Meta-Analysis Comparing Endovascular Treatment Modalities for Femoropopliteal Peripheral Artery Disease

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Endovascular interventions are commonly utilized for treatment of femoropopliteal peripheral artery disease. The relative efficacy of these interventions remains unclear. A Bayesian network meta-analysis was performed comparing 5 endovascular treatment modalities: balloon angioplasty (BA), bare metal stent (BMS), covered stent (CS), drug-coated balloon (DCB), drug-eluting stent (DES) for femoropopliteal peripheral artery disease. The primary efficacy end points were freedom from target lesion revascularization (TLR) and primary patency at 12 months. BA was the reference treatment. Twenty-two trials including 4,381 participants provided data on TLR. Sixteen trials including 3,691 participants provided data on primary patency. Point estimates for DCB suggested that it was the most efficacious treatment for freedom from TLR (odds ratio [OR] 4.23; 95% credible intervals [CrI] 2.43 to 7.66) followed by CS (OR 3.65; 95% CrI 1.11 to 12.55), DES (OR 2.64; 95% CrI 0.72 to 9.77), and BMS (OR 2.3; 95% CrI 1.11 to 4.76). Similarly, point estimates for primary patency were highest with DES (OR 8.93; 95% CrI 3.04, 27.14) followed by CS (OR 3.91; 95% CrI 1.18, 13.84), DCB (OR 3.32; 95% CrI 1.8, 6.25), and BMS (OR 3.5; 95% CrI 1.58, 7.99). In conclusion, DCB has the lowest need for TLR whereas DES has the highest primary patency rate. DCB, CS, and BMS were associated with significant reductions in TLR compared with BA, whereas DCB, DES, CS, and BMS were associated with significantly improved primary patency compared with BA. **(Am J Cardiol 2020;128:181−188)**

Peripheral artery disease (PAD) affects over 200 million subjects worldwide and over 8.5 million in the United States,[1] significantly impairs functional status and health-related quality of life and in its most extreme manifestation can result in limb loss. Lower extremity percutaneous and surgical revascularization improve these outcomes and the 2016 American College of Cardiology/American Heart Association guidelines support these therapies for appropriately selected patients with claudication and critical limb ischemia. Endovascular interventions are now performed more commonly than surgical bypass in these settings. Given the high rates of restenosis and target lesion revascularization (TLR) associated with conventional balloon angioplasty (BA), multiple alternative definitive endovascular treatment modalities have emerged, including bare metal stents (BMS), drug-eluting stent (DES), covered stents (CS), and drug-coated balloons (DCBs). Although all are superior to BA at improving patency and reducing TLR, the comparative efficacy of each has not been well characterized. The primary objective of the present study was to evaluate the comparative efficacy of various endovascular treatment modalities for arterial occlusive disease of the femoropopliteal segment, utilizing network meta-analysis under a Bayesian framework.

Methods

This study was performed in accordance with Preferred Reporting Items for Systematic Review and Meta-Analysis[2] guidelines and the Preferred Reporting Items for Systematic Review and Meta-Analysis extension statement for reporting of systematic reviews incorporating Network Meta-analysis of Health Care Interventions.[3]

A systematic search of PubMed, Embase, and Cochrane Central databases was performed using the following key terms: Balloon Angioplasty OR Drug-Eluting Stent OR Sirolimus Eluting Stent OR Paclitaxel Eluting Stent OR Drug-Coated Balloon OR Paclitaxel-Coated Balloon OR Nitinol Stents OR Covered Stents OR Heparin Covered Stents AND Peripheral Artery Disease OR Superficial Femoral Artery OR Popliteal Artery OR Femoropopliteal. The search was limited to human studies. No language restrictions were applied. Abstracts and meeting presentations were excluded.

After completion of the electronic search, 2 investigators (MSK and AM) independently reviewed study titles and

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See page 187 for disclosure information.

