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Network Meta-analysis Of Drug-coated Balloon Angioplasty Versus Primary Nitinol Stenting for Femoropopliteal Atherosclerotic Disease

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Abstract

Objective: Primary nitinol stenting (PNS) and drug coated balloon angioplasty (DCB) are two of the most common endovascular interventions for femoropopliteal atherosclerotic disease. While many prospective randomized controlled trials have compared PNS or DCB to plain balloon angioplasty (POBA), no studies have directly compared PNS against DCB therapy. The purpose of this network meta-analysis is to determine whether there is a significant difference in outcomes between PNS and DCB.

Methods: The primary outcome measure was binary restenosis, the secondary outcome measures were target lesion revascularization (TLR) and change in ankle brachial index (ABI). Outcomes were evaluated at 6, 12, and 24 months. A literature review identified all randomized controlled trials published prior to March 2020 that compared DCB to POBA or PNS to POBA in the treatment of native atherosclerotic lesions of the femoropopliteal artery. Studies were excluded if they contained in-stent stenosis or tibial artery disease that could not be delineated out in a subgroup analysis. Network meta-analysis was performed using the network and mvmeta commands in STATA 14.

Results: Twenty-seven publications covering 19 trials were identified, eight trials compared PNS to POBA and 11 trials compared DCB to POBA. The odds of freedom from binary restenosis for patients treated with DCB compared to PNS at 6 months was 1.19 (95% CI 0.63 – 2.22), at 12 months was 1.67 (95% CI 1.04 – 2.68), and at 24 months was 1.36 (95% CI 0.78 – 2.37). The odds of freedom from target lesion revascularization for patients treated with DCB compared to PNS at 6 months was 0.66 (95% CI 0.12 – 3.80), at 12 months was 1.89 (95% CI 1.04 – 3.45), and at 24 months was 1.68 (95% CI 0.82 – 3.44). The mean increase in ABI for patients treated with PNS

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compared to DCB at 6 months was 0.06 higher (95% CI −0.03 – 0.15), at 12 months was 0.05 higher (95% CI 0.00 – 0.09), and at 24 months was 0.07 higher (95% CI −0.01 – 0.14).

Conclusion: Both DCB and PNS demonstrated a lower rate of binary restenosis compared to POBA at the 6-month, 12-month, and 24-month timepoints. When comparing DCB to PNS through network meta-analysis, DCB had a statistically lower rate of a binary restenosis and target lesion revascularization at the 12-month timepoint. This network meta-analysis demonstrates that both DCB and PNS are superior to POBA, and that PNS is a satisfactory substitute for DCB when paclitaxel is not desirable.

Keywords

Network Meta-analysis; Drug-coated balloon; Bare Metal stent; Nitinol stenting; Peripheral arterial disease

Introduction

Over the past 30 years, endovascular therapy for femoropopliteal arterial occlusive disease has evolved to be the first-line treatment for most patients. As the adoption of endovascular therapy for peripheral arterial disease (PAD) grows, so do its technical variations. The first widely adopted endovascular intervention for PAD was plain balloon angioplasty (POBA), which remains a common treatment. Today, clinicians have a wide range of endovascular modalities to choose from including balloon-expandable stainless-steel stents, primary nitinol stenting (PNS), drug-eluting stents (DES), drug-coated balloons (DCB), and atherectomy.

Multiple randomized-controlled trials (RCTs) have demonstrated that both PNS and DCB have superior patency rates to POBA for most native femoropopliteal atherosclerotic lesions.[1,2] However, there are unique concerns about both PNS and DCB. PNS leaves behind a permanent foreign object which could potentially alter future surgical options.[3] DCB exposes the patient to paclitaxel which has been associated with increased all-cause mortality.[4]

While both PNS and DCB have had RCTs demonstrating their superiority to POBA, the two therapies have not been directly compared to each other. Although there are other options such as DES and PNS combined with DCB, VQIP data demonstrates that DCB and PNS remain the two most frequently performed interventions for femoropopliteal disease at 37% and 26% respectively.[5] In addition, with the controversy surrounding paclitaxel-based devices, surgeons are interested in alternatives to DCB. Since a trial directly comparing DCB to PNS is unlikely to occur, we performed a network meta-analysis to determine whether PNS remains a reasonable alternative to DCB.

