Robustness of Longitudinal Safety and Efficacy After Paclitaxel-Based Endovascular Therapy for Treatment of Femoro-Popliteal Artery Occlusive Disease: An Updated Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Background: The aims of this study were: i) to assess fragility indices (FIs) of individual randomized controlled trials (RCTs) that compared paclitaxel-based drug-coated balloons (DCBs) or drug-eluting stents (DESs) versus standard endovascular devices, and ii) to meta-analyze mid-term and long-term safety and efficacy outcomes from available RCT data while also estimating the FI of pooled results.

Methods: This systematic review has been registered in the PROSPERO public database (CRD42022304326 http://www.crd.york.ac.uk/PROSPERO). A query of PubMed (Medline), EMBASE (Excerpta Medical Database), Scopus, and CENTRAL (Cochrane Central Register of Controlled Trials) databases was performed to identify eligible RCTs. Rates of primary patency (PP) and target lesion revascularization (TLR) were assessed as efficacy outcomes, while lower limb amputation (LLA) consisting of major amputation that is. below or above the knee and all-cause mortality were estimated as safety outcomes. All outcomes were pooled with a random effects model to account for any clinical and study design heterogeneity. The analyses were performed by dividing the RCTs according to their maximal follow-up length

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(mid-term was defined as results up to 2−3 years, while long-term was defined as results up to 4−5 years). For each individual outcome, the FI and reverse fragility index (RFI) were calculated according to whether the outcome results were statistically significant or not, respectively. The fragility quotient (FQ) and reverse fragility quotient (RFQ), which are the FI or RFI divided by the sample size, were also calculated.

Results: A total of 2,337 patients were included in the systematic review and meta-analysis. There were 2 RCTs examining DES devices and 14 RCTs evaluating different DCBs. For efficacy outcomes, there was evidence that paclitaxel-based endovascular therapy increased the PP rate and reduced the TLR rate at mid-term, with a calculated pooled risk ratio (RR) of 1.66 for patency (95% CI, 1.55−1.86; $P < 0.001$), with a corresponding number needed-to-treat (NNT) of 3 patients (95% CI, 2.9−3.8) and RR of 0.44 for TLR (95% CI, 0.35−0.54; $P = 0.027$), respectively. Similarly, there was evidence that paclitaxel-based endovascular therapy both increased PP and decreased TLR rates at long-term, with calculated pooled RR values of 1.73 (95% CI, 1.12−2.61; $P = 0.004$) and 0.53 (95% CI, 0.45−0.62; $P = 0.82$), respectively. For safety outcomes, there was evidence that paclitaxel-based endovascular therapy increased all-cause mortality at mid-term, with a calculated pooled RR of 2.05 (95% CI, 1.21−3.24). However, there was no difference between treatment arms in LLA at mid-term (95% CI, 0.1−2.7; $P = 0.68$). Similarly, neither all-cause mortality nor LLA at long-term differed between treatment arms, with a calculated pooled RR of 0.66, 1.02 (95% CI, 0.31−3.42) and 1.02 (95% CI, 0.30−5.21; $P = 0.22$), respectively. The pooled estimates of PP at mid-term were robust (FI = 28 and FQ = 1.9%) as were pooled rates of TLR (FI = 18 and FQ = 0.9%). However, when safety outcomes were analyzed, the robustness of the meta-analysis decreased significantly. In fact, the relationship between the use of paclitaxel-coated devices and all-cause mortality at mid-term showed very low robustness (FI = 4 and FQ = 0.2%). At 5 years, only the benefit of paclitaxel-based devices to reduce TLR remained robust, with an FI of 32 and an FQ of 3.1%.

Conclusions: The data supporting clinical efficacy endpoints of RCTs that examined paclitaxel-based devices in the treatment of femoral-popliteal arterial occlusive disease were robust; however, the pooled safety endpoints were highly fragile and prone to bias due to loss of patient follow-up in the original studies. These findings should be considered in the ongoing debate concerning the safety of paclitaxel-based devices.

INTRODUCTION

Several randomized controlled trials (RCTs) have demonstrated the efficacy of paclitaxel-based endovascular therapy for treatment of femoral-popliteal peripheral artery occlusive disease (PAOD).[1−5] Indeed, recent meta-analyses of RCTs with low risk of bias have amassed evidence about the effectiveness of paclitaxel-based stents and balloons in significantly reducing restenosis and thereby decreasing the risk of target lesion revascularization (TLR).[6−8] While the magnitude of the benefit for the efficacy endpoints was consistent in all trials with 24-month primary patency (PP) of 57−90% and on freedom from TLR of 64−97% after femoropopliteal drug-coated balloons (DCBs) angioplasty, the observed effects on the safety endpoints may have been under evaluated. In fact, the controversial systematic review and meta-analysis of summary-level data by Katsanos et al.[9] detected an increased mortality signal after the use of paclitaxel-based balloons and stents, thereby leading to numerous warnings and recommendations by regulators and guideline writing committees to restrict their use. Concurrently, the international vascular community, quality improvement organizations, and the medical device industry have undertaken a significant effort to determine safety risks after the use of these devices by studying patient-level data. Further, because of the intense focus by key stakeholders to determine if the mortality signal can be verified, a number of derivative studies have ensued. Importantly, a more contemporary meta-analysis[10,11] now contradicts the original findings of Katsanos et al.,[9] and vigorous debate has emerged to try and identify potential reasons that could explain the conflicting evidence.

An important and often overlooked issue on this topic is the fact that none of the paclitaxel-based femoral-popliteal interventional RCTs were appropriately designed to validly assess the mortality endpoint. However, the robustness of statistically significant and nonsignificant dichotomous outcomes can be evaluated using newer statistical tools, namely the fragility index (FI) and reverse fragility index (RFI).[12,13] Indeed, these indices can help evaluate the robustness of trial results while estimating bias, in addition to standard measures of statistical significance but to date, these techniques have not

been applied in this clinical scenario. Therefore, using this framework, the aims of this study were: i) to assess the FI of individual RCTs that compared paclitaxel-based balloons or stents versus standard endovascular devices, and ii) to meta-analyze mid-term and long-term safety and efficacy outcomes from available RCT data while also estimating the FI of pooled results.