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abstracts. Studies that fulfilled the inclusion criteria were retrieved for full text evaluation. Any disagreement was discussed with a third investigator (ARK) and resolved by consensus. A study was considered eligible for inclusion in the analysis if it was; (1) randomized and controlled, and; (2) compared at least 2 of treatment modalities in a patient population with a new or restenotic lesion of the femoropopliteal artery. BA, BMS, CS, DCB, and DES treatment modalities were included. The quality of the included studies and potential risks of bias was evaluated by the Cochrane risk of bias tool.

The primary outcomes of interest in this analysis were freedom from TLR and primary patency. TLR was defined as the need for any repeat revascularization procedure because of in-lesion restenosis. Primary patency was defined as freedom from TLR and the absence of restenosis of ≥50% as determined by invasive vascular angiography or Doppler ultrasonography. Follow-up duration was set to 12 months as that was the most commonly reported duration among eligible studies.

This network meta-analysis was conducted under a Bayesian approach using Markov Chain Monte Carlo simulation. The number of outcome events was assumed to follow a binomial distribution and a generalized linear mixed model with fixed intercepts was used to calculate the posterior distributions of model parameters. The summary statistical measure used was the odds ratio (OR) with 95% credible intervals (CrI). To ensure that data drives the analysis, noninformative previous distributions (vague) were selected. Both direct and indirect treatment comparisons were performed, and results were presented using contrast treatment effect plots. A contrast treatment effect plot is a forest plot of estimated effect with CrIs for all possible comparisons. The probability that each treatment was best was estimated to provide a more comprehensive measure of treatment efficacy. Rank probabilities were depicted graphically and numerically by construction of rankograms. Cumulative rank probabilities for each treatment and the surface under the cumulative rank curve (SUCRA) were calculated. The SUCRA plot is used to provide a hierarchy of the treatments and accounts for both the location and the variance of all relative treatment effects. The advantage of the SUCRA plot over ranking treatments according to their probability of being best is that it accounts for uncertainty in the relative treatment effects. SUCRA values range from 0 to 1. Values close to 1 indicate therapies that are ranked highly; values closer to zero indicate lower ranked therapies.

Model fit was assessed with the Deviance Information Criterion and posterior mean of the total residual deviance. The DIC is a measure of model fit that accounts for model complexity. When comparing 2 Deviance Information Criterion values, a difference of 5 or greater is regarded as a meaningful difference. Transitivity (that there are no significant differences between the comparison groups other than

Table 1
Baseline variables from the included trials grouped by treatment comparisons

Characteristic	BMS vs BA [n] Mean (SD)	CS vs BA [n] Mean (SD)	DCB vs BA [n] Mean (SD)	DES vs BA [n] Mean (SD)	BMS vs CS [n] Mean (SD)	BMS vs DES [n] Mean (SD)
Trials	5	1	12	1	2	2
Average age (years)	[5] 68 (2.5)	[1] 68	[12] 69 (2.0)	[1] 68	[2] 68 (2)	[2] 70 (5)
Men	[5] 67 (10%)	[1] (74%)	[12] 65 (6%)	[1] 65%	[2] 67 (4)%	[2] 69 (4%)
Hypertension	[5] 83 (10%)	[1] (67%)	[11] 81 (9.5%)	[1] 85%	[2] 72 (16)%	[2] 76 (10%)
Smoker	[4] 54 (25%)	[0] NA	[10] 48 (22%)	[1] 85%	[2] 77 (11)%	[2] 58 (28%)
Lesion length (mm)	[5] 74 (34)	[1] 182	[11] 86 (31)	[1] 65	[2] 183 (2)	[2] 93 (14)
Occlusion	[5] 42 (30)	[1] 24	[9] 24 (8)	[1] 27	[2] 67 (11)	[1] 63
Average BMI	[3] 30 (0.5)	[0] NA	[4] 30 (3)	[1] 28	[0] NA	[1] 22
Hyperlipidemia	[2] 75 (20)	[0] NA	[9] 65 (20)	[0] NA	[1] 68	[1] 64
Coronary disease	[2] 41 (3)	[0] NA	[4] 4 (7)	[0] NA	[1] 2	[1] 46
Carotid disease	[3] 47 (29)	[0] NA	[1] 17	[0] NA	[0] NA	[0] NA

A = artery; BA = balloon angioplasty; BMS = bare metal stent; BMI = body mass index; CS = covered stent; DCB = drug-coated balloon; DES = drug-eluting stent; N = number of trials reporting outcomes; NA = not available; SD = standard deviation.