Methods

Search Strategy

The Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov, and PubMed were queried for publications or trials prior to March, 2020 with a title including

the word “femoral”, “popliteal”, or “femoropopliteal” along with the word “endovascular”, “percutaneous”, “transluminal”, “angioplasty”, “stent”, or “balloon.”

Selection Criteria

Studies were included if they were an RCT that contained at least a POBA arm and either a PNS arm or a DCB arm. Studies had to be limited to, or contain sub-analysis for, native femoropopliteal atherosclerotic disease exclusive of in-stent stenosis and tibial disease. Studies had to contain one of the three timepoints of interest (6 months, 12 months, and 24 months) and one of the three outcome measures of interest (binary restenosis, target lesion revascularization, and change in mean ankle brachial index). Studies were excluded if they utilized balloon-expandable stents instead of self-expanding stents.

Outcome measures

The primary outcome measure was freedom from binary restenosis. Binary restenosis was defined as a duplex ultrasound derived peak systolic velocity ratio of >2.5 or 2.4, or if duplex ultrasound was not available, a >50% stenosis as seen on arteriography. The secondary outcome measures were freedom from target lesion revascularization (TLR) and change in ankle-brachial index (ABI). Target lesion revascularization was defined as reintervention on the target lesion to maintain or restore patency. Change in ABI was defined as the change from the baseline pre-intervention ABI to the follow-up ABI.

Data Extraction

Intention-to-treat data were extracted. If a patient required an adjunct, such as stent placement due to dissection during dilation, this was not considered a loss of patency, restenosis, or target-lesion revascularization. Binary restenosis was assumed to be equal to primary patency if the protocol stated that target-lesion revascularization would only occur with ≥50% restenosis and if the authors defined primary patency as restenosis on imaging or a protocol-driven target lesion revascularization. A normal distribution was assumed for ABI thus allowing for median values and interquartile ranges to be interchanged to means and standard distribution using guidelines from the Cochrane Handbook.[6] If standard deviations or interquartile ranges were missing, these were imputed by calculating a correlation coefficient from the other studies. Studies were reviewed for risk of bias using the Cochrane Collaboration’s risk of bias tool.[7]

Statistics

A network meta-analysis was performed using frequentist methods implemented in the *network* and *mvmeta* commands in STATA 15 by fitting a multivariate random-effects meta-analysis model using restricted maximum likelihood (REML). Between-studies variance $\tau 2$ was assumed to be common across comparisons. At each timepoint, direct and indirect comparisons were presented as odds ratio (OR) and 95% confidence intervals (CI) for the freedom from binary restenosis and freedom from target lesion revascularization outcomes and as mean differences (MD) and 95% CIs for ABI. Since our networks were simple star-shaped and contained no loops with direct PNS-DCB comparisons, we were not able to evaluate or test for inconsistency. Publication bias and small study effects were inspected by

generating comparison-adjusted funnel plots for each outcome at each timepoint and by further visual inspection using the criterion of symmetry.

Results:

Study Characteristics

The search strategy and selection process identified 27 publications detailing 19 studies (Supplementary Figure 1.) Eight studies compared PNS to POBA and 11 studies compared DCB to POBA; these 19 studies had a combined enrollment of 3,287 patients (Table 1.) All studies included 12-month results, but 6-month and 24-month results were less frequently reported. All studies reported binary restenosis. Most studies excluded Rutherford class 1 and Rutherford class 6 patients. The shortest lesions studied ranged 1 cm to 10 cm and the longest ranged 5 cm to 22 cm. Among the 565 patients randomized to POBA in the studies comparing PNS to POBA, 145 patients were crossed over to stenting for an adjunctive stenting rate of 25.0%. Among the 2,111 patients in the studies comparing DCB to POBA, 253 underwent adjunctive stenting for a rate of 12.0%. Studies were similar in their risk of bias (Supplementary Figures 2–3.) All studies used random sequence generation and an independent core laboratory for interpretation of duplex results. No study was able to blind personnel to the treatment selected. The majority specified an allocation concealment method, provided complete outcome data, and avoided selective reporting. All DCB versus POBA studies and 5 of 8 PNS versus POBA studies were industry sponsored. The comparison-adjusted funnel plots appear symmetric, suggesting the absence of small-study effects in the network (Supplementary Figure 4.)

