

Comparative efficacy of five balloons for treating autogenous arteriovenous fistula stenosis: a Bayesian network meta-analysis

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Background: Arteriovenous fistula (AVF) was the lifeline of patients with maintenance hemodialysis (MHD). However, stenosis of AVF may limit its use. Currently, AVF stenosis is commonly treated with balloon angioplasty. Meanwhile, several balloons were available. Therefore, this study aimed to explore the effectiveness of angioplasty with five different balloons in patients with AVF stenosis.

Methods: A network meta-analysis (NMA) was performed to synthesize direct and indirect evidence. We carried out a comprehensive literature search in PubMed, Embase, the Cochrane Central Register of Controlled Trials, Scopus, and ClinicalTrials.gov databases from database inception to January 31, 2021. The main outcomes were primary patency rates of AVF after 3, 6, 9, and 12 months. The NMA was performed using Stata 15 (network and mymeta commands) and GeMTC software.

Results: Twenty randomized controlled trials (RCTs) involving 2,607 participants were included. Direct meta-analyses revealed no significant difference in primary patency rates between different balloons after 3, 6 and 9 months. However, NMA demonstrated that the effectiveness of plain balloon angioplasty (PBA) was inferior to that of the drug-coated balloon (DCB) after 3 and 9 months. Moreover, the results suggested that the high-pressure balloon (HPB) was inferior to DCB after 9 months. Thereafter, the analysis of the surface under the cumulative ranking curve (SUCRA) revealed that DCB was ranked as the first effective treatment after 3 months. The drug-eluting balloon (DEB) was the most effective treatment after 6, 9, and 12 months. The analyses revealed no significant publication bias.

Discussion: DEB may be the most effective treatment of AVF stenosis, followed by DCB. However, prospective studies involving large sample sizes of clinical trials and a direct comparison between DEB and DCB are required to clarify the individual value of different treatment options.

Keywords: Arteriovenous fistula (AVF); network meta-analysis (NMA); plain balloon angioplasty (PBA); new type of balloon

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Introduction

Chronic kidney disease (CKD) is a condition of irreversible destruction of renal parenchyma, with a progressive loss of kidney function over several years. Meanwhile, the morbidity of CKD has gradually increased in the last decades (1). Maintenance hemodialysis (MHD) has been recommended as the best alternative for renal transplants due to the shortage of donor organs. However, patients undergoing MHD need a functional vascular access. This is especially critical for the patients' survival and quality of life. Autogenous arteriovenous fistula (AVF) is the optimal vascular access for patients undergoing MHD, which is reflected in the Kidney Disease Outcomes and Quality Initiative guidelines (2). AVF is constructed by the subcutaneous anastomosis of an artery with an adjacent vein. Meanwhile, radiocephalic AVF may be the first choice (3). However, the application of AVF may be limited by vascular stenosis, which may attribute to intimal hyperplasia.

Balloon angioplasty (BA) has been recommended for treating AVF stenosis by the ESVES European guidelines (4). The first widely adopted endovascular treatment for AVF stenosis was plain balloon angioplasty (PBA), which remains a common treatment. However, it is susceptible to acute vessel elastic recoil. Therefore, several new types of balloons have been proposed and tested. High-pressure balloon (HPB), whose burst pressure is more than 14 atm, may be better for resistant lesions than PBA (5). An alternative to HPB is a cutting balloon (CtB). The application of CtB in treating resistant stenosis was first described in 1995 in a case report (6). Three or four cutting blades were incorporated into the CtB. It could cut and disrupt the fibroelastic continuity of the ring of neointimal hyperplasia. A drug-coated balloon (DCB) and a drugeluting balloon (DEB) are also common balloons; both of them have a drug coating. However, the manufacturing processes may not be identical, leading to differences in effectiveness. In general, direct evidence on different balloons is rare. Therefore which new type of balloons can provide better outcomes still remains unclear.

Network meta-analysis (NMA) is a new research strategy in which direct evidence of different treatments can be combined with indirect evidence derived from studies sharing a common comparator within the network frame (7,8). NMA has gained interest among doctors based on its importance in assessing the comparative effectiveness of different treatments in clinical practice. Therefore, the study was conducted to comprehensively analyze the effectiveness of different balloons in patients with AVF stenosis. We present the following article in accordance with the PRISMA reporting checklist (available at https://apm.amegroups.com/ article/view/10.21037/apm-21-2898/rc) (9).

Methods

Search strategy and data extraction

We searched PubMed, Embase, the Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, and Scopus databases to identify published studies related to AVF stenosis and their various treatments from database inception to January 31, 2021. Both subject words and free words were used to retrieve information. We used the search terms "autogenous arteriovenous fistula*" OR "arteriovenous fistula*" OR "AV fistula*" OR "AVF" combined with a list of endovascular treatments (PBA, HPB, CtB, DCB, and DEB).

Two investigators (Yu Li and Wenhao Cui) within the reviewing team reviewed retrieved references independently. Any discrepancies were resolved by consensus and arbitrated by a third investigator (Tao Luo). The following data were collected from the references: patient characteristics, site of lesions, type of AVFs, and patency rates of AVF after 3, 6, 9, and 12 months. In the absence of information or supplementary data from the authors, patency rates were acquired with validated software (10).

Selection criteria

- (I) Studies included in the NMA were randomized controlled trials (RCTs) from database inception to January 31, 2021;
- (II) Stenotic AVF was defined as stenosis ≥50%, and the blood flow rate (Qa) in the fistula was less than 500 mL/min, which could not meet the requirement of MHD;
- (III) No restriction was imposed with regard to the publication status and language;
- (IV) Studies were limited to human trials, with at least 3 months of follow-up.

Exclusion criteria

- Unrelated research, repeated literature, reviews, case reports, animal experiments, letters, and anatomical reports;
- (II) Different diagnostic criteria or incomplete data;
- (III) Studies that investigated other vascular accesses.

Quality assessment and data extraction

We used the Cochrane risk-of-bias assessment tool to assess the quality and risk of bias of studies, including the following items: allocation sequence generation, allocation concealment, participant masking, personnel and outcome assessors, completeness of outcome data, and selective outcome reporting and other biases. Two investigators (Yu Li and Wenhao Cui) reviewed the studies and judged the risk of bias independently. The main outcome measurements were primary patency rates after 3, 6, 9 and 12 months, which represented the effectiveness of different treatment strategies.

