



Drug-Coated Versus Uncoated Percutaneous Transluminal Angioplasty Balloons for the Treatment of Infrapopliteal Peripheral Artery Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract

Background. Peripheral artery disease is a growing pandemic with an estimated prevalence higher than ischemic heart disease and cancer combined. Critical limb ischemia, the deadliest form of the disease, is often associated with infrapopliteal artery disease. The use of drug-coated balloons (DCBs) in percutaneous revascularization for infrapopliteal arteries is of growing interest in the medical community, but individual studies have been inconclusive. **Methods.** We performed a meta-analysis of randomized controlled trials investigating the clinical outcomes of patients undergoing percutaneous revascularization with DCB vs percutaneous transluminal angioplasty (PTA) of infrapopliteal arteries. Study quality and heterogeneity were assessed using Jadad score and Cochran's Q statistics, respectively. Mantel-Haenszel odds ratios (ORs) were calculated using random-effect models as the primary analysis. **Results.** We identified 10 studies including 1479 patients that met the inclusion criteria. All studies included in this analysis were outcomes observed from 9-month to 5-year follow-up. DCB use was associated with decreased target-lesion revascularization (OR, 0.43; 95% confidence interval [CI], 0.23 to 0.81; $P < .01$), restenosis or occlusion (OR, 0.42; 95% CI, 0.19 to 0.93; $P = .03$), and late lumen loss (mean difference [MD], -0.52; 95% CI, -0.84 to -0.20; $P < .01$). DCB use was also associated with increased complete healing (OR, 2.12; 95% CI, 1.34 to 3.34; $P < .01$) and shorter time to healing (MD, -1.41 months; 95% CI, -2.48 to -0.34; $P = .01$). There was no difference in all-cause mortality (OR, 1.14; 95% CI, 0.75 to 1.72; $P = .54$), major amputation (OR, 1.35; 95% CI, 0.84-2.19; $P = .22$), or amputation-free survival (relative risk, 1.24; 95% CI, 0.86-1.80; $P = .25$). **Conclusion.** DCB use in infrapopliteal arteries is superior to PTA in improving clinical outcomes, angiographic results, and wound healing with no increase in all-cause mortality or major amputations.

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Key words: critical limb ischemia, paclitaxel, peripheral arterial disease

Peripheral artery disease (PAD) is a leading cause of disease burden, with estimated prevalence exceeding that of ischemic heart disease and cancer combined.¹ Critical limb ischemia (CLI) is associated with higher morbidity and mortality than most

cancers and commonly manifests with ulcers and gangrene caused by obstruction of infrapopliteal arteries.^{2,3}

Surgical revascularization of CLI patients is often not possible due to poor distal targets, lack of suitable venous conduits, and

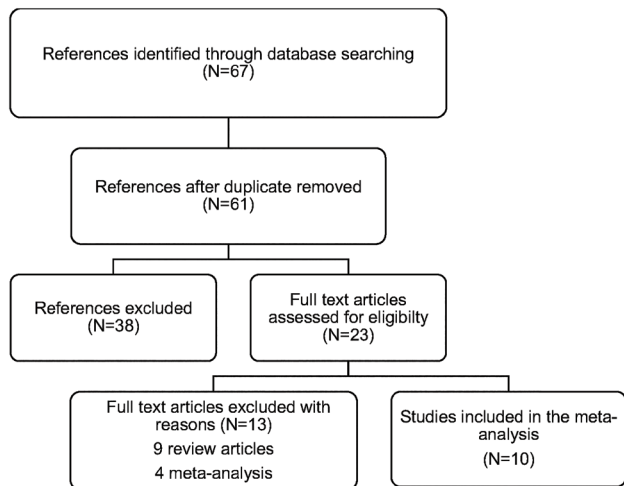


FIGURE 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) diagram.

the presence of multiple comorbidities.⁴ Uncoated percutaneous transluminal angioplasty (PTA), the current endovascular standard of care for infrapopliteal disease, is limited by high restenosis rates that often require repeat revascularization.⁵

Drug-coated balloons (DCBs) that deliver paclitaxel are aimed at reducing restenosis and have been a valuable addition in treating PAD patients with femoropopliteal disease.⁶ Multiple studies have been published that compare DCBs with PTA in patients with infrapopliteal disease.⁷⁻¹⁶ Prior meta-analyses have reported conflicting results regarding the value of DCBs vs PTA in treating patients with infrapopliteal disease; however, additional randomized controlled trials (RCTs) have since become available.¹⁷⁻²¹

Our aim was to conduct an updated meta-analysis of RCTs comparing DCBs with PTA in patients with infrapopliteal artery disease to examine clinical, angiographic, and wound-healing outcomes.