MATERIALS AND METHODS

Literature Search

The authors declare that all supporting data are available within the tables, figures, and supplemental material of the present article. This systematic review has been registered in the PROSPERO public database (CRD42022304326 http://www.crd.york.ac.uk/PROSPERO). Electronic search of PubMed (Medline), EMBASE (Excerpta Medical Database), Scopus, and CENTRAL (Cochrane Central Register of Controlled Trials) was performed to identify eligible RCTs. Only English language and fully published articles were selected. The literature was screened for RCT-investigating paclitaxel-based DCB or paclitaxel-based drug-eluting stents (DESs) in the femoral popliteal artery. Search terms included: ''Cochrane, femoral artery, popliteal artery, femoral popliteal artery, late lumen loss, restenosis, TLR, peripheral angioplasty, stent, randomized, balloon angioplasty, paclitaxel-eluting balloons, paclitaxel-coated balloons, paclitaxel-eluting stents, paclitaxel-coated stents, paclitaxel-eluting stents, DCBs, and DESs, as well as the corresponding Medical Subjects Headings with Boolean syntax (i.e., the logic terms AND and/or OR). The literature search was last updated in January 2022.

The following population, intervention, control, and outcomes (PICO) question was used to design the current systematic review: in patients with PAOD (patients) treated with DCB or DES in the femoral popliteal artery (intervention) in RCT versus nonpaclitaxel-based endovascular devices (comparison), what is the robustness of mid-term and long-term safety and efficacy outcomes (outcomes)? To be included in the current meta-analysis, studies had to meet all the following prespecified inclusion criteria: 1) study design was an RCT; 2) investigation involved use of a DCB or a DES in the femoral popliteal artery; 3) patient population with PAOD and symptoms of intermittent claudication (IC) and/or chronic limb-threatening ischemia; 4) follow-up longer than 1 year; 5) the studies reported appropriate clinical outcome measures as defined subsequently for data synthesis.

Data Extraction and Outcome Measures

The selection process for the RCTs complied with the preferred reporting items for systematic reviews and meta-analyses. The reference lists of all selected articles were also queried for the identification of potentially missed study candidates. Two authors (M.D. and D.M.) selected the studies to be included in quantitative synthesis and independently extracted relevant raw data in duplicate. Any disagreements were resolved by consensus with a third investigator (S.L.). Our meta-analysis concentrated on a core set of safety and efficacy outcomes, as further detailed. For the evaluation of device efficacy, we extracted data on PP and TLR, whereas data on lower limb amputation (LLA), consisting of major amputations that is. below or above the knee, and all-cause mortality were sought to assess device safety. All outcomes were analyzed at mid-term (i.e., published RCT with cumulative data at 2 or up to 3 years) and long-term (i.e., published RCT with cumulative data at 4 or up to 5 years) with separate inclusion of relevant RCTs in the meta-analysis, as applicable.

Statistical Analysis

Categorical variables were expressed as counts and percentages, while continuous variables as means ± SD if normally distributed. Rates of PP, TLR, LLA, and all-cause mortality were pooled with a random effects model to account for any clinical and study design heterogeneity. The analyses were performed by dividing the RCTs according to their maximal follow-up length as outlined above. Publication bias was assessed qualitatively using funnel plots. For each individual outcome, the FI and RFI were calculated according to whether the outcome results were statistically significant or not, respectively, in the manner described by Walsh et al.[14] The total number of events in each group over the entire follow-up was considered. Lower FI/RFI indicates less statistical robustness; however, as there is no standardized cut-off defined for acceptable fragility, the FI or RFI values were visually plotted against the number of patients lost to follow-up. When loss to follow-up exceeds the FI or RFI, results should be cautiously interpreted as events of interest may occur in patients lost to follow-up, and factoring these may shift the results. fragility quotient (FQ), which is the FI divided by the sample size, was also calculated to assess what proportion of patients must change status to modify

the significance of the results. For nonsignificant outcomes, the reverse fragility quotient (RFQ) was calculated in a similar fashion by dividing the RFI by the sample size. The FI, RFI, FQ, and RFQ were calculated using the R Studio version 3.51 (R Project for Statistical Computing).

A random effects model was used for the meta-analysis. Weights were assigned using the Mantel–Haenszel method. Summary statistics were expressed as risk ratios (RRs) with the associated 95% confidence intervals (CIs). To help further inform interpretation and support clinical judgment, the number needed-to-treat (NNT) and number needed-to-harm (NNH) with corresponding 95% CIs were also calculated for efficacy and safety outcomes, respectively. The FI, RFI, FQ, and RFQ were also calculated for meta-analytical outputs. Quantitative synthesis of the included RCTs was performed in R language environment (version 3.4.1) with the ''meta'' package (version 4.9-2) and MedCalc Statistical Software version 19.2.6 (MedCalc Software bv, Ostend, Belgium; https://www.medcalc.org; 2020).

Sensitivity and subgroup analyses were performed to test the validity and stability of the results. Trial sequential analysis (TSA)[15] is a statistical method that combines required information size (RIS) estimation with an adjusted threshold for statistical significance and was performed using TSA software (version 0.9.5.10, Copenhagen Trial Unit, Copenhagen, Denmark) to determine whether the evidence is reliable and conclusive by providing the RIS for our meta-analysis and boundaries. TSA was performed to test the availability of adequate patient sample size and adjust positive findings, especially because none of the included studies were designed or powered to investigate differences in patient mortality. The information size required for a valid meta-analysis may be assumed to be at least as large as the sample size of a single well-powered RCT designed to confirm or reject the null hypothesis. Therefore, TSA was conducted for each mid-term and long-term outcome that had been meta-analysed. The RIS and adjusted significance thresholds were calculated based on the following assumptions: a two-sided adjustment with a 5% risk of type I error with a power of 90%.

Bias Assessment

Assessment of the quality and risk of bias of the selected studies was performed independently by 2 authors (M.D. and D.M.) using the Cochrane Collaboration's tool for assessing risk of bias, which evaluates 7 key design items and evaluates each of them as high, low, or unclear risk of bias. Any disagreements were resolved by consensus with a third Author (S.L.).

RESULTS

Characteristics of Included RCT

Sixteen RCTs were included in the meta-analysis.[16–31] The PRISMA flowchart of study selection process is shown in Figure 1. The main characteristics of the studies, involving a total of 2,337 patients, are presented in Table I. There were 2 RCTs with a DES and 14 RCTs testing different DCB platforms. Seven RCTs had a maximum follow-up of 2 years, while 3 RCTs reported data with a maximum follow-up of 3 years and were collectively analyzed as mid-term. Three RCTs reached a maximum follow-up of 5 years and were collectively analyzed as long-term.

Baseline patient demographics and morphologic lesion characteristics were largely homogeneously distributed across all studies. The design characteristics of the 16 selected RCTs are shown in Supplementary Table I. Briefly, paclitaxel-coated balloons and stents were used primarily for the treatment of IC (Rutherford category 1–3) ($n = 1,949$) in the majority of the study population, and less frequently for chronic limb-threatening ischemia (Rutherford category 4–5) ($n = 224$). Overall, approximately two-thirds of the patients were male and the mean age ranged from 67 to 76 years. Only 697 patients were treated for a chronic total occlusion and most of the studies involved short lesions. With few exceptions, most protocols recommended a short period of 1–3 months of dual antiplatelet therapy.