Statistical analysis

First, we carried out a pair-wise meta-analysis. Then, the pooled estimates of odds ratios (ORs) together with the corresponding 95% confidence intervals (CIs) were calculated. The fixed-effects and random-effects models were used to analyze nonheterogeneous and heterogeneous data, respectively. Visual inspection and I^2 statistic of the forest plots were used to investigate the possibility of statistical heterogeneity across studies. Statistical analyses were carried out using Stata version 15.0 with mvmeta command.

Second, the NMA methodology allows the comparison of any two treatments within the network even a direct comparison from a trial is not available. Therefore, NMA was performed to compare different treatments. The models were fit using GeMTC software. ORs <1 or >1 favored one of the compared treatments over the other, whereas ORs equal to 1 indicated equivalent patency rates. Briefly, statistical significance was indicated by the exclusion of 1 from 95% CIs.

The probability values of each treatment were summarized as the surface under the cumulative ranking curve (SUCRA) (0–100%), with larger surface under the curve denoting more effective treatments. The probability of effectiveness of each treatment strategy was assessed, and accordingly, the strategy was documented as the most effective therapy, second best therapy, third best therapy, fourth best therapy, and fifth best effective therapy. All Bayesian results were reported as ORs with corresponding 95% CIs, as well as the ranking probabilities of different treatments.

A variance calculation and a node-splitting analysis using GeMTC software were applied to evaluate the inconsistency within the NMA. Significant inconsistency was scored positive when the P value of disagreement between direct and indirect evidence was more than 0.05. Finally, potential publication bias was estimated using a funnel plot. A roughly symmetrical funnel plot indicated insignificant publication bias. Moreover, ethical approval was not required for this study.

Results

Characteristics of eligible studies

The literature search identified 2,148 published studies. Following duplicate exclusions and abstract screening, 124 potential studies were selected for full-text reading. A total of 104 studies were excluded for the following reasons: 20 were prospective observational studies, 32 were clinical guidelines, and 1 could not be retrieved. Meanwhile, we could not extract any data from 51 studies. Finally, twenty studies (11-30) were selected for NMA, none of which was performed on mutually overlapping populations. The systematic search process is shown in *Figure 1*.

Twenty RCTs were included in the final NMA involving 2,607 patients randomized in 5 treatments. The network plot for the primary patency of AVF is shown in *Figure 2*. Meanwhile, the characteristics of included studies are summarized in *Table 1*. The analysis of the risk of bias of eligible trials and the reporting of methodological quality according to the Cochrane Collaboration tool are shown in *Table 2*. All the eligible trials were generally of high quality.

Pooled weighted outcomes of the direct meta-analysis

The results of the conventional pair-wise meta-analysis of primary patency are presented in *Figure 3A,3B*. Regarding stenotic AVF, treatment with new balloons was more efficient than treatment with PBA. In terms of primary patency, the OR of new balloon versus PBA after 3, 6, 9, and 12 months was 1.77 (95% CI, 1.32–2.36; P=0.802), 2.16 (95% CI, 1.73–2.69; P=0.095), 1.78 (95% CI, 1.46–2.17; P=0.061), and 1.62 (95% CI, 1.27–2.07; P=0.004), respectively. A funnel plot representing the publication bias of the studies is presented in *Figure 4*. The funnel plot was symmetrical, indicating a slight publication bias.

NMA for primary patency

Figure 5 shows a summary of the results of the multipletreatment meta-analyses regarding patency rates after 3, 6, 9, and 12 months according to the network plot. As shown in the figure, the effectiveness of PBA was inferior to that of DCB after 3 and 9 months, and the OR was 0.62 (95%

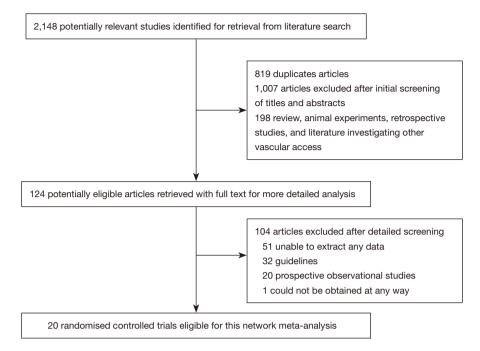


Figure 1 Study selection process.

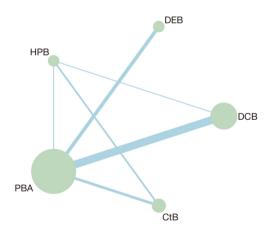


Figure 2 NMA of eligible comparisons for primary patency rates. Width of the lines is proportional to the number of trials comparing every pair of treatments. Size of every circle is proportional to the number of randomly assigned participants (i.e., sample size). HPB, high-pressure balloon; PBA, plain balloon angioplasty; DEB, drug-eluting balloon; DCB, drug-coated balloon; CtB, cutting balloon; NMA, network meta-analysis.

CI, 0.34–0.82) and 0.53 (95% CI, 0.23–0.74), respectively. Moreover, the results suggested that HPB was inferior to DCB after 9 months, and the ORs were 0.35 (95% CI, 0.08–0.37). In addition, the coherence between direct and indirect comparisons based on networks was confirmed.

Rank probabilities

The SUCRA values are depicted in *Figure 6*. A large SUCRA value scored positive, indicating better treatment. Based on the network plot, the cumulative probabilities of the most efficacious treatments were (patency rates after 3, 6, 9, and 12 months) as follows, respectively: DEB (67%, 86.1%, 84.2%, and 80%), DCB (70.5%, 59%, 78.3%, and 74.1%), CtB (65.2%, 73.2%, 50.7%, and 42.8%), HPB (31.5%, 14.5%, 8.4%, and 25.1%), and PBA (15.8%, 17.1%, 28.4%, and 28.0%). As shown in *Figure 6*, DCB was superior to other balloons in terms of the patency rate after 3 months. Consistent with the result after 3 months, DEB was superior to other balloons after 6, 9, and 12 months.