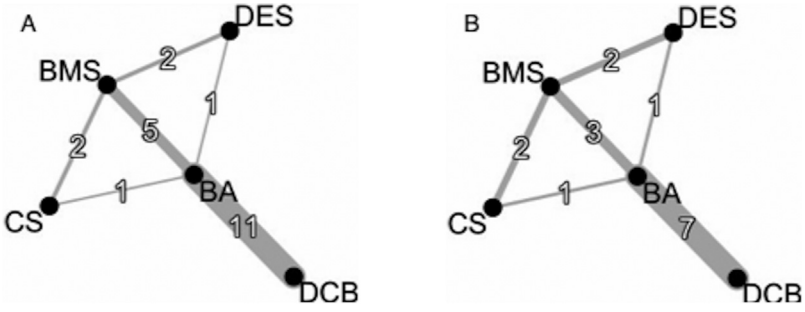

Figure 1. *(A)* Network of evidence for freedom from target lesion revascularization. *(B)* Network of evidence for primary patency. The edges connecting the treatment nodes denote direct head-to-head comparisons. The number on the line indicates the number of trials for each comparison. The line thickness is proportional to the number of trials for each comparison. BA = balloon angioplasty; BMS = bare metal stent; CS = covered stent; DCB = drug-coated balloon; DES = drug-eluting stent.

Table 2
Design and outcomes of included trials

RCT	Year	Design	Comparison	Number of patients (experimental/control)	TLR at 12 months		Primary patency at 12 months	
					Experimental	Control	Experimental	Control
ABSOLUTE	2006	Single center, Open label	BMS v BA	104 (51/53)	14	16	NA	NA
FAST	2007	Multicenter, Open label	BMS v BA	244 (123/121)	19	19	112	38
RESILIENT	2010	Multicenter, Open label	BMS v BA	206 (134/72)	17	40	109	26
SUPER	2012	Multicenter, Open label	BMS v BA	150 (74/76)	9	15	28	26
ETAP	2013	Multicenter, Open label	BMS v BA	246 (119/127)	15	44	64	48
VIABAHN	2008	Multicenter, Open label	CS v BA	197 (97/100)	34	59	14	9
VIBRANT	2013	Multicenter, Single blind	CS v BMS	148 (72/76)	12	14	63	55
VIASTAR	2013	Multicenter, Single blind	CS v BMS	141 (72/69)	13	16	45	30
THUNDER	2008	Multicenter, Single blind	DCB v BA	102 (48/54)	5	26	NA	NA
FEMPAC	2008	Multicenter, Single blind	DCB v BA	87 (45/42)	NA	NA	NA	NA
PACIFIER	2012	Multicenter, Single blind	DCB v BA	91 (44/47)	3	15	NA	NA
LEVANT-I	2014	Multicenter, Single blind	DCB v BA	101 (49/52)	13	14	30	23
LEVANT-II	2015	Multicenter, Single blind	DCB v BA	476 (316/160)	35	24	172	71
IN. PACT SFA	2015	Multicenter,Single blind	DCB v BA	331 (220/111)	5	22	157	54
BIOLUX P-1	2015	Multicenter, Single blind	DCB v BA	60 (30/30)	4	10	NA	NA
ACOART I	2016	Multicenter, Single blind	DCB v BA	200 (100/100)	7	38	67	30
ILLUMENATE PIVOTAL	2017	Multicenter, Single blind	DCB v BA	300 (200/100)	15	16	135	53
ILLUMENATE EU	2017	Multicenter, Single blind	DCB v BA	294 (222/72)	9	6	188	40
CONSEQUENT	2017	Multicenter, Single blind	DCB v BA	153 (78/75)	13	26	NA	NA
MD 2113-SFA	2018	Multicenter, Single blind	DCB v BA	100 (68/32)	2	6	58	15
ZILVER PTX	2011	Multicenter, Open label	DES v BA	474 (236/238)	21	39	181	74
SIROCCO	2006	Multicenter, Double blind	DES v BMS	93 (47/46)	1	0	NA	NA
DEBATE in SFA	2018	Multicenter, Open label	DES v BMS	170 (85/85)	3	8	55	49

BA = balloon angioplasty; BMS = bare metal stent; CS = covered stent; DCB = drug-coated balloon; DES = drug-eluting stent; NA = not available; RCT = randomized control trial; TLR = target lesion revascularization; v = versus.