Binary Restenosis

The odds of freedom from binary restenosis for patients treated with PNS compared to POBA at 6 months was 2.65 (95% CI 1.59 – 4.42), at 12 months was 1.89 (95% CI 1.31 – 2.71), and at 24 months was 1.98 (95% CI 1.27 – 3.10) (Figure 1.) The odds of freedom from binary restenosis for patients treated with DCB compared to POBA at 6 months was 3.14 (95% CI 2.12 – 4.67), at 12 months was 3.16 (95% CI 2.31 – 4.32), and at 24 months was 2.69 (95% CI 1.96 – 3.68). The odds of freedom from binary restenosis for patients treated with DCB compared to PNS at 6 months was 1.19 (95% CI 0.63 – 2.22), at 12 months was 1.67 (95% CI 1.04 – 2.68), and at 24 months was 1.36 (95% CI 0.78 – 2.37).

Target Lesion Revascularization

The odds of freedom from target lesion revascularization for patients treated with PNS compared to POBA at 6 months was 3.66 (95% CI 0.72 – 18.53), at 12 months was 1.61 (95% CI 1.01 – 2.58), and at 24 months was 1.64 (95% CI 0.87 – 3.08) (Figure 2.) The odds of freedom from target lesion revascularization for patients treated with DCB compared to POBA at 6 months was 2.42 (95% CI 1.28 – 4.56), at 12 months was 3.05 (95% CI 2.10 – 4.43), and at 24 months was 2.75 (95% CI 1.95 – 3.88). The odds of freedom from target lesion revascularization for patients treated with DCB compared to PNS at 6 months was 0.66 (95% CI 0.12 – 3.80), at 12 months was 1.89 (95% CI 1.04 – 3.45), and at 24 months was 1.68 (95% CI 0.82 – 3.44).

Ankle-Brachial Index

The mean increase in ABI for patients treated with PNS compared to POBA at 6 months was 0.07 higher (95% CI 0.00 – 0.13), at 12 months was 0.04 higher (95% CI 0.00 – 0.08), and at 24 months was 0.03 higher (95% CI −0.03 – 0.09) (Figure 3.) The mean increase in ABI for patients treated with DCB compared to POBA at 6 months was 0.01 higher (95% CI −0.06 – 0.07), at 12 months was equal (95% CI −0.03 – 0.02), and at 24 months was 0.04 lower (95% CI −0.08 – 0.01). The mean increase in ABI for patients treated with PNS compared to DCB at 6 months was 0.06 higher (95% CI −0.03 – 0.15), at 12 months was 0.05 higher (95% CI 0.00 – 0.09), and at 24 months was 0.07 higher (95% CI −0.01 – 0.14).

Discussion

Both DCB and PNS demonstrated a statistically lower rate of binary restenosis compared with POBA at all timepoints. Indirect comparisons via network meta-analysis demonstrated that DCB had a smaller, but still significant, advantage over PNS at preventing binary restenosis and target lesion revascularization at the 12-month timepoint but not at the 6-month or 24-month timepoints. The clinical significance of a difference in binary restenosis and TLR at 12 months, but not at six months or 24 months, is open to debate. The reader should note, however, that there was less data reported at 6 months and 24 months resulting in wider confidence intervals at these timepoints. For example, there were only two studies reporting TLR at 6 months when comparing POBA and PNS resulting in a 95% confidence interval ranging from 0.72 to 18.53.