Discussion

With the increase in the survival time of patients with MHD, the treatments aimed at extending the patency time of AVFs are important. According to the consensus of vascular access experts in China in 2019 (31), the surgical indications of AVF stenosis, including Qa <500 mL/min (could not meet the requirement of hemodialysis), high static pulse pressure, and puncture complications leading

Table 1 Characteristics of the studies included in NMA

Ctudy	Palloona	Sample	Outcome of interest			Type of AVF			Site of target		
Study	Balloons	size	3 months	6 months	9 months	12 months	R-C	B-C	B-B	Other	lesion
Rasuli,	CtB	19	11	5	4	2	10	9	-	-	AN, OV, CA,
2015 (11)	HPB	20	14	8	6	5	7	13	-	-	other
Wakamoto,	PBA	32	26	20	19	15	-	-	-	-	AN, OV
2018 (12)	HPB	37	30	21	19	18	-	-	-	-	
Lai, 2014 (13)	PBA	10	6	0	0	0	10	-	-	-	Un-report
	DCB	10	10	7	4	2	10	-	-	-	
Kitrou,	HPB	20	15	6	4	2	-	-	-	-	AN, OV
2015 (14)	DCB	20	17	13	11	5	-	-	-	-	
Fukasawa,	PBA	57	45	28	16	-	-	-	-	-	AN, OV, other
2019 (15)	DCB	111	93	63	34	-	-	-	-	-	
Lučev,	PBA	31	29	19	16	9	20	8	3	-	AN, IN
2018 (16)	DCB	31	31	28	26	24	17	12	2	-	
Maleux,	PBA	31	25	20	-	12	13	15	2	1	Un-report
2018 (17)	DCB	33	29	22	-	14	17	11	3	2	
Lookstein,	PBA	160	142	88	76	-	-	-	-	-	Un-report
2020 (18)	DCB	170	164	125	123	-	-	-	-	-	
Trerotola,	PBA	144	125	80	42	7	-	-	-	-	AN, OV, CA,
2020 (19)	DCB	141	130	97	66	28	_	-	_	_	IN, CZ
Björkman,	PBA	18	17	14	12	10	17	1	_	_	Un-report
2019 (20)	DCB	18	12	4	3	2	16	2	_	_	
Moreno-	PBA	78	65	45	43	37	_	-	_	_	AN, CA
Sánchez, 2020 (21)	DCB	70	60	57	44	41	-	-	-	-	
Teo, 2013 (22)	PBA	30	-	18	-	-	-	-	-	-	Un-report
	DEB	30	-	21	-	-	-	-	-	-	
Kitrou,	PBA	20	4	2	1	0	-	6	1	13	AN, OV
2015 (23)	DEB	20	6	4	4	2	-	7	1	12	
Irani, 2018 (24)	PBA	60	42	28	22	15	30	18	7	5	AN, OV, CZ
	DEB	59	50	42	29	26	40	10	9	0	
Swinnen,	PBA	60	58	28	31	14	33	11	9	7	Un-report
2019 (25)	DEB	68	65	52	50	25	39	13	7	9	
Kariya,	PBA	52	31	18	17	13	-	-	-	-	AN, OV
2007 (26)	CtB	62	50	43	32	24	-	-	-	-	
Saleh,	PBA	307	125	105	84	71	-	-	-	-	AN, OV, IN
2014 (27)	CtB	316	151	138	105	76	-	-	-	-	
Murakami,	PBA	77	-	11	-	-	-	-	-	-	Un-report
2019 (28)	CtB	80	-	23	-	-	-	-	-	-	
Aftab,	HPB	35	28	13	5	3	9	19	5	2	AN, CA, CZ
2014 (29)	CtB	36	32	23	11	9	17	15	2	2	
Roosen, 2017 (30)	PBA DCB	18 16	15 11	8 3	-	3 2	-	-	-	-	Un-report

NMA, network meta-analysis; CtB, cutting balloon; HPB, high-pressure balloon; PBA, plain balloon angioplasty; DCB, drug-coated balloon; DEB, drug-eluting balloon; AVF, arteriovenous fistula; R-C, radiocephalic; B-C, brachiocephalic; B-B, brachiobasilic; AN, anastomotic lesion; OV, outflow venous; CA, cephalic arch; IN, inflow lesion; CZ, cannulation zone.

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RCTs	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other biases
Rasuli, 2015	Low risk	Unclear	Unclear	Low risk	Low risk	Unclear	Low risk
Wakamoto, 2018	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk
Lai, 2014	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Kitrou, 2015	Low risk	Low risk	High risk	Unclear	Low risk	Unclear	Low risk
Fukasawa, 2019	Low risk	Low risk	Unclear	Unclear	Low risk	Unclear	Low risk
Lučev, 2018	Low risk	Unclear	Low risk	Low risk	Low risk	Unclear	Low risk
Maleux, 2018	Low risk	Low risk	High risk	Unclear	Low risk	Unclear	Low risk
Lookstein, 2020	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Trerotola, 2020	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Björkman, 2019	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk
Moreno- Sánchez, 2020	Low risk	Unclear	High risk	Low risk	Low risk	Unclear	Low risk
Teo, 2013	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Kitrou, 2015	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk	Low risk
Irani, 2018	Low risk	Unclear	High risk	Unclear	Low risk	Low risk	Low risk
Swinnen, 2019	Low risk	Unclear	Unclear	Low risk	Low risk	Unclear	Low risk
Kariya, 2007	Unclear	Unclear	Unclear	Low risk	Low risk	Unclear	Low risk
Saleh, 2014	Low risk	Low risk	Unclear	Low risk	Unclear	Unclear	Low risk
Murakami, 2019	Unclear	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk
Aftab, 2014	Unclear	Unclear	Unclear	Low risk	Low risk	Unclear	Low risk
Roosen, 2017	Low risk	Unclear	Unclear	Low risk	Low risk	Unclear	Low risk

Table 2 Analysi	s of the risk of	bias according to	the Cochrane	Collaboration tool
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RCTs, randomized controlled trials.

to low dialysis adequacy. However, the conclusions of previous studies were inconsistent, presenting a challenge that required urgent resolution. BA is often performed using PBA, HPB, CtB, DCB, and DEB. PBA is the most common one among the balloons. Therefore, we used it as a reference treatment.

The results of direct meta-analyses revealed that new types of balloons might not be superior to PBA in terms of primary patency after 3, 6, and 9 months. Moreover, the primary patency rate of new balloons after 12 months was significantly better than of PBA.