Methods

This meta-analysis was performed according to the guidelines of the preferred reporting items for systematic reviews and meta-analyses (PRISMA).²²

Literature review. We searched 5 databases, including Pubmed, Medline, Embase, Ovid, and Cochrane, for relevant studies from January 1990 to June 2021. We searched prior systemic reviews to ensure inclusion of all eligible studies. We searched ClinicalTrials.gov to identify any ongoing RCTs. This search was independently conducted by 2 investigators (SA and ET). Key terms included peripheral vascular disease, chronic limb ischemia, infrapopliteal disease, drug-coated balloons, percutaneous balloon angioplasty,

endovascular therapy, mortality, amputations, target-lesion revascularization and wound healing.

Selection criteria and quality analysis. We included RCTs published in English comparing DCBs with PTA in patients undergoing treatment of infrapopliteal arteries. We used the following inclusion criteria: (1) prospective RCT design; (2) patients with infrapopliteal artery disease; (3) comparing DCBs with PTA strategy; and (4) reporting at least 1 outcome at 6 months. Studies that compared DCBs with PTA in superficial femoral artery disease only were excluded. RCTs were assessed using Jadad's scale.²³ Included RCTs had a quality score of ≥ 2 .

Data extraction. Extracted data included (but was not limited to) age, gender, comorbidities, indication for endovascular intervention, mortality, amputation, target-lesion revascularization (TLR), angiographic outcomes, and wound healing. Discrepancies were discussed and resolved by consensus.

Outcomes. The primary outcome was TLR. We performed multiple secondary analyses, including mortality, major amputations, late lumen loss, occlusion or restenosis, complete wound healing, and time to wound healing.

Statistical analysis. Random-effect models were used for all reported outcomes. Additional analysis was conducted using the fixed-effect model. We reported the effect measure for each outcome as the odds ratio (OR) with the related 95% confidence interval (CI). Heterogeneity among studies was assessed with the inconsistency index (I^2) statistic, which ranges from 0% to 100% and is defined as the percentage of the observed inter-trial variability that is due to heterogeneity rather than chance for each outcome ($I^2 > 75\%$ denotes significant heterogeneity). Potential publication bias was evaluated by means of Begg's funnel plot method.²⁴ To further detect any clinical heterogeneity, several sensitivity analyses were performed, as described below.

Two-tailed probability values of $< .05$ were considered significant. RevMan, version 5.4 (The Nordic Cochrane Center, The Cochrane Collaboration) was used for all analyses.

Results

Study selection. Of 424 papers originally retrieved by searching the databases, 10 met the inclusion criteria (Figure 1).

Characteristics of the included studies and patients. Ten RCTs involving 1479 patients were published between 2013 and 2020. DCB was used in 863 patients and PTA was used in 616 patients. Studies were conducted in the United States, Canada, Europe, China, and the Middle East.

The mean age of the study population was 71.1 years. The proportion of women was 34.5%. CLI was the primary presentation

TABLE 1. Study characteristics of included randomized controlled trials.