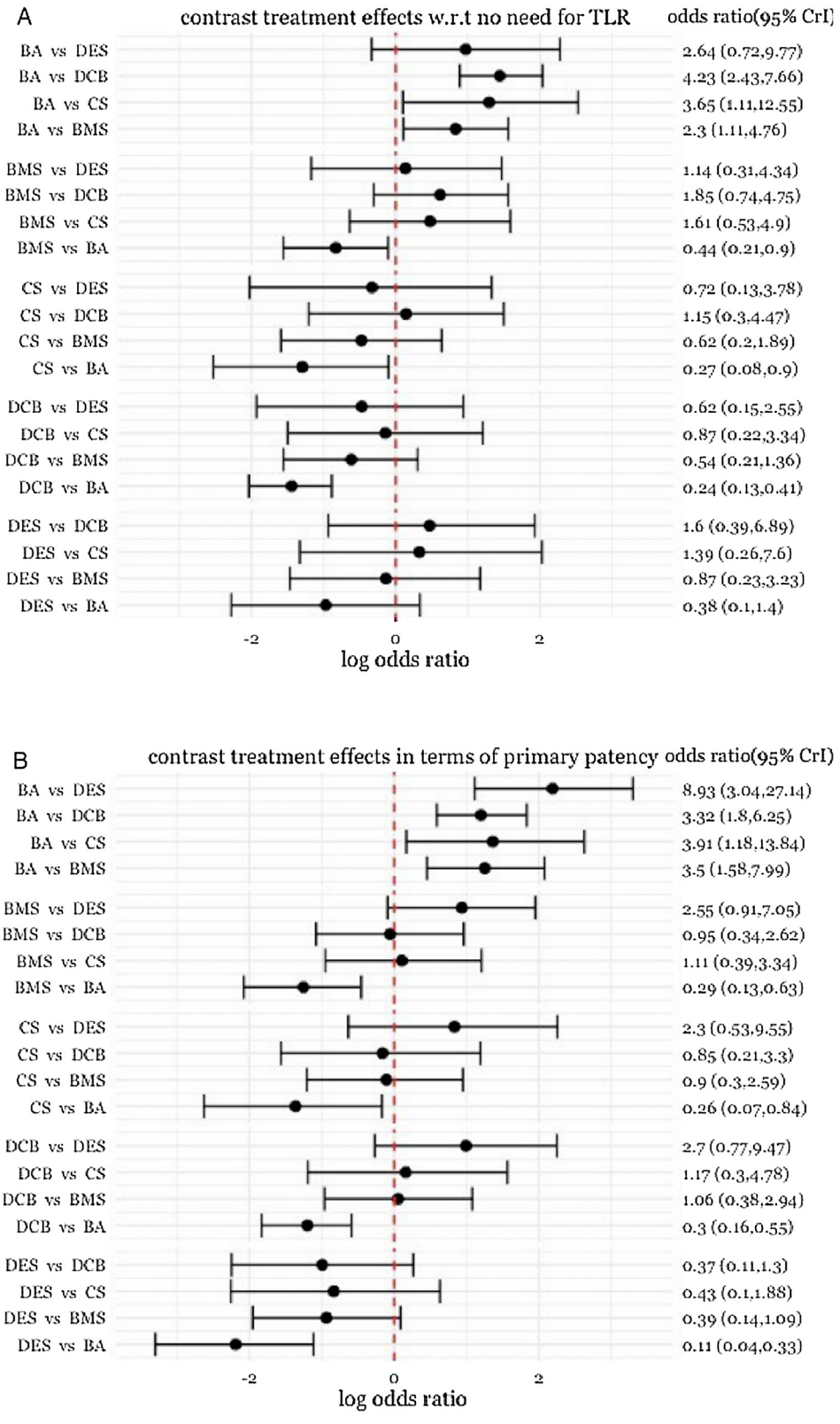

Figure 2. *(A)* Contrast treatment effect plot for freedom from target lesion revascularization. *(B)* Contrast treatment effect plot for primary patency. BA = balloon angioplasty; BMS = bare metal stent; CrI = credible interval; CS = covered stent; DCB = drug-coated balloon; DES = drug-eluting stent, TLR = target lesion revascularization; w.r.t = with respect to; vs = versus.

the treatment being compared) was assessed by extracting baseline patient characteristics from all studies and comparing the distribution of these characteristics in each comparison group. Network inconsistency was assessed by the node splitting method. When there is a closed loop in the network, the node splitting method separates the direct evidence on that comparison from the indirect evidence. For the network to be consistent, the direct and indirect effect estimates should be similar to each other. Direct and indirect effect estimates were compared using a Z-test and a p value of <0.05 was considered evidence of network inconsistency. All analyses were performed in the GeMTC package in R using a link to the JAGS program. Risk of bias assessment was performed using RevMan v5.3.5.

Results

The initial search identified 2,755 potentially relevant articles, of which 2,419 remained after removing duplicates. After applying eligibility criteria, 23 RCTs[4–26] comparing a subset of the 5 treatments of interest were selected (Supplementary Figure 1). Baseline study characteristics by treatment comparisons tested are summarized in Table 1. There were 12 DCB versus BA,[12–23] 5 BMS versus BA,[4–8] 2 BMS versus CS and BMS versus DES[10,11,25,26] and 1 CS versus BA and DES versus BA[9,24] studies. Most baseline characteristics were evenly distributed across studies excepting lesion length and percentage of total occlusions. Studies