In designing this network meta-analysis, we chose binary restenosis as our primary outcome measure because it was ubiquitous, operator-independent, and uniformly defined. During our initial review of the literature, we found many papers which used primary patency as an outcome measure. Unfortunately, the definitions of primary patency were inconsistent. However, we were able to infer binary restenosis rates from primary patency rates with supporting data. Target lesion revascularization, though commonly included and clearly defined, is often dependent on the clinical decisions made by an unblinded interventionist and thus prone to bias. This problem is magnified in studies where routine follow-up angiography is performed thus forcing an unblinded operator to quickly decide the need for target lesion revascularization. Ankle-brachial index was clearly defined, but imprecise, and studies had inconsistent methods for addressing patients who had undergone interim target-lesion revascularization.

This study was subject to the usual limitations of network meta-analyses such as inconsistency in reporting standards, incomplete data, the transitivity assumption, and industry bias. Additionally, we were not able to evaluate inconsistency between direct and indirect PNS-DCB comparisons due to our star-shaped network geometry. A limitation unique to this network meta-analysis was the high rate of adjunctive stenting. Among the 565 patients randomized to POBA in the studies comparing PNS against POBA, 145 patients were crossed over to stenting for an adjunctive stenting rate of 25.0%. In the studies comparing POBA against DCB, the adjunctive stenting rates were lower as many trials were designed such that randomization would occur after a successful pre-dilation. Among the 2,111 patients in the studies comparing DCB against POBA, 253 underwent adjunctive

stenting for a rate of 12.0%. Although most PNS versus POBA studies provided adequate as-treated subgroup analysis, similar data was not available from the DCB versus POBA studies. Therefore, we are unable to perform valuable as-treated analysis.

As of 2020, paclitaxel-based devices remain controversial. In 2020, the consortium led by the VIVA Physicians produced a patient-level meta-analysis using data from 2185 patients in eight paclitaxel-containing device trials with a median follow-up of four years; at five years mortality for patients receiving paclitaxel-based devices was 18.3% versus 13.7% for controls.[8] Multiple publications have investigated the concern that stenting may eliminate future therapeutic options, such as open bypass, due to the presence of a permanent foreign body in the artery. Conway examined 621 patients who underwent femoropopliteal stenting of whom 30 had subsequent stent occlusion. Within this group they identified 7 patients whose theoretical bypass target would become more distal. Joels et al examined 276 patients who underwent femoral stenting and noted that 9% had early failure (<200 day) and that early failure altered the distal bypass target in 28% of those cases.[9] Gur et al identified 239 patients who underwent femoropopliteal stenting, 69 lost patency, and 2 ultimately had bypasses which, if not for the presence of a stent, would have had a more proximal target.[10] Thus, while a metallic stent can impede a future open bypass, such scenarios are uncommon in practice.

There are concerns that reintervention following stent failure is complicated. Unfortunately, there is limited prospective randomized data regarding secondary patency following primary nitinol stenting. Among the eight studies comparing POBA to PNS, only two studies reported secondary patency. The ETAP study reported a two-year secondary patency rate of 78.3% for PNS and 77.8% for POBA. The RESILIENT study reported a one-year secondary patency rate of 100% for PNS and 98.3% for PTA. The Schillinger study did not report secondary patency but did mention that three of the thirteen PNS patients who required reintervention received bypass surgery compared to none among the sixteen reinterventions in the POBA cohort. Therefore, while concerns regarding reintervention following PNS are valid, there is limited data regarding outcomes following reintervention.