Study	Author	Study Design/Location	Paclitaxel-Coated Balloon	Paclitaxel Dosage/ Excipient	Longest FU (months)
ACOART BTK ⁶	Liistro et al, 2019	single center; Italy	Litos ^b	3.0 µg/mm ² ; magnesium stearate	12
ACOART II ⁷	Jia et al, 2019	multicenter; China	Litos and Tulip ^b	3.3 µg/mm ² ; magnesium stearate	12
BIOLUX PII ⁸	Zeller et al, 2015	multicenter; Germany	Passeo-18 Lux ^c	3.0 µg/mm ² ; BTHC	12
DEBATE BTK ⁹	Liistro et al, 2013	single center ; Italy	IN.PACT Amphirion ^a	3.5 µg/mm ² ; urea	12
DEBELLUM ¹⁰	Fanelli et al, 2014	single center; Italy	IN.PACT Amphirion ^a	3.5 µg/mm ² ; urea	12
HADDAD ET AL ¹¹	Haddad et al, 2017	single center; Jordan	Luminor 14 ^d	3.0 µg/mm ² ; organic ester	12
IN.PACT BTK ¹²	Zeller et al, 2020	multicenter; Italy, Greece, Belgium, France, and Switzerland	IN.PACT 014 ^a	3.5 µg/mm ² ; urea	9
IN.PACT DEEP ¹³	Zeller et al, 2014	multicenter; Austria, Belgium, Germany, Italy, Netherlands, Switzerland	IN.PACT Amphirion ^a	3.5 µg/mm ² ; urea	60
LUTONIX BTK ¹⁴	Mustapha et al, 2019	multicenter; United States, Canada, Europe, Japan, and Australia	Lutonix 014 ^e	2 µg/mm ² ; polysorbate and sorbitol	12
SINGA-PACLI ¹⁵	Tan et al, 2019	multicenter; Singapore	Passeo-18 Lux ^c	3.0 µg/mm ² ; BTHC	12

BTHC= butyryl trihexyl citrate; FU = follow-up. ^aMedtronic; ^bAcotec Scientific; ^cBiotronik; ^dVascular; ^eBard Peripheral Vascular.

TABLE 2. Baseline patient characteristics.

Trials	Patients (n)	Age (years)	Male (%)	Smoking (%)	DM (%)	HTN (%)	CAD (%)	CKD (%)	CLI (%)	Lesion Length (mm)	DS (%)	Lesions Treated (n)	CTO (%)
ACOART BTK ⁶	105	75	76	50	97	84	35	43	100	178	92	128	68
ACOART II ⁷	120	71	60	27	73	79	35	NA	99	175	96	131	79
BIOLUX PII ⁸	72	71	79	56	67	86	42	28	78	114	73	104	NA
DEBATE BTK ⁹	132	75	80	15	100	75	17	11	100	130	97	158	80
DEBELLUM ^{10a}	30	67	73	72	52	68	NA	NA	52	77	87	30	21
HADDAD ET AL ¹¹	93	64	NA	74	96	85	NA	0	100	NA	NA	54	NA
IN.PACT BTK ¹²	50	72	79	15	85	81	40	NA	100	148	97	53	100
IN.PACT DEEP ¹³	358	73	74	14	73	90	31	11	100	115	85	548	42
LUTONIX ¹⁴	442	73	69	59	70	94	51	21	91	104	NA	605	35
SINGAPACLI ¹⁵	138	63	68	36	94	83	60	53	100	86	NA	NA	NA

Data reported as overall mean of patients baseline characteristics enrolled in trials included in the study.

^aPatients with infrapopliteal lesions only.

CAD = coronary artery disease; CKD = chronic kidney disease; CLI = chronic limb ischemia; CTO = chronic total occlusion; DM = diabetes mellitus; DS = diameter stenosis; HTN = hypertension; NA = not available.

in 84.5% of patients. Patients had a high prevalence of diabetes, hypertension, and coronary artery disease. Paclitaxel was the drug used in all DCBs and dose used ranged from 2 to 3.5 µg/mm². Follow-up was at least 9 months in the included studies and ranged from 9 months to 5 years. Further patient and study characteristics are listed in **Table 1** and **Table 2**.

Studies were of good quality according to the Jadad scoring system. The operators were not blinded to the use of DCB vs PTA.

Clinical outcomes. Data for TLR was available from 9 studies (1410 patients). The use of DCBs was associated with decreased TLR when compared with PTA (OR, 0.43; 95% CI, 0.23 to 0.81; P<.01).