However, the results of the NMA revealed that the shortterm (3 and 6 months) outcomes of HPB were better than those of PBA. However, our study failed to demonstrate that the long-term (9 and 12 months) outcomes of HPB were also better than those of PBA. Similar conclusions could also be drawn from our previous study (32). A previous study revealed that HPB was superior to PBA in treating coronary atherosclerotic stenosis (33). In addition, the latest Kidney Disease Outcomes Quality Initiative guidelines (2) recommend HPB as a first choice for AVF stenosis, which is partly consistent with the results of our study. The results of our study could be attributed to endothelial damage caused by the high pressure of HPB (34). Schiele et al. also demonstrated that moderate inflation pressure of balloons could benefit patients with restenosis (35). Therefore, although HPB has better short-term treatment outcomes, it was still worse than DCB and DEB, which conformed with the results of RCT performed by Kitrou (14). However, HPB had its unique advantages as well. A retrospective study suggested that the efficacy of HPB for resistant lesions might be better than that of PBA (36). Meanwhile,

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ĸ	Author (year)	3 months	Odds Ratio (95% CI)	Weight%	Author (year)	6 months	Odds Ratio (95% CI)	Weight
	Koki Wakamoto (2018)		0.99 (0.29, 3.32)	100.00	Koki Wakamoto (2018)	+	0.79 (0.30, 2.07)	100.00
	Overall, MH (I ² = 0.0%, p = .)		0.99 (0.29, 3.32)	100.00	Overall, MH ((² = 0.0%, p = .)		0.79 (0.30, 2.07)	100.00
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,	.25 Author (year)	1	4 Odds Ratio (95% CI)	Weight%	.25 Author (year)	1	4 Odds Ratio (95% CI)	Weight
c	Chi-Cheng Lai (2014)		14.54 (0.67, 316.69)	0.00	Chi-Cheng Lai (2014)		45.00 (2.01, 1006.75)	0.0
N	Mizuya Fukasawa (2018)		1.38 (0.61, 3.10)	23.65	Mizuya Fukasawa (2018)	•	1.36 (0.72, 2.58)	19.6
	lernej Luc ⁻ ev (2018)	- <u>-</u>	5.34 (0.25, 115.89)	0.00	Jernej Luc 'ev (2018)	T	5.89 (1.46, 23.73)	2.2
	Geert Maleux (2018) Robert A. Lookstein (2020)		1.74 (0.44, 6.87) 3.46 (1.34, 8.97)	7.66 12.66	Geert Maleux (2018)		1.10 (0.39, 3.09)	8.4
	Scott O. Trerotola (2020)		1.80 (0.82, 3.93)	23.66	Robert A. Lookstein (2020)	-	2.27 (1.43, 3.61)	29.5
	Moreno-Sánchez, T. (2020)		1.20 (0.49, 2.94)	21.54	Scott O. Trerotola (2020)		1.76 (1.09, 2.86)	30.3
	Roosen, L. J. (2017)	• 1	0.44 (0.09, 2.24)	10.82	Moreno-Sánchez, T. (2020)		3.22 (1.52, 6.82)	9.7
c	Overall, MH (l ² = 13.7%, p = 0.323)	_ �	1.78 (1.22, 2.59)	100.00	Overall, MH (l ² = 45.3%, p = 0.089)	\diamond	2.10 (1.62, 2.71)	100.0
	.0039062	1	256		.0009766	1	1024	
	Author (year)		Odds Ratio (95% CI)	Weight%	Author (year)		Odds Ratio (95% CI)	Weigt
	Panagiotis M. Kitrou (2015)		4.50 (0.34, 60.15)	11.42	Panagiotis M. Kitrou (2015)		3.33 (0.36, 30.70)	6.3
	Irani, F. G. (2018)		2.38 (0.42, 13.65)	34.26	Irani, F. G. (2018)		2.70 (1.09, 6.70)	42.1
	Swinnen, J. J. (2019)	•	0.75 (0.12, 4.63)	54.33	Swinnen, J. J. (2019) Overall, MH (1 ² = 0.0%, p = 0.869)		3.71 (1.74, 7.91) 3.26 (1.86, 5.72)	51.5
	Overall, MH (l ² = 0.0%, p = 0.481)		1.74 (0.59, 5.12)	100.00	Civerall, MH (1 = 0.0%, p = 0.009)			100.00
,	.015625 Author (vear)	1	64 Odds Ratio (95% CI)	Weight%	.03125 Author (year)	1	32 Odds Ratio (95% Ci)	Weight
к	Kariya, S. (2007)		2.82 (0.76, 10.44)	12.84	Kariya, S. (2007)		4.34 (1.73, 10.89)	41.13
	Saleh, H. M. (2014)		1.41 (0.78, 2.55)	87.16	Saleh, H. M. (2014)		1.71 (1.04, 2.81)	58.87
	Overall, MH (I ² = 0.0%, p = 0.343)		1.59 (0.93, 2.73)	100.00	Overall, DL (I ² = 67.5%, p = 0.080)		2.50 (1.02, 6.17)	100.00
_	1							
	.125 Study	1	8 Odds Ratio (95% CI)	Weight%	.125 Study	1 8	Odds Ratio (95% CI)	Weigh
			0.99 (0.29, 3.32)	5.59		1		
	HPB				НРВ —		0.79 (0.30, 2.07)	5.21
	DCB		1.78 (1.22, 2.59)	58.64	DCB		2.10 (1.62, 2.71)	73.40
	DEB	-	1.74 (0.59, 5.12)	7.12	DEB		3.26 (1.86, 5.72)	15.40
	СіВ		1.59 (0.93, 2.73)	28.66	CtB		- 2.50 (1.02, 6.17)	6.00