Conclusion

This network meta-analysis demonstrates that both DCB and PNS are superior to POBA. When comparing DCB to PNS across multiple timepoints and outcome measures, we observed DCB narrowly outperform PNS in binary restenosis and target lesion revascularization at the 12-month timepoint. However, these differences are much smaller than those observed when comparing DCB or PNS to POBA. This study demonstrates that for femoropopliteal atherosclerotic lesions, PNS remains a reasonable alternative to DCB when the use of paclitaxel is not desirable.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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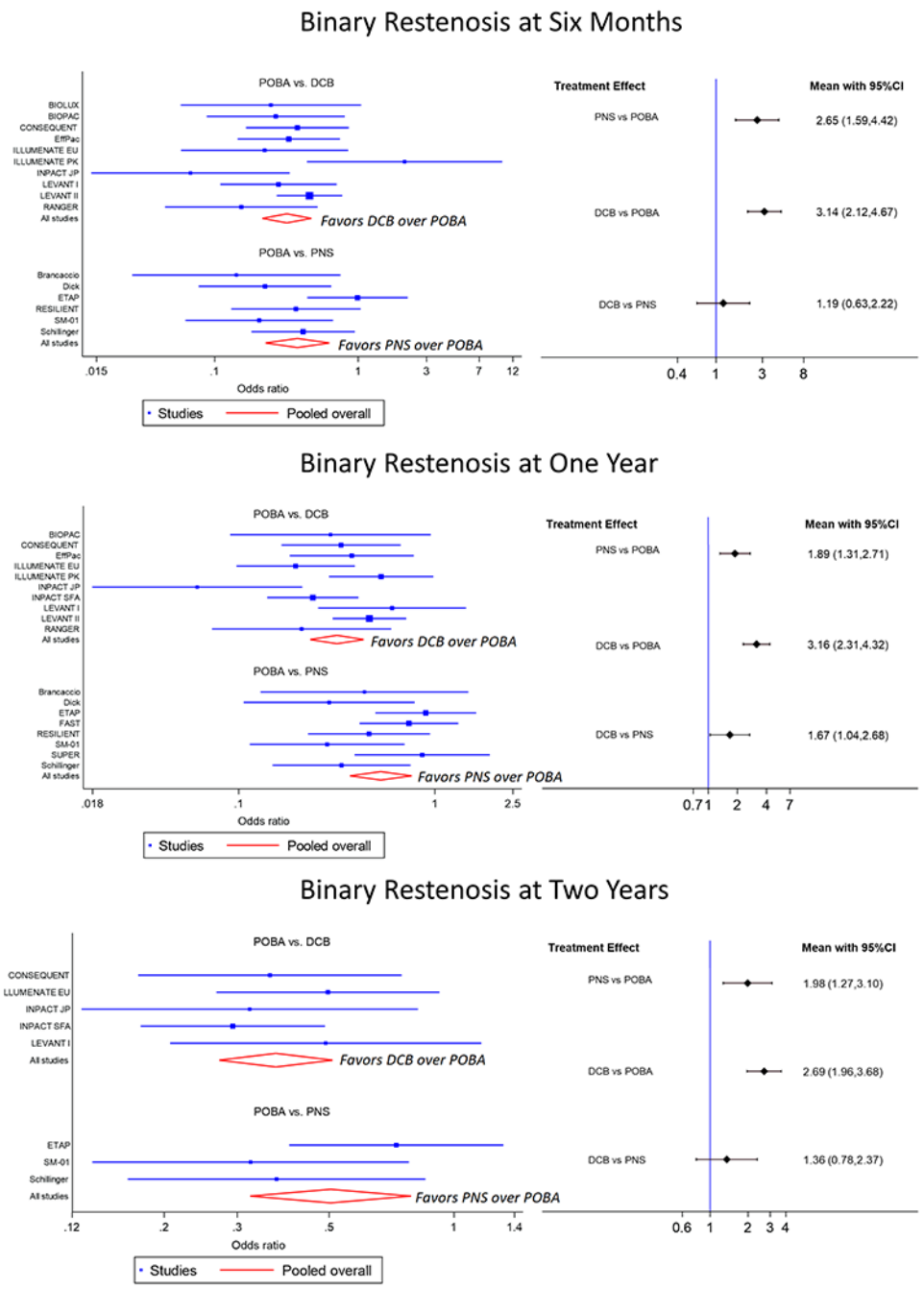

Figure 1.

The left side shows forest plots for freedom from binary restenosis at 6 months (top), 12 months (middle), and 24 months (bottom). The right side shows interval plots for freedom from binary restenosis at 6 months (top), 12 months (middle), and 24 months (bottom). Black horizonal lines represent confidence intervals (CI).