Mid-term Efficacy Outcomes

There was evidence that paclitaxel-based endovascular therapy increased the PP rate at mid-term (Fig. 2). There were 646 PP events reported among 888 cases compared with 266 PP events among 620 control subjects. The calculated pooled RR was 1.66 (95% CI, 1.55–1.86; $P < 0.001$), with a corresponding NNT of 3 patients (95% CI, 2.9–3.8). Similarly, there was evidence that paclitaxel-based endovascular therapy reduced the TLR rate at mid-term. There were 139 TLR events reported among 1,004 cases compared with 234 TLR events among 693 control subjects. The calculated pooled RR was 0.44 (95% CI, 0.35–0.54; $P = 0.027$), with a corresponding NNT of 5 patients (95% CI, 4.1–6.2).

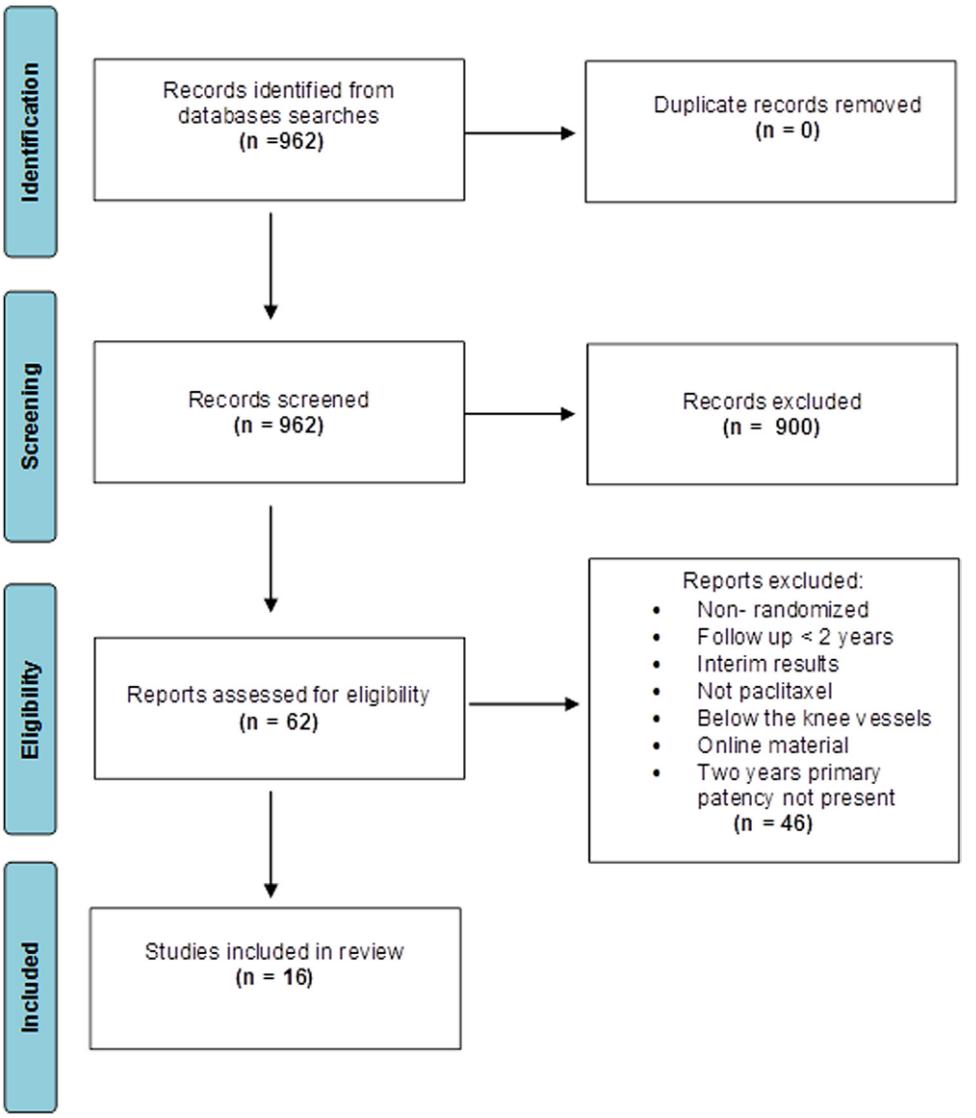


Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart.

Long-Term Efficacy Outcomes

There was evidence that paclitaxel-based endovascular therapy increased the PP rate at long-term (Fig. 3). There were 283 PP events reported among 403 cases compared with 101 PP events among 283 control subjects. The calculated pooled RR was 1.73 (95% CI, 1.12−2.61; $P = 0.004$), with a corresponding NNT of 3 patients (95% CI, 2.4X−3.6X). In addition, there was evidence that paclitaxel-based endovascular therapy decreased the TLR rate at long-term. There were 126 TLR events reported among 601 cases compared with 175 TLR events among 418 control subjects. The calculated pooled RR was 0.53 (95% CI, 0.45−0.62; $P = 0.82$), with a corresponding number NNT of 5 patients (95% CI, 3.7−6.5).

Mid-Term Safety Outcomes

There was evidence that paclitaxel-based endovascular therapy increased all-cause mortality at mid-term (Fig. 4). There were 75 events out of 1,076 cases compared with 24 events in 808 control subjects. The calculated pooled RR was 2.05 (95% CI, 1.21−3.24) with a corresponding NNH of 25 patients (95% CI, 16−50; $P < 0.001$). There was no evidence that paclitaxel-based endovascular therapy increased the risk of LLA at mid-term. There were 4 events among 1,037 cases compared with 4 events