	Overall, IV (I ² = 0.0%, p = 0.802)	\diamond	1.77 (1.32, 2.36)	100.00	Overall, IV (I ² = 53.0%, p = 0.095)	\diamond	2.16 (1.73, 2.69)	100.00
-	.5 1	1.5			.5	1 1.5		
				.5				
3	Author (year)	9 months	Odds Ratio (95% CI)	Weight%	Author (year)	12 months	Odds Ratio (95% CI)	Weight%
			00001000(00100)	in agric se				
		1.			Kali Makamata (2018)	1	4.07 (0.42, 2.77)	100.00
	Koki Wakamoto (2018)	*	0.72 (0.28, 1.88)	100.00	Koki Wakamoto (2018)	-	1.07 (0.42, 2.77)	100.00
	Koki Wakamoto (2018) Overali, MH (l ² = 0.0%, p = .)		0.72 (0.28, 1.88) 0.72 (0.28, 1.88)	100.00 100.00	Overall, MH (I ² = 0.0%, p = .)		1.07 (0.42, 2.77)	100.00 100.00
		1				1		
	Overall, MH (I ² = 0.0%, p = .) I .25 Author (year)		0.72 (0.28, 1.88) I 4 Odds Ratio (95% C1)	100.00 Weight%	Overall, MH (1 ² = 0.0%, p = .)		1.07 (0.42, 2.77)	100.00 Weight%
	Overall, MH (I ² = 0.0%, p = .) .25 Author (year) Mizuya Fukasawa (2018)		0.72 (0.28, 1.88) 4 Odds Ratio (95% CI) 1.13 (0.56, 2.29)	100.00 Weight% 19.27	Overall, MH (I ² = 0.0%, p = .) .5 Author (year) Chi-Cheng Lai (2014)		1.07 (0.42, 2.77) 2 Odds Ratio (95% CI) 6.18 (0.26, 146.78)	100.00 Weight% 0.00
	Overati, Mit (i ² = 0.0%, p = .) 28 Author (verr) Mitzya Fukasawa (2018) Jermej Luc ² ev (2018)		0.72 (0.28, 1.89) 4 Odds Ratio (95% Cl) 1.13 (0.56, 2.29) 4.88 (1.49, 16.00)	100.00 Weight% 19.27 3.39	Overall, MH (1 ² - 0.0%, p = .)		1.07 (0.42, 2.77) 2 Odds Ratio (95% CI) 6.18 (0.26, 146.78) 8.38 (2.67, 26.33)	100.00 Weight% 0.00 6.96
	Overall, MH (I ² = 0.0%, p = .) .25 Author (year) Mizuya Fukasawa (2018)		0.72 (0.28, 1.88) 4 Odds Ratio (95% CI) 1.13 (0.56, 2.29)	100.00 Weight% 19.27	Overall, MH (I ² = 0.0%, p = .) .5 Author (year) Chi-Cheng Lai (2014)		1.07 (0.42, 2.77) 2 Odds Ratio (95% CI) 6.18 (0.26, 146.78)	100.00 Weight% 0.00
	Overati, Mit (i ² = 0.0%, p = .) 28 Author (verr) Mitzya Fukasawa (2018) Jermej Luc ² ev (2018)		0.72 (0.28, 1.89) 4 Odds Ratio (95% Cl) 1.13 (0.56, 2.29) 4.88 (1.49, 16.00)	100.00 Weight% 19.27 3.39	Overall, MH (1 ² - 0.0%, p = .)		1.07 (0.42, 2.77) 2 Odds Ratio (95% CI) 6.18 (0.26, 146.78) 8.38 (2.67, 26.33)	100.00 Weight% 0.00 6.96
	Overati, Mit (i) ² = 0.0%, p = .)		0.72 (0.28, 1.88)	100.00 Weight% 19.27 3.39 28.44	Overall, MH (1 ² = 0.0%, p = .) .s Author (yew) Chi-Cheng Lai (2014) Jemej Luc 'ev (2018) Geet Maleux (2018)		1.07 (0.42, 2.77) 2 Odds Ratio (95% Cl) 6.18 (0.26, 146.78) 8.38 (2.67, 26.33) 1.17 (0.43, 3.17)	100.00 Weight% 0.00 6.96 24.39
	Overrati, MH (t) ² = 0.0%, p = .)		0.72 (0.28, 1.88) 	100.00 Weight% 19.27 3.39 28.44 29.04 19.85	Overall, MH (1 ⁴ = 0.0%, p = .) .s Author (yew) Chi-Cheng Lai (2014) Jemej Luc "ev (2018) Geet Maleux (2018) Scott 0. Trenotal (2020)		1.07 (0.42, 2.77) 2 Cdds Ratio (86% C1) 6.18 (0.26, 146.78) 8.38 (2.67, 26.33) 1.17 (0.43, 3.17) 4.85 (2.04, 11.52)	100.00 Weight% 0.00 6.96 24.39 19.00
	Overrat, MH (I ² = 0.0%, p = .) Author (vew) Mituya Fukasawa (2018) Jernej Luc "ev (2019) Robert A. Lookstein (2020) Soott O. Tierotola (2020) Moreno-Sánchez, T. (2020) Overall, MH (I ² = 52.1%, p = 0.080)		0.72 (0.28, 1.89) 	100.00 Weight% 19.27 3.39 28.44 29.04	Overall, MH (1 ² = 0.0%, p = .) .o Author (yew) Chi-Cheng Lal (2014) Jernel Luc "ev (2016) Geet Maleux (2018) Scott O. Trenolola (2020) Moreno-Sanchez, T. (2020) Overall, MH (1 ² = 64.0%, p = 0.025)		1.07 (0.42, 2.77) 2 Codes Ratio (05% C1) 6.18 (0.26, 146.78) 8.38 (2.67, 26.33) 1.17 (0.43, 3.17) 4.85 (2.04, 11.52) 1.57 (0.82, 3.00) 2.57 (0.82, 3.07)	100.00 Weight% 0.00 6.96 24.39 19.00 49.64
	Overrati, MH (t ² = 0.0%, p = .) Author (vear) Mitzuya Fukasawa (2018) Jarnej Luc "ev (2018) Robert A. Lookstein (2020) Scott O. Trerotola (2020) Moreno-Sánchez, T. (2020) Overall, MH (t ² = 52.1%, p = 0.080) Jozep		0.72 (0.28, 1.89) 	100.00 Weight % 19.27 3.39 28.44 29.04 19.85 100.00	Overall, MH (1 ⁴ = 0.0%, p = .) .o Author (vew) Chi-Cheng Lai (2014) Jemej Luc 'ev (2018) Geef Maleux (2018) Stott D. Trenolai (2020) Moreno-Sänchez, T. (2020) Overall, MH (1 ² = 64.0%, p = 0.025) .co7rs125		1.07 (0.42, 2.77) 	100.00 Weight% 0.00 6.96 24.39 19.00 49.64 100.00