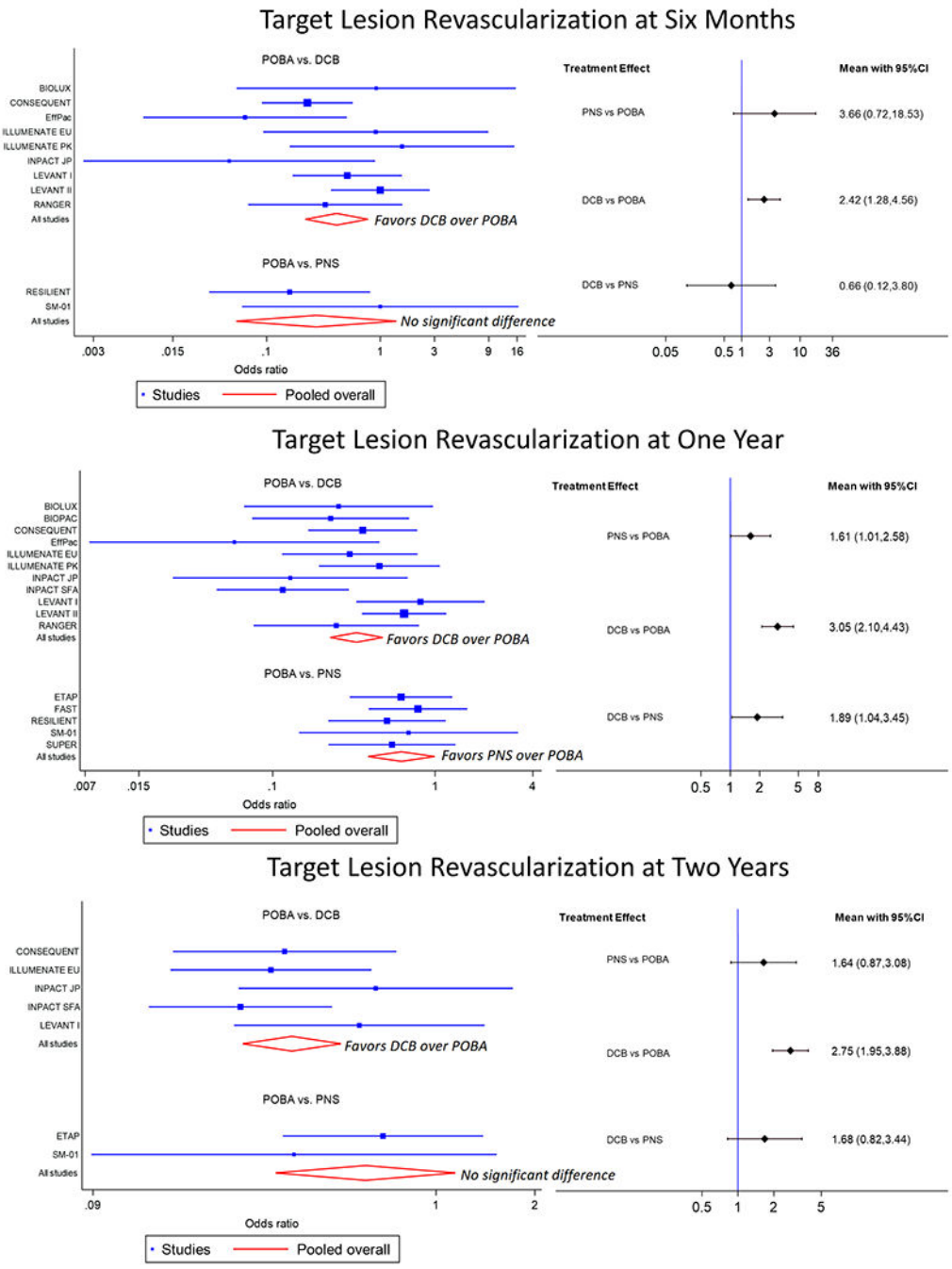

Figure 2.

The left side shows forest plots for freedom from target lesion restenosis at 6 months (top), 12 months (middle), and 24 months (bottom). The right side shows interval plots for freedom from target lesion revascularization at 6 months (top), 12 months (middle), and 24 months (bottom). Black horizonal lines represent confidence intervals (CI).