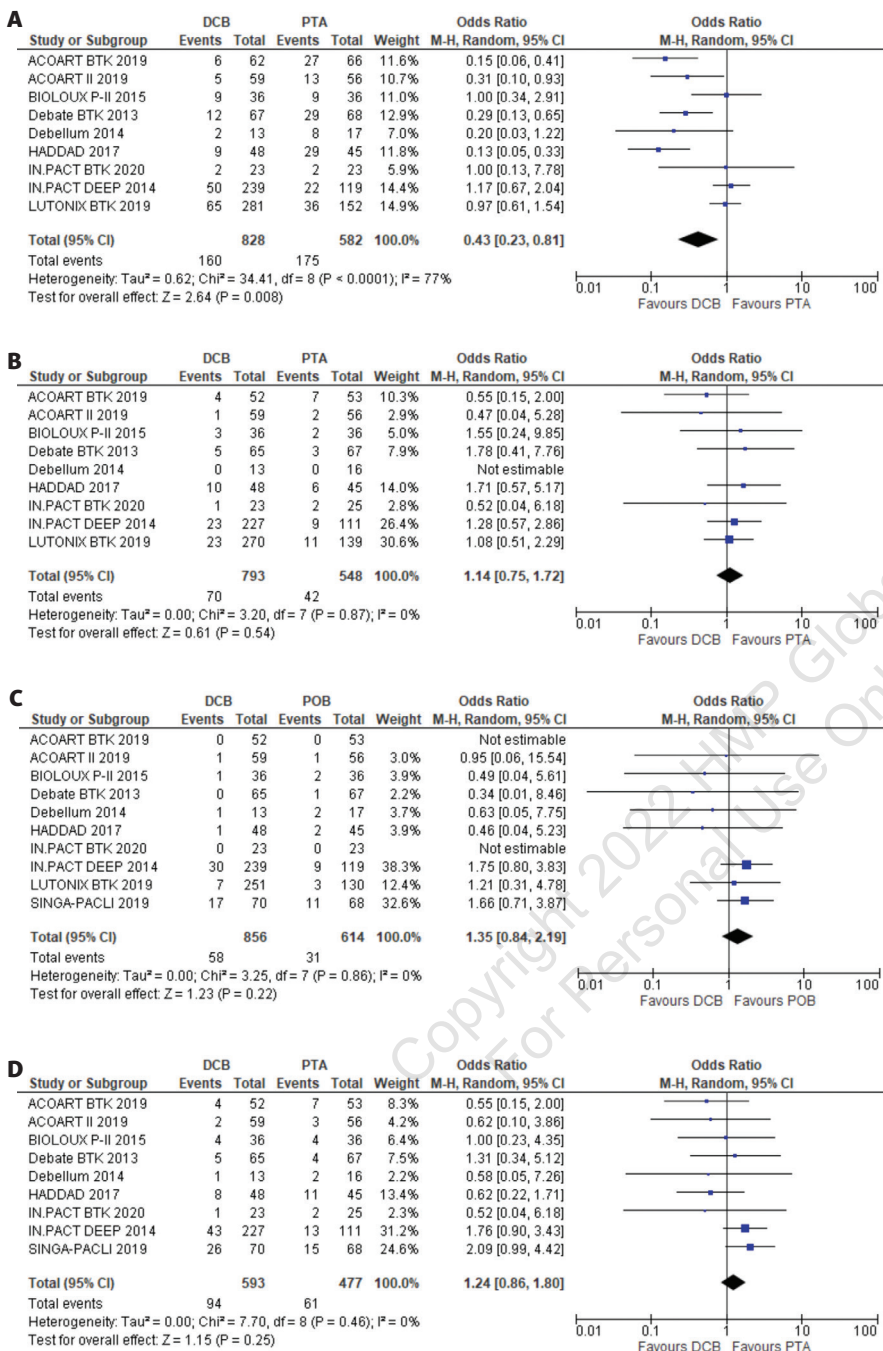


FIGURE 2A-2D. Odds ratios (ORs) and 95% confidence intervals (CIs) in studies comparing drug-coated balloon (DCB) to percutaneous transluminal angioplasty (PTA) in infrapopliteal disease. (A) Target-lesion revascularization. (B) All-cause mortality. (C) Major amputations. (D) Amputation-free survival.

The number needed to prevent 1 TLR was 9.3 patients. There was evidence of considerable heterogeneity ($I^2=77%$) (Figure 2A).

Data for all-cause mortality (1341 patients) and major amputations (1470 patients) were available from 9 studies. Amputation-free survival (AFS) is a computed outcome that was used when data were available. DCB use was not associated with any difference

in all-cause mortality (OR, 1.14; 95% CI, 0.75 to 1.72; $P=.54$), major amputations (OR, 1.35; 95% CI, 0.84 to 2.19; $P=.22$), or AFS (OR, 1.24; 95% CI, 0.86 to 1.80; $P=.25$). There was no heterogeneity among the reported outcome in the included studies (Figure 2B, Figure 2C, Figure 2D).