that compared CS versus BA and BMS versus CS-recruited patients with longer lesions than other comparison groups. The proportion of patients with total occlusions was higher in BMS versus CS and BMS versus DES comparison groups as compared with the remaining treatment groups. Summary data for each study are provided in Supplementary Table 1.

The risk of bias assessment for the included trials is presented in Supplementary Figure 2. All trials reported using random sequence generation. Concealment of allocation was not mentioned in 7 trials and therefore risk of allocation concealment remains unclear in these trials.[6,9,10,12,16,22,23] Only 1 trial had double-blind study design and therefore was at low risk of performance bias.[25] The remainder of the trials were either single blinded or had open label study design.[4–24,26] The risk of performance bias was high in these trials as the operators were not blinded to the assigned treatment. Twenty-one trials clearly stated blinding of outcomes assessment and therefore had lower risk of detection bias[4–8,10,12–25]; whereas risk of detection bias was unclear in 3 trials.[9,11,26] Risk of attrition bias was deemed high in 2 trials due to high loss of follow up.[10,18] In the rest of the studies, the risk of attrition bias was low.[4–9,11–17,19–26] In 4 trials there was unclear risk of reporting bias as data werenot presented for some of the outcomes,[6,10,11,17] whereas it was deemed low for the rest.[4,5,7–9,12–16,18–26]

Twenty-two trials including 4,381 participants provided data on TLR at 12 months.[4–12,14–26] Sixteen trials including 3,691 participants provided data on primary patency at 12 months.[6–11,15–21,23,24,26] The networks of evidence for these 2 outcomes are shown in Figure 1 and reported outcomes of TLR and primary patency for each trial is shown in Table 2.