Table I. Design characteristics of included RCT

Study and sources	Year and study design	Allocation in study arms	Maximum follow- up period	Inclusion criteria	Paclitaxel-coated device
AcoArt I	2016 Multicenter single-blind (1:1)	DCB ($n = 100$) vs. PTA ($n = 100$)	5 year	- Rutherford class 2−5 - Femoropopliteal artery lesions ≤40 cm	Orchid by Acotec Scientific
BIOPAC	2021 Multicenter single-blind (1:1)	DCB ($n = 33$) vs. PTA ($n = 33$)	3 year	- Occlusive, total single de novo or nonstent restenotic lesions - Successful guidewire crossing	Microcrystalline paclitaxel-coated balloon, PAK; Balton
BATTLE	2018 Multicenter open label (1:1)	DES ($n = 86$) vs. BMS ($n = 85$)	2 year	- Rutherford stages 2 to - de novo athero-sclerotic lesions (stenosis and/or occlusion) of the superficial femoral artery, the prox-imal popliteal artery, or both.	ZILVER-paclitaxel (PTX) Stent by Cook Medical
CONSEQUENT	2017 Multicenter single-blind (1:1)	DCB ($n = 78$) vs. PTA ($n = 75$)	2 year	- Rutherford classes 2−4 - A diameter stenosis ≥70% and 4−27 cm in length	SeQuent Please by B. Braun Late
EFFPAC	2018 Multicenter single-blind (1:1)	DCB ($n = 85$) vs. PTA ($n = 86$)	2 year	- Single short or medium-length stenosis occlusion ≤150 mm)	Luminor by iVascular
ILLUMENATE	2017 Multicenter single-blind (3:1)	DCB ($n = 222$) vs. PTA ($n = 72$)	2 year	- Claudication and rest pain - ≥70% stenosis of the superficial femoral and/or popliteal artery.	Stellarex by Spectranetics
INPACT SFA	2015 Multicenter single-blind (2:1)	DCB ($n = 220$) vs. PTA ($n = 111$)	3 year	- Rutherford 2−4 - Stenosis of 70−99% with lesion lengths between 4 and 18 cm or occlusion with lengths of ≤10 cm involving the superficial femoral and proximal popliteal arteries	IN.PACT Admiral by Medtronic
INPACT SFA J	2018 Multicenter Single-blind (2:1)	DCB ($n = 68$) vs. PTA ($n = 32$)	3 year	- Rutherford categories 2−4 - Stenotic (70%−99%) lesion between 4- and 20-cm long or an occlusion ≤10-cm long involving the superficial femoral and/ or proximal popliteal arteries	IN.PACT Admiral by Medtronic
ISAR-PEBIS	2017 Two-center open label (1:1) for ISR	DCB ($n = 36$) vs. PTA ($n = 34$)	2 year	- Symptomatic ISR >70% or occlusion of SFA at the stented site.	IN.PACT Admiral by Medtronic
ISAR-STATH	2017 Two-center open label (1:1:1)	DCB + BMS ($n = 48$) vs. PTA + BMS ($n = 52$)	2 year	- De novo stenosis >70% or occlusion of the SFA	IN.PACT Admiral by Medtronic
MDT2113	2018 Multicenter single-blind (2:1)	DCB ($n = 68$) vs. PTA ($n = 32$)	2 year	- Rutherford clinical category 2−4 - Superficial femoral and/or proximal popli-teal artery lesion stenosis severity of 70−99%.	IN.PACT Admiral by Medtronic

(*Continued*)

Table I. Continued

Study and sources	Year and study design	Allocation in study arms	Maximum follow- up period	Inclusion criteria	Paclitaxel-coated device
THUNDER	2008 Multicenter single-blind (1:1:1)	DCB ($n = 48$) vs. PTA ($n = 54$)	5 year	- Rutherford stages 1–5 - Obstructive lesions, either new lesions or restenoses, at least 70% of vessel diameter and at least 2 cm in length, in the superficial femoral artery, the popliteal artery, or both	Cotavance Balloon by Bavaria Medizin
ZILVER PTX	2011 Multicenter open label (1:1)	DES ($n = 241$) vs. PTA ($n = 238$)	5 year	- Rutherford category 2–5 - >50% diameter stenosis, reference vessel diameter 4–9 mm, lesion length up to 14 cm, and at least 1 patent runoff vessel with <50% stenosis	ZILVER-PTX Stent by Cook Medical

among 778 control subjects. The calculated pooled RR was 0.66 (95% CI, 0.15−2.73; $P = 0.68$).

Long-Term Safety Outcomes

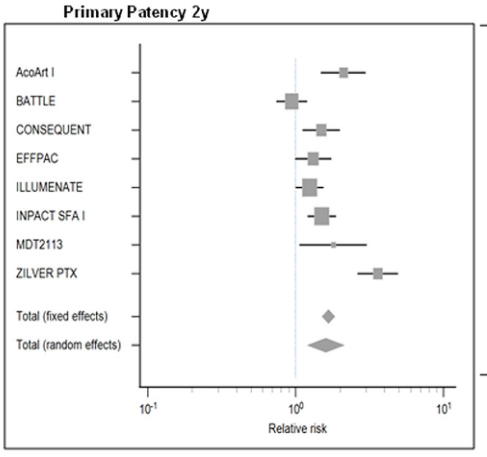
There was no evidence that paclitaxel-based endovascular therapy increased the risk of all-cause mortality at long-term (Fig. 5). There were 6 events out of 415 cases compared with 5 events in 275 control subjects. The calculated pooled risk ratio of 1.02 (95% CI, 0.31−3.42) with a corresponding NNT of 14 patients (95% CI, 9−36; $P = 0.22$). In addition, there was no evidence that paclitaxel-based endovascular therapy increased the risk of LLA at long-term. There were 6 events among 415 cases compared with 5 events among 275 control subjects. The calculated pooled RR was 1.02 (95% CI, 0.30−5.21; $P = 0.22$).

Fragility Index (FI), Reverse Fragility Index (RFI), and Fragility Quotient (FQ)

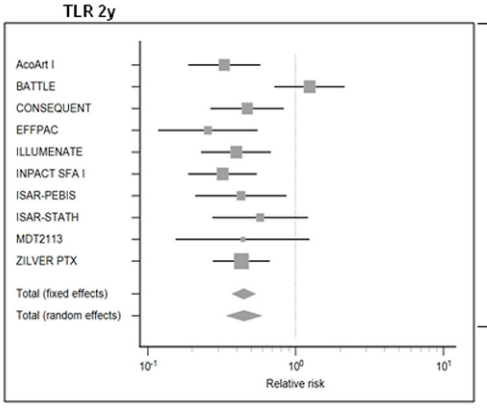
Supplementary Table II and Figure 6 summarize the findings for each trial at 2 and 5 years, displaying the FI, RFI, FQ, and the number of patients lost to follow-up. As shown in Tables II and III, the pooled estimates of PP at mid-term were robust (FI = 28 and FQ = 1.9%) as were pooled rates of TLR (FI = 18 and FQ = 0.9%). However, when safety outcomes were analyzed, the robustness of the meta-analysis decreased significantly. Specifically, the relationship between the use of paclitaxel-coated devices and all-cause mortality at mid-term was characterized by very low robustness (FI = 4 and FQ = 0.2%). At 5 years, only the benefit of paclitaxel-based devices to reduce TLR remained robust, with an FI of 32 and an FQ of 3.1%, whereas again, the relationship between paclitaxel-coated devices and all-cause mortality remained vulnerable to bias (FI and FQ).