Data for restenosis or occlusion (1128 patients) and late lumen loss (606 patients) were available from 9 and 7 studies, respectively. DCB use was associated with decreased restenosis or occlusion (OR, 0.42; 95% CI, 0.19 to 0.93; $P=.03$) and late lumen loss (mean difference, -0.52; 95% CI, -0.84 to -0.20; $P<.01$). Considerable heterogeneity was noted among the angiographic outcomes ($I^2=85%$) (Figure 2E, Figure 2F).

Wound-healing outcomes. Data for complete wound healing (444 patients) and time to healing (286 patients) were available from 4 and 3 studies, respectively. DCB resulted in twice the rate of complete wound healing (OR, 2.12; 95% CI, 1.34 to 3.34; $P<.01$) compared with PTA. The time to wound healing was decreased by 1.4 months when DCB was used (mean difference, -1.41 months; 95% CI, -2.48 to -0.34; $P=.01$). There was no significant heterogeneity among the reported outcomes in the included studies (Figure 2G, Figure 2H).

Sensitivity analysis. We performed a sensitivity analysis including only those RCTs that were published in peer-reviewed journals and there was no change in the outcomes. We also performed a sensitivity analysis that included data from 1 study that had 5-year outcome reported with no change in outcomes. Our last sensitivity analysis was done excluding a study that included a proportionally high percentage of patients with end-stage renal disease (52.9%) and found a minor improvement in restenosis or occlusion (OR, 0.38; 95% CI, 0.15 to 0.94; $P=.04$).¹⁶

Funnel plots were not suggestive of significant publication bias.

Discussion

The present meta-analysis demonstrates that among patients who underwent percutaneous revascularization of infrapopliteal