Compared with BA, DCB (OR 4.23; 95% CrI 2.43 to 7.66), CS (OR 3.65; 95% CrI 1.11 to 12.55), and BMS (OR 2.3; 95% CrI 1.11 to 4.76) were associated with greater freedom from TLR. TLR was numerically but not statistically lower for DES compared to BA (OR 2.64; 95% CrI 0.72 to 9.77). No significant differences were identified among remaining pairwise comparisons (Figure 2). Figure 3 contains rankograms and probability of being the best treatment for each of these treatments. DCB was ranked highest with 47% probability of being the best, followed by CS (36%), DES (16%), BMS (1%), and BA (0%). Figure 4 illustrates the cumulative probabilities as well as the SUCRA values. DCB was ranked highest with a SUCRA of 0.82, followed by CS, DES, BMS, and BA with SUCRAs of 0.72, 0.52, 0.42, and 0, respectively.

All treatment modalities showed significant improvement in primary patency at 12 months as compared with BA (DES vs BA; OR 8.93; 95% CrI 3.04 to 27.14, CS vs BA; OR 3.91; 95% CrI 1.18 to 13.84, DCB vs BA; OR 3.32; 95% CrI 1.8 to 6.25, BMS vs BA; OR 3.5; 95% CrI 1.58 to 7.99). No significant differences were identified in the remaining pairwise comparisons. Figure 2 shows contrast treatment effect plot of all the treatment modalities. Figure 3 shows rankograms and probability of being the best treatment for each compared treatment. DES had an 84% probability being the best treatment, followed by CS

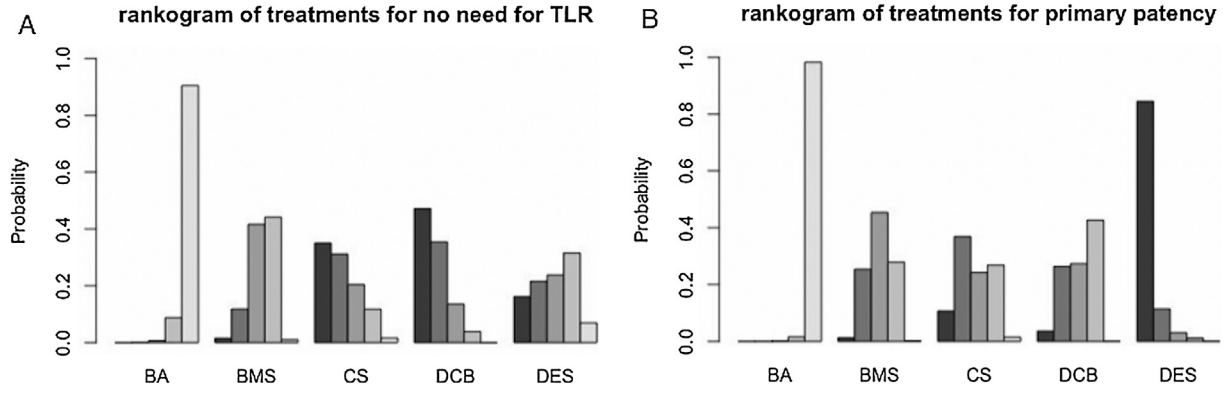

Figure 3. *(A)* Rankogram for target lesion revascularization. *(B)* Rankogram for primary patency. Ranks run from first (darkest color) to fifth (lightest color) from left to right. The height of the bar indicates the probability of the rank. BA = balloon angioplasty; BMS = bare metal stent; CS = covered stent; DCB = drug-coated balloon; DES = drug-eluting stent; TLR = target lesion revascularization.