Risk of Bias

Randomization and allocation concealment were performed adequately in all studies, and methodological quality was high for all trials with the exception of an inherently high risk of performance bias in all 16 RCTs because of the universal absence of systematic blinding of the operators during application of the devices (Supplementary Fig. 1). For each outcome, Begg's funnel plot was performed and analyzed (Supplementary Fig. 2). Given the heterogeneity of the studies for the 2-year and 5-year PP rate, the Baujat plot inspecting was performed to analyze the individual impact on heterogeneity (Supplementary Fig. 3). Using this method, we identified 2 trials that amplified the I^2 at 2 years



Intervention	Controls	Relative risk	95% CI	Weight (%)	
				Fixed	Random
53/80	27/86	2,110	1,4 to 2,9	7,80	12,02
43/68	51/76	0,942	0,7 to 1,1	16,53	13,27
47/65	31/64	1,493	1,1 to 2,0	11,01	12,68
43/59	31/56	1,317	0,9 to 1,7	11,97	12,81
145/191	36/59	1,244	0,9 to 1,5	19,85	13,47
128/170	47/94	1,506	1,2 to 1,8	19,72	13,47
38/57	10/27	1,800	1,0 to 3,0	3,46	9,83
149/198	33/158	3,603	2,6 to 4,9	9,67	12,45
646/888	266/620	1,667	1,5 to 1,8	100,00	100,00
646/888	266/620	1,600	1,2 to 2,1	100,00	100,00
Significance level			P < 0,0001		
I^2 (inconsistency)			87,84%		
95% CI for I^2			78,30 to 93,19		
Kendall's Tau			0,5000		



13/96	39/95	0,330	0,1 to 0,5	11,41	11,12
20/68	18/76	1,242	0,7 to 2,1	11,98	11,36
13/68	26/64	0,471	0,2 to 0,8	10,95	10,92
7/62	19/43	0,256	0,1 to 0,5	5,96	7,92
23/190	18/59	0,397	0,2 to 0,6	12,12	11,42
18/198	30/106	0,321	0,1 to 0,5	12,51	11,57
7/28	17/29	0,426	0,2 to 0,8	7,08	8,75
7/30	17/42	0,576	0,2 to 1,2	6,44	8,29
6/66	6/29	0,439	0,1 to 1,2	3,28	5,31
25/198	44/150	0,430	0,2 to 0,6	18,25	13,33
139/1004	234/693	0,445	0,3 to 0,5	100,00	100,00
139/1004	234/693	0,448	0,3 to 0,5	100,00	100,00
Significance level			P = 0,0273		
I^2 (inconsistency)			52,03%		
95% CI for I^2			1,54 to 76,62		
Kendall's Tau			0,1111		

Fig. 2. Random effects forest plot of efficacy outcomes through 2 years. The summary effect was expressed as risk ratio.

(the BATTLE study[18] and the ZILVER paclitaxel (PTX) trial[31]). Similarly, the THUNDER trial[26] and the ZILVER PTX study[28] amplified the I^2 at 5 years. By removing the combination of these trials, the heterogeneity was no longer significant.

Trial Sequential Analysis (TSA)

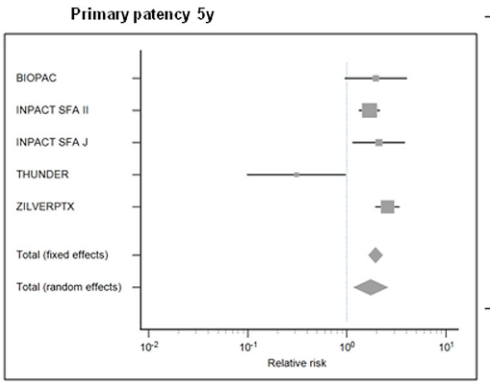
As shown in Supplementary Figure 4 and Supplementary Figure 5, the blue cumulative z-curve reached the RIS line except for the long-term all-cause mortality, but it crossed the conventional boundary and the TSA monitoring boundary for benefit, indicating that the result was robust. It was not possible to perform the TSA for the LLA outcome because there were too few events.

Sensitivity Analyses and Subgroup Analyses

Sensitivity and subgroup analyses were performed to further explore potential sources of heterogeneity. In subgroup analysis based on use of DES only or DCB only, the all-cause mortality risk estimate increased significantly in the paclitaxel group, but was nonsignificant (RR = 1.20, 95% CI: 0.61−2.42; and RR = 1.7X, 95% CI: 0.9X-3.2; respectively, but the FI (=1) and FQ (=0.1) remained very low. Further details are shown in Tables IV and V.

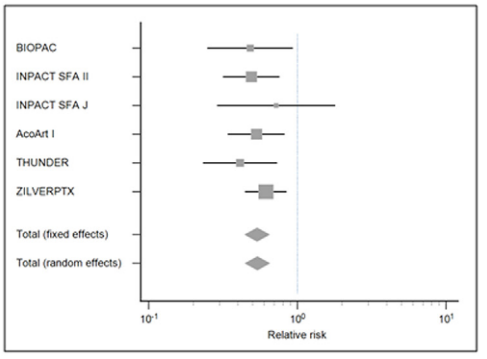
DISCUSSION

Significant concerns have been raised about the long-term risk of all-cause death with the use of paclitaxel-coated devices in the lower limbs.[32] Results from the 2018 meta-analysis by Katsasnos et al.[9] were corroborated by the US Food and Drug Administration (FDA) and later confirmed by an individual patient data meta-analysis. However, population-based and registry-based observational studies have largely produced contradictory results. For example, the recently published Swedish drug-elution trial in PAOD patients (SWEDEPAD)[33] also did not confirm a significant mortality risk as well as more updated systematic reviews of the available evidence.[34] Besides all-cause mortality, there has been increasing scrutiny surrounding the risk of



Intervention	Controls	Relative risk	95% CI	Weight (%)	
				Fixed	Random
12/21	7/24	1,959	0,9 to 4,0	5,48	15,80
121/161	41/92	1,686	1,3 to 2,1	48,19	28,87
38/61	8/27	2,102	1,1 to 3,8	7,67	18,49
3/18	7/13	0,310	0,09 to 0,9	2,18	8,92
109/142	38/127	2,565	1,9 to 3,3	36,48	27,92
283/403	101/283	1,945	1,6 to 2,3	100,00	100,00
283/403	101/283	1,738	1,1 to 2,6	100,00	100,00

Significance level	P = 0,0049
I^2 (inconsistency)	73,20%
95% CI for I^2	33,01 to 89,27
Kendall's Tau	-0,4000