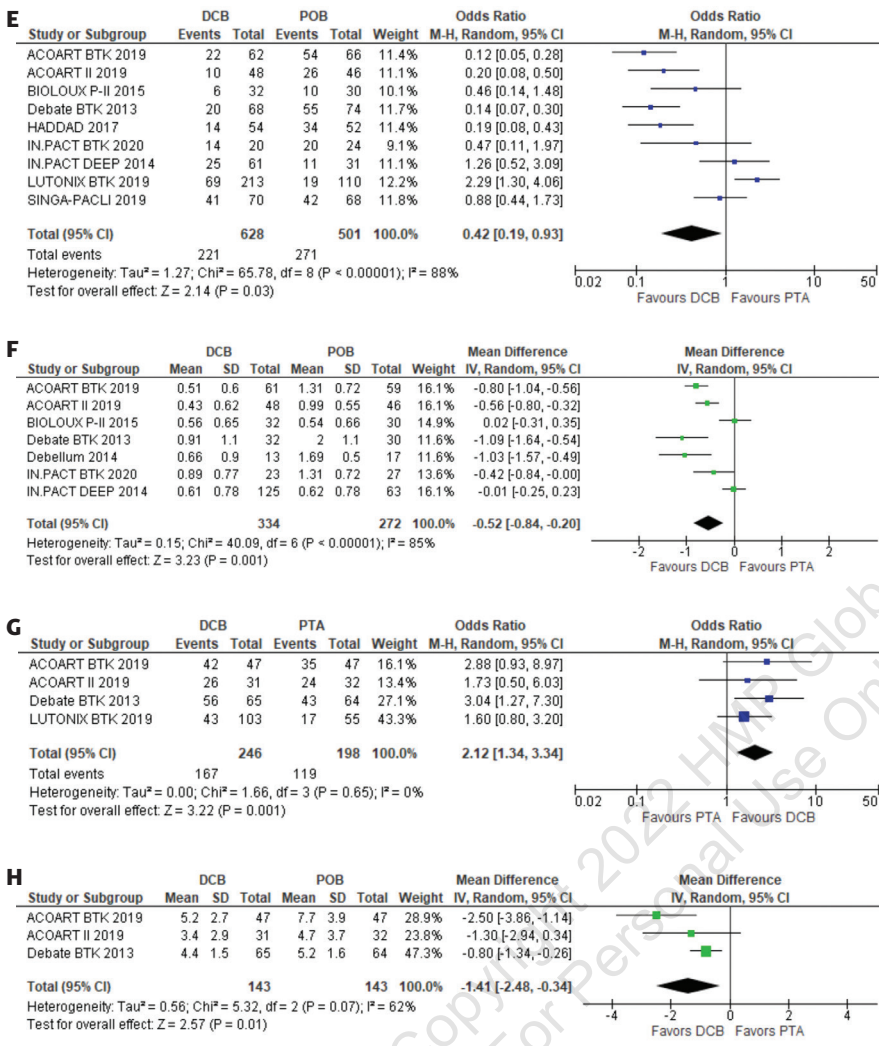


FIGURE 2E-2H. Odds ratios (ORs) and 95% confidence intervals (CIs) in studies comparing drug-coated balloon (DCB) to percutaneous transluminal angioplasty (PTA) in infrapopliteal disease. (E) Restenosis or occlusion. (F) Late lumen loss. (G) Complete healing. (H) Time to healing.

arteries, DCB compared with PTA demonstrated improved TLR, restenosis or occlusion, and wound healing, without apparent excess in all-cause mortality, amputations, or AFS.

Prior meta-analyses investigating the impact of DCB vs PTA for infrapopliteal arteries have demonstrated mixed results. Katsanos et al reported that DCB use was associated with decreased TLR and AFS rates.¹⁷ It is important to note that AFS is an outcome that is not consistently reported in the trials and had to be calculated by the authors of the meta-analysis, introducing an opportunity for error. For example, the aforementioned meta-analysis under-reported deaths in the PTA arm in 2 of the included trials.^{7,8} They reported deaths in the PTA arm of the ACOART-BTK trial as n = 2 and AcoArt II-BTK trial as n = 0, where the published data showed n = 7 deaths and n = 2 deaths, respectively. In addition, the Katsanos meta-analysis did not find a difference in AFS when they relied only on studies published

in peer-reviewed journals. Our study did not find a difference in AFS between the 2 treatment groups after correcting for the above and including the newly presented IN.PACT BTK trial,¹³ consistent with a previously published meta-analysis. The Cassese et al meta-analysis concluded that in the treatment of infrapopliteal arteries at 12-month follow-up, DCBs were associated with similar clinical outcomes and favorable angiographic efficacy compared with PTA.¹⁹ Ipema et al found no differences in limb salvage, survival, and AFS, with a numerically improved TLR rate in the DCB arm.²⁰ Dinh et al found that use of DCBs did not increase mortality compared with PTA in treating CLI patients with infrapopliteal disease.²¹ Since the publication of prior meta-analyses, 2 RCTs were published and 1 was recently presented.^{7,8,13}

Despite increased success in treating infrapopliteal arteries, TLR and restenosis or occlusion remain the Achilles' heel of this therapy. An important finding of our study is the significant decrease in TLR and restenosis or occlusion with the use of DCB. The number needed to treat to decrease TLR with DCB compared with PTA is 8 patients.

Wound healing is the ultimate goal of treating CLI patients, and achieving complete wound healing is associated with improved prognosis and quality of life.²⁵ A novel finding of this meta-analysis is that DCBs were associated with increased

complete wound healing and shorter time to achieving complete healing. With a small cohort of only 4 studies reporting these data, additional studies will need to be conducted to provide greater evidence for this finding.^{8,10,13}

In the present meta-analysis, we found no difference in all-cause mortality. This is consistent with a growing body of data that show no increased mortality in patients undergoing therapy with DCB.^{21,26} Further doubts about paclitaxel mortality have been debunked, as the literature has not shown a plausible mechanism of action leading to increased mortality or a clear association between dose and mortality.²⁷⁻²⁹

Study limitations. This meta-analysis is comprised of data collected from 10 RCTs and therefore shares the flaws from the original trials. Furthermore, only 1 RCT presented 5-year data, precluding us from making long-term conclusions.³⁰

Conclusion

Following percutaneous revascularization of infrapopliteal arteries, DCB demonstrated superior clinical outcomes vs PTA, without apparent excess of all-cause mortality or major amputation. Our study suggests that DCB use is more efficacious than PTA, with a similar safety profile.

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