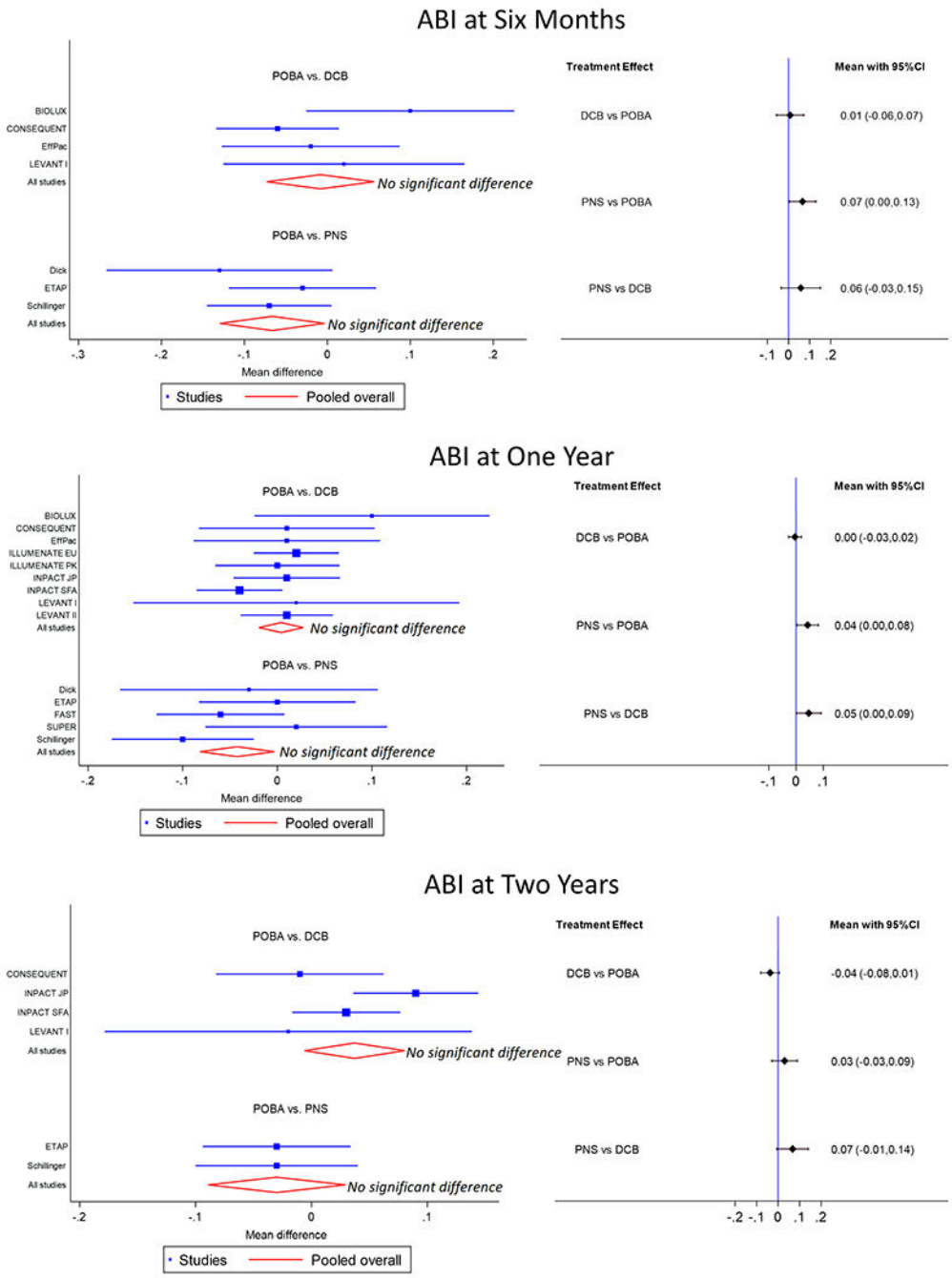

Figure 3.

The left side shows forest plots for mean increase in ABI at 6 months (top), 12 months (middle), and 24 months (bottom). The right side shows interval plots for mean increase in ABI at 6 months (top), 12 months (middle), and 24 months (bottom). Black horizonal lines represent confidence intervals (CI).