8/28	16/27	0,482	0,2 to 0,9	8,56	8,56
30/197	32/103	0,490	0,3 to 0,7	19,72	19,72
10/67	6/29	0,721	0,2 to 1,7	4,52	4,52
21/91	40/92	0,531	0,3 to 0,8	19,35	19,35
10/38	30/47	0,412	0,2 to 0,7	11,46	11,46
47/180	51/120	0,614	0,4 to 0,8	36,39	36,39
126/601	175/418	0,536	0,4 to 0,6	100,00	100,00
126/601	175/418	0,538	0,4 to 0,6	100,00	100,00

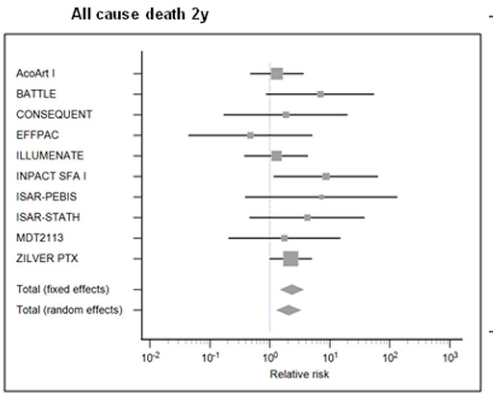
Significance level	P = 0,8267
I^2 (inconsistency)	0,00%
95% CI for I^2	0,00 to 42,93
Kendall's Tau	-0,06667

Fig. 3. Random effects forest plot of safety outcomes through 2 years. The summary effect was expressed as risk ratio.

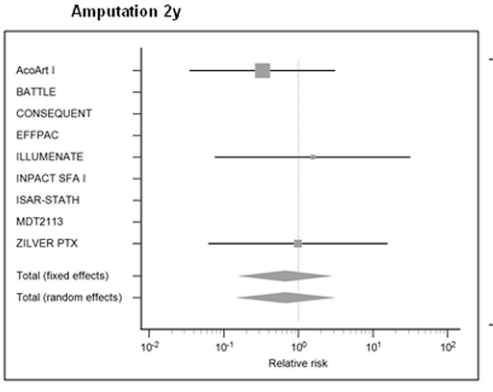
LLA with paclitaxel-coated devices, especially when used in the infrapopliteal arteries.[35] Therefore, the controversy may remain unabated, while research is ongoing and highlights the important types of epidemiological bias that pertain to the ongoing debate on paclitaxel.[36] Moreover, an individual patient data meta-analysis identified an absolute 4.6% increased mortality risk associated with PTX use.[37]

Finally, the recent US FDA statement on PTX peripheral devices states that the data does not support an excess mortality risk for paclitaxel-coated device. In this meta-analysis of 16 individual trials evaluating paclitaxel-based devices in the treatment of femoral popliteal arteries, the pooled efficacy of paclitaxel-coated devices was indeed clear and largely robust. However, safety endpoints, in particular long-term mortality, lacked the same statistical robustness. At mid-term follow-up, the FI suggested very low robustness for mortality endpoints, and statistical significance was not demonstrated at 5 years. Furthermore, no clear signal could be ascertained regarding whether the risk of LLA may be increased, largely owing to the low number of events, since most of the original trials included predominantly IC populations. These findings add an important and novel perspective to the ongoing debate in the vascular community surrounding the aforementioned possible excess mortality signal in PAOD patients exposed to paclitaxel-based stents or balloons. The opponents of such observation(s) have often raised several relevant questions concerning the necessary statistical power and original study design methodology used by Katasanos et al. to examine all-cause mortality endpoints from available RCTs, and our meta-analysis suggests that the initial statistical signal was likely influenced by the high lost to follow-up number.

Most interestingly, findings from this study largely seem to demonstrate that the available data from paclitaxel-based RCTs was in fact inadequate to answer safety concerns but proved to be in favor of efficacy endpoints such as increased patency rates and reduced need for TLR. Within this context, the differences between RCTs versus observational research and the inherent selection bias in trials



Intervention	Controls	Relative risk	95% CI	Weight (%)	
				Fixed	Random
8/96	6/95	1,319	0,4 to 3,6	21,28	21,28
7/91	1/90	6,923	0,86 to 55,1	5,14	5,14
2/70	1/65	1,857	0,1 to 19,9	3,92	3,92
1/61	2/58	0,475	0,04 to 5,1	3,93	3,93
13/199	3/59	1,285	0,3 to 4,3	14,84	14,84
16/198	1/106	8,566	1,1 to 63,7	5,50	5,50
3/28	0/29	7,241	0,3 to 134,1	2,60	2,60
3/30	1/42	4,200	0,4 to 38,4	4,51	4,51
4/66	1/29	1,758	0,2 to 15,0	4,80	4,80
18/237	8/235	2,231	0,9 to 5,0	33,48	33,48
75/1076	24/808	2,326	1,48to 3,6	100,00	100,00
75/1076	24/808	2,056	1,2 to 3,2	100,00	100,00
Significance level		P = 0,5891			
I^2 (inconsistency)		0,00%			
95% CI for I^2		0,00 to 54,85			
Kendall'sTau		0,06667			

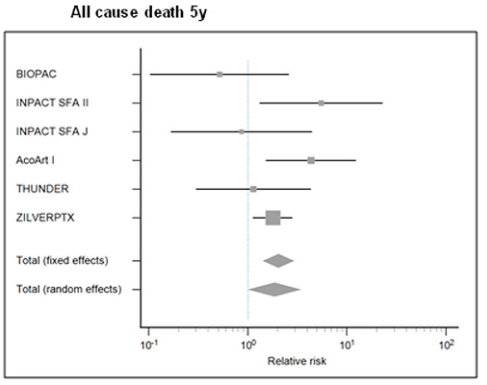


1/96	3/95	0,330	0,03 to 3,1	45,23	45,23
0/91	0/90	-			
0/70	0/65	-			
0/61	0/58	-			
2/188	0/58	1,561	0,07 to 32,0	24,96	24,96
0/198	0/106	-			
0/30	0/42	-			
0/66	0/29	-			
1/237	1/235	0,992	0,06to15,7	29,81	29,81
4/1037	4/778	0,665	0,1 to 2,7	100,00	100,00
4/1037	4/778	0,675	0,1 to 3,0	100,00	100,00
Significance level		P = 0,6836			
I^2 (inconsistency)		0,00%			
95% CI for I^2		0,00 to 91,18			
Kendall'sTau		1,0000			

Fig. 4. Random effects forest plot of efficacy outcomes through 5 years. The summary effect was expressed as risk ratio.