	Overrati, MH (i) ² = 0.0%, p = .)		0.72 (0.28, 1.89) 	100.00 Weight % 19.27 3.39 28.44 29.04 19.85 100.00 Weight %	Overall, MH (1 ² = 0.0%, p = .) .o Author (vew) Chi-Cheng Lai (2014) Jernej Luc 'ev (2018) Geet Maleux (2018) Scott O. Trenotola (2020) Moreno-Sánchez, T. (2020) Overall, MH (1 ² = 64.0%, p = 0.025) 		1.07 (0.42, 2.77) Codis Ratio (85% CI) 6.18 (0.26, 146.78) 8.38 (2.67, 26.33) 1.17 (0.43, 3.17) 4.85 (2.04, 11.52) 1.57 (0.82, 3.00) 2.64 (1.75, 3.97) 128 Odds Ratio (85% CI)	100.00 Weight% 0.00 6.96 24.39 19.00 49.64 100.00 Weight%
	Overati, MH (I ⁰ = 0.0%, p = .)		0.72 (0.28, 1.89) 	100.00 Weight % 19.27 3.39 28.44 29.04 19.85 100.00 Weight %	Overall, MH (1 ² = 0.0%, p = .) .or Author (year) Chi-Cheng Lai (2014) Jernej Luc 'ev (2018) Geett Maleux (2016) Scott O. Trenotola (2020) Moreno-Sanchez, T. (2020) Overall, MH (1 ² = 64.0%, p = 0.025) Author (year) Panagiotis M. Kitrou (2015)		1.67 (6.42, 2.77) 	100.00 Weight% 0.00 6.96 24.39 19.00 49.64 100.00 Weight%
	Overrati, MH (i) ² = 0.0%, p = .)		0.72 (0.28, 1.89) 	100.00 Weight % 19.27 3.39 28.44 29.04 19.85 100.00 Weight % yweight % 2.200	Overall, MH (1 ² = 0.0%, p = .) .o Author (vew) Chi-Cheng Lai (2014) Jernej Luc 'ev (2018) Geet Maleux (2018) Scott O. Trenotola (2020) Moreno-Sánchez, T. (2020) Overall, MH (1 ² = 64.0%, p = 0.025) 		1.07 (0.42, 2.77) Codis Ratio (85% CI) 6.18 (0.26, 146.78) 8.38 (2.67, 26.33) 1.17 (0.43, 3.17) 4.85 (2.04, 11.52) 1.57 (0.82, 3.00) 2.64 (1.75, 3.97) 128 Odds Ratio (85% CI)	100.00 Weight% 0.00 6.96 24.39 19.00 49.64 100.00 Weight% 0.00 45.83
	Overrat, MH (f = 0.0%, p = .)		0.72 (0.28, 1.89) 	100.00 Weight % 19.27 3.39 28.44 29.04 19.85 100.00 Weight %) 2.20 53.03	Overall, MH (1 ² = 0.0%, p = .) .o Author (yew) Chi-Cheng Lal (2014) Jernej Luc 'ev (2015) Goot O. Trenolal (2020) Moreno-Sanchez, T. (2020) Overall, MH (1 ² = 64.0%, p = 0.025) Author (yew) Panagotis M. Kitrov (2015) Lam, F. G. (2016)		1.07 (0.42, 2.77) Codes Ratio (86% Cr) 6.18 (0.26, 146.78) 8.38 (2.67, 26.33) 1.17 (0.43, 3.17) 4.85 (2.04, 11.52) 1.57 (0.82, 3.00) 2.64 (1.75, 3.97) Codes Ratio (86% Cr) 0.632 (0.27, 172.29) 2.07 (0.81, 4.70)	100.00 Weight% 0.00 6.96 24.39 19.00 49.64 100.00 Weight% 0.00 45.83
	Overrati, MH (I ⁰ = 0.0%, p = .)		0.72 (0.28, 1.89) 	100.00 Weight % 19.27 3.39 28.44 29.04 19.85 100.00 Weight % 0 2.200 53.03 44.77	Overall, MH (1 ² = 0.0%, p = .) .o Author (vew) Chi-Cheng Lai (2014) Jernej Luc 'ev (2018) Geot Maleux (2018) Scott O. Trenotola (2020) Moreno-Sánchez, T. (2020) Overall, MH (1 ² = 64.0%, p = 0.025) .ozrstzs Author (vew) Panagiots M. Kitou (2016) trant, F. G. (2016) Semen, J. J. (2019)		1.07 (0.42, 2.77) 	100.00 Weight% 0.00 6.96 24.39 19.00 49.64 100.00 Weight% 0.00 45.83 54.17
	Overrati, MH (0 ² = 0.0%, p = .)		0.72 (0.28, 1.89)	100.00 Weight % 19.27 3.39 28.44 29.04 19.85 100.00 Weight % 0 2.200 53.03 44.77	Overall, MH (1 ² = 0.0%, p = .) .s Author (vew) Chi-Cheng Lal (2014) Jennej Luc 'ev (2018) Geet Maleuc (2015) Sott O. Trenolola (2020) Moreno-Sanchez, T. (2020) Overall, MH (1 ² = 64.0%, p = 0.025)		1.07 (0.42, 2.77) 2 Cods Ratio (86% Ci) 6.18 (0.26, 146.76) 8.38 (2.67, 26.33) 1.17 (0.43, 3.17) 4.85 (2.04, 11.52) 1.57 (0.82, 3.00) 2.64 (1.75, 3.97) 120 Cods Ratio (86% Ci) Cods Ratio (86% Ci) 0.00 (0.82, 0.027, 172.29) 2.07 (0.81, 4.70) 1.31 (0.83, 4.15) 2.10 (1.20, 3.86)	100.00 Weight% 0.00 6.96 24.39 19.00 49.64 100.00 Weight% 0.00 45.83 54.17
