel treatment with drug-eluting balloons: 6-month results from the DEBELLUM randomized trial. *J Endovasc Ther* 2012;**19**:571–80.

68 Zeller T, Baumgartner I, Scheinert D, Brodmann M, Bosiers M, Micari A, et al. Drug-eluting balloon versus standard balloon angioplasty for infrapopliteal arterial revascularization in critical limb ischaemia: 12-month results from the IN.PACT DEEP randomized trial. *J Am Coll Cardiol* 2014;**64**:1568–76.

69 Brodmann M. Lutonix BTK IDE study: 12-month results and interim safety analyses at 3 years. In: *Presented at: Cardiovascular Interventional Radiological Society Europe (CIRSE) Summit September*; 2020. Available at, https://library.cirse.org/cirse2020/library/congressresources.

Please cite this article as: Katsanos K et al., Risk of Major Amputation Following Application of Paclitaxel Coated Balloons in the Lower Limb Arteries: A Systematic Review and Meta-Analysis of Randomised Controlled Trials, European Journal of Vascular and Endovascular Surgery, https://doi.org/10.1016/j.ejvs.2021.05.027