Table 1.

Characteristics of included studies

PNS vs POBA	Publication year(s)	PNS n	POBA n	Time, months	Outcomes studied	Lesion location	RC	Lesion length	Industry sponsor	Adjunct stenting
Brancaccio[1]	2012	25	25	6, 12	BR	SFA	3-5	Unknown	No	14 POBA
Dick[2]	2009	34	39	6, 12	BR, ABI	SFA	3-5	3-20cm	No	10 POBA
FAST[3]	2007	123	121	12	BR, TLR, ABI	SFA	2-5	1-10cm	Yes	13 POBA
ETAP[4,5]	2013, 2015	119	127	6, 12, 24	BR, TLR, ABI	Pop	2-5	5-180mm	Yes	32 POBA
RESILIENT[6,7]	2009, 2012	134	72	6, 12,	BR, TLR	SFA + Pop	1-3	< 15cm	Yes	29 POBA
SM-01[8]	2019	51	52	6, 12, 24	BR, TLR	SFA + Pop	1-3	4-15cm	Yes	26 POBA
SUPER[9]	2012	74	76	12	BR, TLR	SFA	1-6	5-22cm	Yes	4 POBA
Schillinger[10,11]	2006, 2007	51	53	6, 12, 24	BR, ABI	SFA + Pop	3-5	>3cm	No	17 POBA
DCB vs POBA	**Publication year(s)**	**DCB n**	**POBA n**	**Time, months**	**Outcomes studied**	**Lesion location**	**RC**	**Lesion length**	**Industry sponsor**	**Adjunct stenting**
BIOLUX[12]	2015	30	30	6, 12	BR, TLR, ABI	SFA + Pop	2-5	3-20cm	Yes	2 DCB 8 POBA
BIOPAC[13]	2018	33	33	6, 12	BR, TLR	SFA	2-4	4-15cm	Yes	13 DCB 13 POBA
CONSEQUENT[14,15]	2017, 2018	78	75	6, 12	BR, TLR, ABI	SFA + Pop	2-4	4-27cm	Yes	11 DCB 14 POBA
EffPac[16]	2019	85	86	6, 12	BR, TLR, ABI	SFA + Pop	2-4	<15cm	Yes	13 DCB 16 POBA†
ILLUMENATE.EU[17,18]	2017, 2018	222	72	6, 12, 24	BR, TLR, ABI	SFA + Pop	2-4	3-20cm	Yes	38 DCB 9 DCB†
ILLUMENATE PK[19]	2017	200	100	6, 12	BR, TLR, ABI	SFA + Pop	2-4	3-18cm	Yes	12 DCB 6 POBA†
INPACT JP[20,21]	2018, 2018	68	32	6, 12, 24	BR, TLR, ABI	SFA + Pop	2-4	4-20 cm	Yes	3 DCB 1 POBA†
INPACT SFA[22,23]	2014, 2015	220	111	6, 12, 24	BR, TLR, ABI	SFA + Pop	2-4	4-18 cm	Yes	16 DCB 14 POBA†
LEVANT I[24]	2014	31	24	6, 12, 24	BR, TLR, ABI	SFA + Pop	2-5	4-15cm	Yes	12 DCB 14 POBA
LEVANT II[25]	2015	316	160	6, 12	BR, TLR, ABI	SFA + Pop	2-4	<15cm	Yes	8 DCB 11 POBA†
RANGER[26,27]	2017, 2018	71	34	6, 12	BR, TLR, ABI	SFA + Pop	2-4	2-15cm	Yes	15 DCB 4 POBA

PNS = Primary Nitinol Stenting, POBA = Uncoated balloon angioplasty, BR = Binary Restenosis, TLR=Target Lesion Revascularization, ABI = Ankle Brachial Index, RC = Rutherford Classification, SFA = Superficial Femoral Artery, Pop = Popliteal Artery

† = These studies were protocoled such that randomization would occur after successful predilation and that patients who dissected during predilation would be screened out of the study.

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