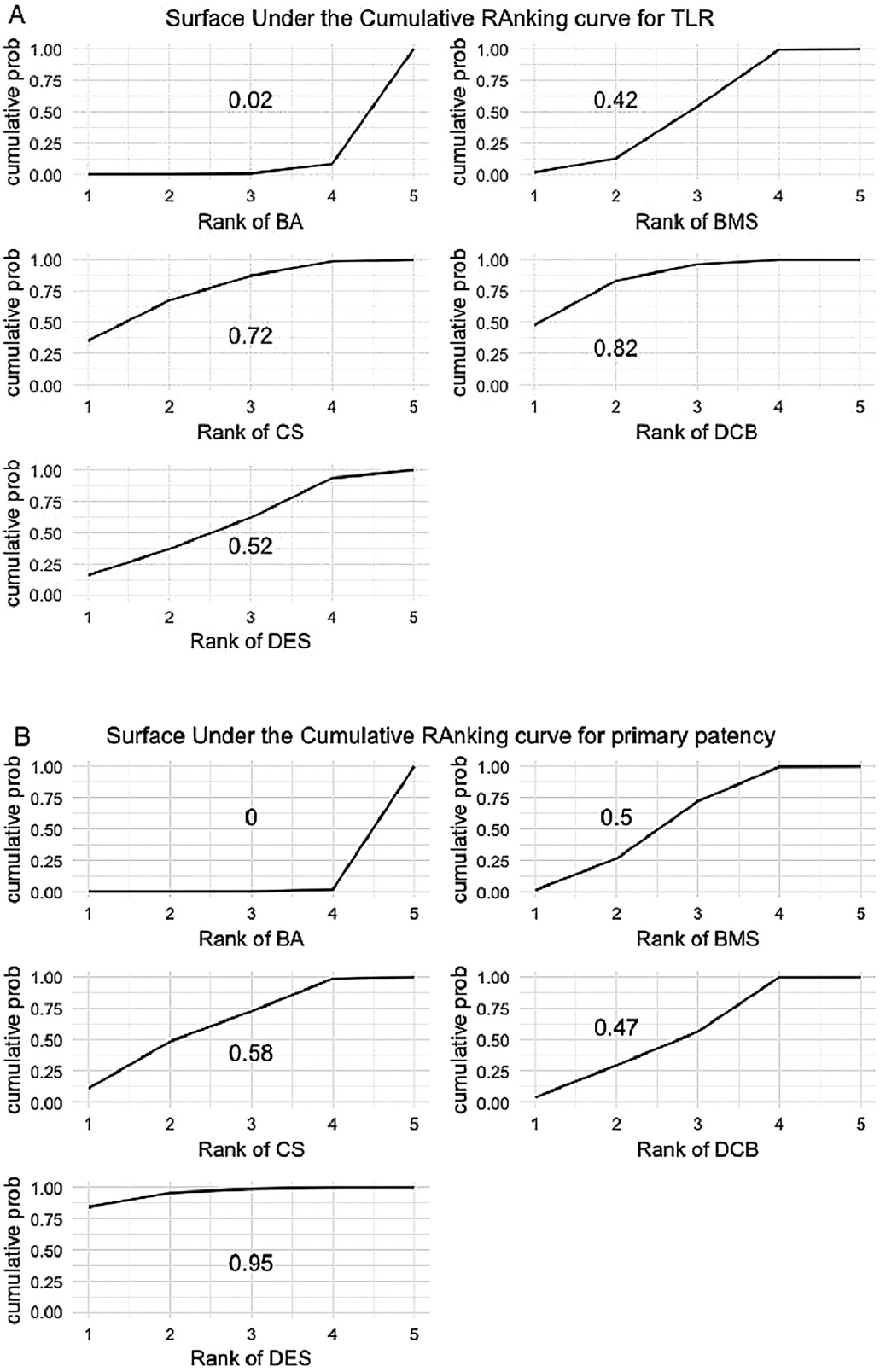

Figure 4. *(A)* Cumulative rank probability plot with SUCRA score for freedom from target lesion revascularization. *(B)* Cumulative rank probability plot with SUCRA score for primary patency. BA = balloon angioplasty; BMS = bare metal stent; CS = covered stent; DCB = drug-coated balloon; DES = drug-eluting stent; prob = probability; TLR = target lesion revascularization.

(11%), DCB (4%), BMS (1%), and BA (0%). Figure 4 shows the cumulative probabilities and SUCRA values. DES was the highest ranked treatment with a SUCRA of 0.96 followed by CS, DCB, BMS, and BA with SUCRAs of 0.57, 0.47, 0.5, and 0 respectively.

As shown in Figure 1, the 2 closed loops are the triangles CS-BA-BMS and BA-BMS-DES. Supplementary Tables 2 and 3 show direct, indirect and network relative estimates for all pairs of treatments in closed loop based on a node-splitting analysis for end points of freedom from TLR and primary patency respectively. No evidence of inconsistency was found in any of the loop, meaning there was agreement between direct and indirect sources of evidence.