	Overati, MH (I ² = 0.9%, p = .) 25 Author (year) Mittya Fukasawa (2018) Jarmej Luc "ev (2018) Robert A. Lookstein (2020) Scott D. Trerotola (2020) Moreno-Sánchez, T. (2020) Overall, MH (I ² = 52.1%, p = 0.080) Author (year) Panaglotis M. Kitrou (2015) trant, F. G. (2016) Overall, MH (I ⁴ = 17.3%, p = 0.288) Overall, MH (I ⁴ = 17.3%, p = 0.288)		0.72 (0.28, 1.89) 0ods Ratio (89% C1) 1.13 (0.56, 2.29) 4.88 (1.49, 16.00) 2.89 (1.83, 4.57) 2.14 (1.31, 3.48) 1.38 (0.71, 2.66) 2.10 (1.61, 2.74) 10 Codds Ratio (89% C1) 2.80 (1.20, 0.40, 1.44) 1.38 (0.82, 3.06) 2.80 (1.20, 0.44) 1.20 (1.23, 3.49) 128	100.00 Weight % 19.27 3.39 28.44 19.85 100.00 Weight % 5.3.03 44.77 100.00	Overall, MH (1 ² = 0.0%, p = .) .or Author (year) Chi-Cheng Lai (2014) Jernej Luc (ev (2018) Geet Malexu (2016) Scott O. Trenotola (2020) Moreno-Sanchez, T. (2020) Overall, MH (1 ² = 64.0%, p = 0.025) Author (year) Panagiotis M. Kitrou (2015) Itran, F. G. (2018) Swinnen, J. J. (2019) Overall, MH (1 ² = 0.0%, p = 0.752)		1.07 (0.42, 2.77) 	100.00 Weight% 0.00 6.96 24.39 19.00 49.64 100.00 0.00 49.64 100.00 0.00 45.83 54.17 100.00
	Overrat, MH (I ⁰ = 0.0%, p = .) 25 Author (year) Mituya Fukasawa (2018) Jernej Luc "ev (2018) Robert A. Lookstein (2020) Scott O. Trerolola (2020) Moreno-Sanchez, T. (2020) Overall, MH (l ² = 52.1%, p = 0.080)		0.72 (0.28, 1.89) 	100.00 Weight % 19.27 3.39 28.44 29.04 19.85 100.00 Weight %) 2.20 5.3.03 44.77 100.00 Weight %	Overall, MH (1 ² = 0.0%, p = .)		1.67 (6.42, 2.77) Codes Ratio (85% Cr) 6.18 (0.26, 146.78) 8.38 (2.67, 26.33) 1.17 (0.43, 3.17) 4.85 (2.04, 11.52) 1.57 (0.82, 3.00) 2.67 (0.82, 3.00) 2.66 (1.75, 3.97) 128 Ocds Ratio (85% Cr) 128 Ocds Ratio (95% Cr) 128 Cods Ratio (95% Cr)	100.00 Weight % 0.00 6.96 24.39 19.00 49.64 100.00 0.00 0.00 0.00 0.00 0.00 0.00 0
	Overrati, MH (0° = 0.0%, p = .)		0.72 (0.28, 1.89) 	100.00 Weight % 19.27 3.39 28.44 29.04 19.85 100.00 Weight % 3.03 44.77 100.00 Weight % 18.48	Overall, MH (I ¹ = 0.0%, p = .) .o Author (yew) Chi-Cheng Lal (2014) Jennel Luc "ev (2018) Geet Maleux (2018) Scott O. Trenolola (2020) Moreno-Sanchez, T. (2020) Overall, MH (I ² = 64.0%, p = 0.025) Author (yew) Panagotist M. Kitrou (2018) Irani, F. G. (2018) Swimen, J. J. (2019) Overall, MH (I ² = 0.0%, p = 0.752) Author (yew) Rarkyor, S. (2007)		1.07 (0.42, 2.77) Codes Ratio (89% C1) 6.18 (0.26, 146.78) 8.38 (2.67, 26.33) 1.17 (0.43, 3.17) 4.85 (2.04, 11.52) 1.57 (0.82, 3.00) 2.57 (0.81, 4.70) 1.28 Codes Ratio (95% C1) 0.42 (0.27, 172.29) 2.07 (0.91, 4.70) 1.21 (0.120, 3.66) 1.28 Codes Ratio (95% C1) 1.54 (0.65, 3.63)	100.00 Weight % 0.00 6.96 24.39 19.00 49.64 100.00 Weight % 0.00 45.85 54.11 100.00 0.00 45.85 100.00
	Overrat, MH (# = 0.0%, p = .)		0.72 (0.28, 1.89)	100.00 Weight % 19.27 3.39 28.44 29.04 19.85 100.00 Weight %) 2.20 53.03 44.77 10.000 \$3.03 44.77 10.000 \$3.03 44.77 10.000	Overall, MH (1 ² = 0.0%, p = .) 		1.07 (0.42, 2.77) Codes Ratio (86% C) 6.18 (0.26, 146.78) 8.38 (2.67, 26.33) 1.17 (0.43, 3.17) 4.85 (2.04, 11.52) 1.57 (0.82, 3.00) 2.64 (1.75, 3.97) Codes Ratio (86% C) 0.632 (0.27, 172.29) 2.70 (1.20, 3.66) 128 Codes Ratio (86% C) 1.54 (0.85, 3.63) 0.89 (0.57, 1.37)	100.00 Weight % 0.00 6.96 24.39 19.00 49.64 100.00 Weight % 0.00 45.85 54.11 100.00 0.00 45.85 54.11 100.00
	Overrat, MH (\$^{0} = 0.0%, p = .)		0.72 (0.28, 1.89) 	100.00 Weight % 19.27 3.39 28.44 29.04 19.85 100.00 Weight %) 2.20 53.03 44.77 10.000 \$3.03 44.77 10.000 \$3.03 44.77 10.000	Overall, MH (I ² = 0.0%, p = .) .o Author (yew) Chi-Cheng Lal (2014) Jernel Luc "ev (2018) Geet Maleur (2018) Scott O. Trenolola (2020) Moreno-Sanchez, T. (2020) Overall, MH (I ² = 64.0%, p = 0.025) Author (yew) Panagolistis M. Kitoru (2018) Irani, F. G. (2018) Switnen, J. J. (2019) Overall, MH (I ² = 0.0%, p = 0.752) Author (yew) Rartyn, S. (2007) Saleh, H. M. (2014) Overall, MH (I ² = 0.5%, p = 0.282)		1.07 (0.42, 2.77) Codes Ratio (86% C) 6.18 (0.26, 146.78) 8.38 (2.67, 26.33) 1.17 (0.43, 3.17) 4.85 (2.04, 11.52) 1.57 (0.82, 3.00) 2.64 (1.75, 3.97) Codes Ratio (86% C) 0.632 (0.27, 172.29) 2.70 (1.20, 3.66) 128 Codes Ratio (86% C) 1.54 (0.85, 3.63) 0.89 (0.57, 1.37)	100.00 Weight 9 0.00 6.96 24.39 19.00 49.64 100.00 0.0. 45.83 64.11 100.00 Weight 9 10.0.00