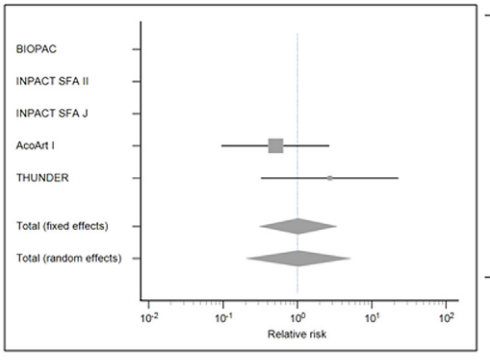
have been extensively discussed during recent years.[38] That said it is well-known that RCTs tend to enroll less women when compared with registries.[39] Most recently, the PACLIVASC study (NCT04683458) suggested that this fact along with differences in baseline characteristics and optimal pharmacological therapy may serve as an explanation for the opposite conclusions derived from both study types. The impact of numerous external factors, especially on trials with weak study design, has gained increasing interest more recently. This methodological aspect however, is not limited to RCTs but also affects observational research. With different statistical parameters and certain changes in the composition of the registry cohorts, it is hypothetically possible to influence or distort the central conclusions, what was recently discussed as the ''pendulum of evidence''.[40]

To objectively evaluate the robustness of trial results, the concept of FI was introduced in several areas.[41,42] This index describes how many (or few) patients need to be exchanged to influence certain outcome estimators. A very robust observation in a properly designed and powered RCT would not be prone to changes in top-line findings with few patient exchanges. However, if the signal is weak and the RCT was affected by methodological flaws, minor changes could influence primary outcomes accordingly. The fact that a few events could change the statistical significance of the all-cause mortality signal from the pooled femoral popliteal paclitaxel-based RCT data underscores the reality that investigators cannot rely on the limited available trial data to evaluate an association with mortality. Moreover, this highlights the importance of powering trials for mortality outcomes. When the primary outcome is a composite including nonfatal events, neither the total number of fatal events nor the duration of trial follow-up supports deriving definitive conclusions regarding mortality. While it is not possible to power trials for all secondary endpoints, considering the risk for mortality in PAOD subjects, strong consideration should be given to designing future trials for confirming mortality results independently by either larger sample size or longer follow-up or both. The considerable small size of recent RCTs along with additional power issues introduced by potentially clustered data in multicentric trials may



Intervention	Controls	Relative risk	95% CI	Weight (%)	
				Fixed	Random
2/27	4/28	0,519	0,1 to 2,6	5,13	10,58
21/197	2/103	5,490	1,3 to 22,9	6,52	12,60
4/67	2/29	0,866	0,1 to 4,4	4,96	10,32
17/89	4/91	4,346	1,5 to 12,4	12,11	18,63
5/35	3/24	1,143	0,3 to 4,3	7,50	13,87
41/168	24/176	1,790	1,1 to 2,8	63,79	34,00
90/583	39/451	2,037	1,4 to 2,9	100,00	100,00
90/583	39/451	1,859	1,0 to 3,4	100,00	100,00

Significance level	P = 0,1223
I^2 (inconsistency)	42,43%
95% CI for I^2	0,00 to 77,21
Kendall'sTau	-0,4667



0/27	0/28	-			
0/197	0/103	-			
0/67	0/29	-			
2/89	4/91	0,511	0,096 to 2,7	61,85	57,97
4/35	1/24	2,743	0,3 to 23,05	38,15	42,03
6/415	5/275	1,026	0,30 to 3,4	100,00	100,00
6/415	5/275	1,036	0,2 to 5,2	100,00	100,00

Significance level	P = 0,2228
I^2 (inconsistency)	32,72%
95% CI for I^2	0,00 to 0,00
Kendall'sTau	1,0000

Fig. 5. Random effects forest plot of safety outcomes through 5 years. The summary effect was expressed as risk ratio.

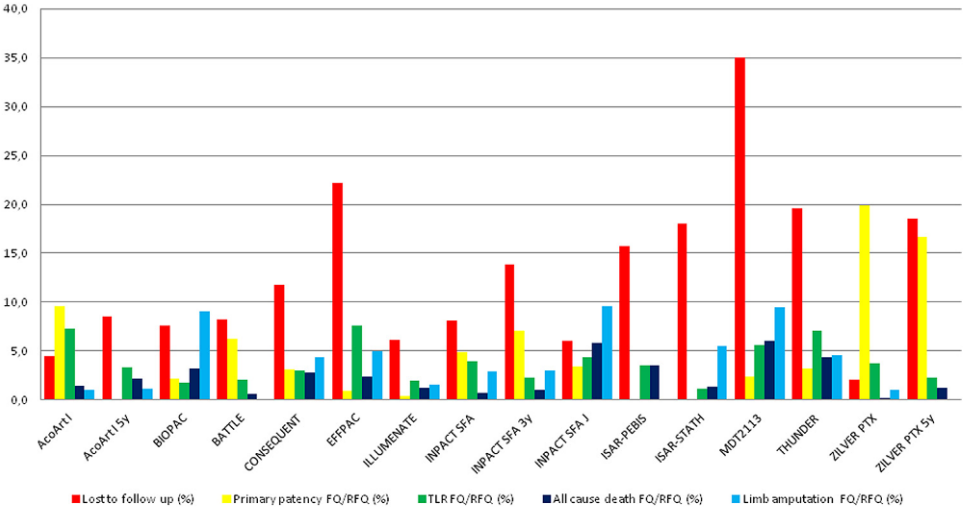


Fig. 6. Fragility quotient (FQ), reverse fragility quotient (RFQ), and percentage of patients lost to follow-up for individual outcomes in the included RCTs.

Table II. Fragility of findings from meta-analysis of included RCT for mid-term outcomes

Outcomes	Events/total PCD	Events/total PTA	RR (CI)	FI/RFI	FQ/RFQ %	NNT (95% C.I.)
Primary patency	283/403	101/283	1.7 (1.1−2.6)	3	0.4	2.8 (2.4−3.6)
TLR	126/601	175/418	0.5 (0.4−0.6)	32	3.1	4.7 (3.7−6.5)
All-cause mortality	90/583	39/451	2.1 (1.4−2.9)	1	0.1	14.7 (9.2−36.7)
Limb amputation	6/415	5/275	1.1 (0.2−3.4)	6	0.9	NA

PCD = paclitaxel coated device; PTA = percutaneous transluminal angioplasty.