Discussion

We conducted a comprehensive network meta-analysis comparing currently approved definitive endovascular revascularization modalities for femoropopliteal disease. The direct comparison by pairwise analysis showed significantly lower TLR for DCB, CS, and BMS compared with BA and significantly improved primary patency for DCB, DES, CS, and BMS compared with BA. Two-way comparisons indicated that results were slightly different for the 2 outcomes of interest; DCB was the most efficacious treatment for improving freedom from TLR and DES was most efficacious for improving primary patency at 12 months.

One possible explanation for the discrepancy between TLR and primary patency findings is differential end point reporting across trials. The outcome, primary patency was not uniformly reported, which could be a potential source of bias impacting the pooled effect estimate. Another plausible explanation is that outcome definitions differed across included trials. We found that definitions of primary patency and TLR varied among included trials. Definitions for both are based on absence of restenosis of ≥50% determined by objective imaging methods. Of these, doppler ultrasonography is the most commonly used imaging method to identify restenosis. Classically, a of ratio highest peak systolic velocity in the stenotic segment compared with a segment of artery proximal to the stenosis (peak systolic velocity ratio of ≥2 was taken to represent >50% stenosis. However, recent data have suggested that a peak systolic velocity ratio ≥2.4 is a more accurate representation of >50% stenosis and is now the more commonly accepted definition. That RCTs comparing DCB and DES directly have not produced similar discrepancies also suggests this finding may be spurious; in the only published head to head RCT comparing DCB with DES for femoropopliteal disease, no such discrepancy between PP and TVR was observed,[27] nor was this discrepancy manifest in a meta-analysis of RCTs comparing DCB with DES for infrapopliteal disease.[28] Nonetheless, the results of our analysis clearly indicate that both DCB and DES are effective treatment strategies for both outcomes of interest for femoropopliteal disease.

The present network meta-analysis differs from previously conducted network metanalyses[29,30] in several aspects: (1) it provides the most updated evidence with inclusion of recently published RCTs[19–23]; (2) we have focused our analysis on TLR and primary patency, which are the 2 most commonly reported efficacy outcomes in the clinical trials and are considered clinically meaningful methods of evaluating treatment modalities in femoropopliteal PAD; and (3) it systematically assesses the key assumptions of network meta-analysis including transitivity and consistency by comparing direct and indirect evidence by the node splitting method.

There are a number of noteworthy limitations to the present study. First, despite including 12 trials comparing DCB and BA, only 1 trial each compared DES and CS versus BA. Second, data on quality of life, mortality, and amputation outcomes were not routinely available. Third, baseline characteristics such as lesion location, lesion length, severity of disease, degree of calcification, and total occlusions differed among included studies and might be a source of heterogeneity. Also, there were differences in adjunct treatment including atherectomy devices as well as medical therapy with lipid lowering and antiplatelets drugs among studies. Although, the node splitting method with comparison of direct and indirect evidence was used, some inconsistency among studies remains unexplained.

In conclusion, among endovascular treatment modalities for femoropopliteal artery disease, DCB results in the lowest need for repeat revascularization. In contrast, DES has the highest primary patency rates. TLR was significantly reduced with DCB, CS, and BMS compared with BA, and primary patency was significantly greater with DCB, DES, CS, and BMS compared with BA.

Disclosures

Dr. Aronow is on the Data Safety and Monitoring Board for the Philips ILLUMENATE Global ISR study.

CRediT Author Statement

Mohammad Saud Khan: Conceptualization, Methodology, Writing-Original Draft. Fuyu Zou: Software, Formal analysis, Data Curation. Abdur Rahman Khan: Investigation, Visualization. Abdelmoniem Moustafa: Investigation, Visualization. Christopher H. Schmid: Software, Resources, Data curation. Muhammad Baig: Visualization, Validation. Omar N. Hyder: Supervision. Herbert D. Aronow: Writing- Review and Editing, Validation, Supervision.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.05.015.

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