Table III. Fragility of findings from meta-analysis of included RCT for long-term outcomes

Outcomes	Events/total PCD	Events/total PTA	RR (CI)	FI/RFI	FQ/RFQ %	NNT (95% C.I.)
Primary patency	646/888	266/620	1.7 (1.5−1.8)	28	1.9	3.35 (3.9−2.8)
TLR	139/1,004	234/693	0.4 (0.3−0.5)	18	0.9	5.02 (4.1−6.2)
All-cause mortality	75/1,076	24/808	2.3 (1.4−3.6)	4	0.2	25.0 (16.5−50.7)
Limb amputation	4/1,037	4/778	0.7 (0.1−3.1)	5	0.3	NA

Table IV. Sensitivity and subgroup analyses for outcomes of interest at mid-term

Paclitaxel DES only 2y	Events/total PCD	Events/total PTA	RR (CI)	FI/RFI	FQ/RFQ %
PP	200/274	76/226	1.9 (0.5−7.3)	13	2.6
TLR	43/274	64/218	0.6 (0.3−1.1)	4	0.8
All-cause mortality	19/327	15/326	1.2 (0.6−2.4)	1	0.2
Limb amputation	NA	NA	NA	NA	NA
Paclitaxel DCB only 2y	**Events/total PCD**	**Events/total PTA**	**RR (CI)**	**FI/RFI**	**FQ/RFQ %**
PP	454/622	182/386	1.5 (1.2−1.7)	26	2.6
TLR	94/738	172/467	0.4 (0.3−0.5)	13	0.9
All-cause mortality	50/748	15/483	1.7 (0.9−3.2)	1	0.1
Limb amputation	3/709	3/453	0.5 (0.1−3.4)	5	0.4
Primary stenosis only 2y (NO ISR)	**Events/total PCD**	**Events/total PTA**	**RR (CI)**	**FI/RFI**	**FQ/RFQ %**
PP	601/816	231/526	1.5 (1.4−1.8)	18	1.3
TLR	117/888	180/561	0.4 (0.3−0.5)	21	1.4
All-cause mortality	58/951	24/685	1.5 (0.7−3.3)	22	1.2
Limb amputation	3/941	1/683	1.2 (0.6−9.4)	4	0.2
Long stenosis only 2y (≥20 cm)	**Events/total PCD**	**Events/total PTA**	**RR (CI)**	**FI/RFI**	**FQ/RFQ %**
PP	286/391	141/247	1.2 (1.1−1.4)	7	0.9
TLR	61/396	83/234	0.5 (0.3−0.7)	5	0.5
All-cause mortality	17/420	13/273	0.7 (0.2−2.1)	1	0.1
Limb amputation	NA	NA	NA	NA	NA

explain why the robustness of the results varied. Most RCTs were initially designed to determine technical endpoints such as TLR or PP. As a result, the majority of trials had high rates of loss to follow-up, which introduces further uncertainty about validity of any previously reported association with safety outcome measures such as all-cause mortality or LLA.

Study Limitations

The findings from the present meta-analysis should be interpreted within the context of some limitations. First, we excluded studies with DCB or DES in the below-the-knee infrapopliteal arteries, as they pertain to a distinctively different patient population, mostly subjects with chronic limb-threatening ischemia that may be associated with

Table V. Sensitivity and subgroup analyses for outcomes of interest at long-term

Paclitaxel DES only 5y	Events/total PCD	Events/total PTA	RR (CI)	FI/RFI	FQ/RFQ %
PP	NA	NA	NA	NA	NA
TLR	NA	NA	NA	NA	NA
All-cause mortality	NA	NA	NA	NA	NA
Limb amputation	NA	NA	NA	NA	NA
Paclitaxel DCB only 5y	**Events/total PCD**	**Events/total PTA**	**RR (CI)**	**FI/RFI**	**FQ/RFQ %**
PP	174/261	63/156	1.4 (0.8–2.4)	2	0.5
TLR	79/421	124/298	0.5 (0.4–0.6)	17	2.4
All-cause mortality	49/415	15/275	1.8 (0.7–4.5)	19	2.3
Limb amputation	6/415	6/275	0.7 (0.2–2.2)	9	1.3
Primary stenosis only 5y (NO ISR)	**Events/total PCD**	**Events/total PTA**	**RR (CI)**	**FI/RFI**	**FQ/RFQ %**
PP	280/385	94/270	2.1 (1.6–2.6)	13	2.0
TLR	95/472	105/279	0.5 (0.4–0.7)	11	1.7
All-cause mortality	68/459	32/336	1.6 (1.2–2.7)	2	0.3
Limb amputation	NA	NA	NA	NA	NA
Long stenosis only 5y (≥20 cm)	**Events/total PCD**	**Events/total PTA**	**RR (CI)**	**FI/RFI**	**FQ/RFQ %**
PP	NA	NA	NA	NA	NA
TLR	29/119	56/119	0.5 (0.3–0.7)	9	3.8
All-cause mortality	19/116	8/119	1.6 (0.2–13.1	5	2.2
Limb amputation	NA	NA	NA	NA	NA

high morbidity (e.g. LLA) and all-cause mortality rates independent of any therapy applied, furthermore, both stents and angioplasty were categorized into 1 group and are unable to separate PTX devices. Second, nearly universally, a single-blind or open-label study design was applied that may have introduced detection or performance bias, respectively. Third, the significant funnel plot asymmetry in relation to PP was considered likely to be representative of ''true'' heterogeneity deriving from the different device types included in the meta-analysis and follow-up protocols within study groups rather than a small study effect. However, due to the limited number of trials available for analysis, especially at long-term, this question cannot be completely answered. It should also be noted that the FI does not account for the difference in time to event and can give fragile results when the number of events in each group is the same but have a difference in the timing of these events. Nonetheless, studies have shown no difference when FI was applied to time-to-event versus frequency data. Because trials are powered to detect the effect on primary outcome, interpretability of FI for secondary outcomes and subgroup analyses may therefore be limited. Finally, the paucity of major adverse events and the significant variations in reporting functional variations of lower limb revascularization with DCB and DES across the trials did not allow the meta-analysis of these outcomes. Indeed, this may explain the observed absence of significant effect to prevent LLA, as the majority of included patients in available RCTs suffered from IC and assessing the robustness of outcomes in patients with below-the-knee artery occlusive disease will be the objective of future studies from our group.

CONCLUSIONS

In conclusion, the efficacy endpoints of PP and TLR for paclitaxel-based endovascular therapy in the femoral popliteal artery were consistent and robust across RCTs. In contrast, the safety endpoint of all-cause mortality was only significant at mid-term follow-up but this observation was highly fragile, largely due to high rates lost to follow-up in the original studies. Accordingly, no association with long-term mortality was identified. These findings raise

additional concerns about the statistical validity of previous studies suggesting an association between paclitaxel-based therapy and all-cause mortality. Furthermore, the pooled estimates of LLA were not associated with paclitaxel-based devices. This underscores the need to design future RCTs with adequate power and follow-up time to assess the impact that paclitaxel-based endovascular interventions in the femoral-popliteal artery may have on amputation and mortality.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.avsg.2023.11.024.

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