	Overrat, MH (I ⁰ = 0.0%, p = .)		0.72 (0.28, 1.89) 0ods Rato (85% Cl) 1.13 (0.55, 2.29) 4.88 (1.49, 16.00) 2.89 (1.83, 4.57) 2.14 (1.31, 3.48) 1.38 (0.71, 2.66) 2.10 (1.61, 2.74) 1.6 0ods Ratio (85% Cl) 2.00 (1.24, 3.44) 2.07 (1.23, 3.49) 1.28 0ods Ratio (85% Cl) 1.29 (0.78, 4.16) 1.23 (0.79, 1.91) 1.34 (0.91, 1.97)	100.00 Weight % 19.27 3.39 28.44 19.85 100.00 Weight %	Overall, MH (I ² = 0.0%, p = .) .o Author (yew) Chi-Cheng Lal (2014) Jennel Luc "ev (2018) Geet Maleux (2018) Scott O. Trenolola (2020) Moreno-Sanchez, T. (2020) Overall, MH (I ² = 64.0%, p = 0.025) Author (yew) Panagolistis M. Kitoru (2018) Itrain, F. G. (2018) Baimen, J. J. (2019) Overall, MH (I ² = 0.0%, p = 0.752) Author (yew) Rariya, S. (2007) Saleh, H. M. (2014) Overall, MH (I ² = 20.5%, p = 0.282) .25 Study		1.07 (0.42, 2.77) Codes Ratio (85% C1) 6.18 (0.26, 146.78) 8.38 (2.67, 26.33) 1.17 (0.43, 3.17) 4.85 (2.04, 11.52) 1.57 (0.82, 3.00) 2.64 (1.75, 3.97) Codes Ratio (85% C1) 0.632 (0.27, 172.29) 2.07 (0.81, 4.79) 1.19 (0.88, 4.19) 2.10 (1.20, 3.68) Odds Ratio (85% C1) Odds Ratio (95% C1) Codes Ratio (95% C1)	100.00 Weight 5' 6.96 24.39 19.00 49.64 100.00 Weight 1 00.00 Weight 1 100.00 Weight 3 100.00
	Overati, MH (I ² = 0.9%, p = .)		0.72 (0.28, 1.88) 0 ods Rato (85% Cl) 1.13 (0.56, 2.29) 4.88 (1.49, 1600) 2.89 (1.83, 4.57) 2.14 (1.31, 3.48) 1.38 (0.71, 2.66) 2.10 (1.61, 2.74) 0 ods Ratio (85% Cl) 1.38 (0.20, 10.84) 1.38 (0.20	100.00 Weight% 19.27 3.39 28.44 28.44 19.85 100.00 Weight% 10.0 Weight% 10.0 Weight% Weight% Weight%	Overall, MH (1 ² = 0.0%, p = .)		1.07 (0.42, 2.77) Codes Ratio (86% C) 6.18 (0.26, 146.76) 8.38 (2.67, 26.33) 1.17 (0.43, 3.17) 4.85 (2.04, 11.52) 1.57 (0.82, 3.00) 2.64 (1.75, 3.97) 128 Codes Ratio (86% C)) 6.82 (0.27, 172.29) 2.77 (0.81, 4.70) 1.34 (0.88, 4.19) 2.10 (1.20, 3.68) Codes Ratio (86% C) 1.54 (0.65, 3.63) 0.89 (0.57, 1.37) 0.99 (0.67, 1.46) Codes Ratio (95% C)) 1.07 (0.42, 2.77)	100.00 Weight 30 0.00 0.56 24.39 19.00 49.64 19.00 0
	Overalt, MH (I ² = 0.9%, p = .) 25 Author (year) Micitya Fukasawa (2018) Jernej Luc "ev (2018) Robert A. Lookstein (2020) Scott D. Trerotola (2020) Moreno-Sánchez, T. (2020) Overalt, MH (I ² = 52.1%, p = 0.080)		0.72 (0.28, 1.89) 	100.00 Weiger% 19.27 3.39 28.44 28.44 19.85 100.00 Weiger% 100.00 Weiger% 88.5 100.00 Weiger% 81.82 100.00 Weiger% 81.82 100.00 Weiger% 00 5.21 9 73.40	Overall, MH (1 ² = 0.0%, p = .) .or Author (year) Chi-Cheng Lai (2014) Jernej Luc (ev (2018) Geet Malexa (2016) Scott O. Trenotola (2020) Moreno-Sanchez, T. (2020) Overall, MH (1 ² = 64.0%, p = 0.025) Author (year) Panagiotis M. Kitrou (2015) Itran, F. G. (2016) Swinnen, J. J. (2019) Overall, MH (1 ² = 0.0%, p = 0.752) Author (year) Panagiotis M. Kitrou (2015) Itran, F. G. (2016) Overall, MH (1 ² = 0.0%, p = 0.752) Overall, MH (1 ² = 0.5%, p = 0.282) - Corentl, MH (1 ² = 20.5%, p = 0.282) - 25 Study HPB DCB		1.07 (0.42, 2.77) Cods Ratio (86% Cr) 6.18 (0.26, 146.76) 8.38 (2.67, 26.33) 1.17 (0.43, 3.17) 4.85 (2.04, 11.52) 1.57 (0.82, 3.00) 2.64 (1.75, 3.97) 120 Cods Ratio (96% Cr) 1.54 (0.85, 4.15) 2.10 (1.20, 3.68) Cods Ratio (95% Cr) 1.54 (0.67, 1.37) 0.99 (0.57, 1.37) 0.90 (0.57	100.00 Weight % 0.00 6.96 24.39 19.00 49.64 100.00 Weight 100.00 Weight 5 6.65 35.28
	Overalt, MH (I ² = 0.9%, p = .) 25 Author (year) Micitya Fukasawa (2018) Jernej Luc "ev (2018) Robert A. Lookstein (2020) Scott D. Trerotola (2020) Moreno-Sánchez, T. (2020) Overall, MH (I ² = 52.1%, p = 0.080)		0.72 (0.28, 1.89) 	100.00 Weight% 19.27 3.39 28.44 19.85 100.00 Weight% 100.00 Weight% 100.00 Weight% 18.48 61.52 100.00 Weight% 0.05.21 9 73.40 5	Overall, MH (1 ² = 0.0%, p = .) .o Author (year) Chi-Cheng Lai (2014) Jernej Luc (ev (2018) Geet Malexa (2016) Scott O. Trenolai (2020) Moren-Sanchez, T. (2020) Overall, MH (1 ² = 64.0%, p = 0.025) Author (year) Panagiotis M. Kitoru (2015) Itran, F. G. (2016) Sainen, J. J. (2019) Overall, MH (1 ² = 0.0%, p = 0.752) Author (year) Author (vear) Author (vear) Coveralt, MH (1 ² = 20.5%, p = 0.252) - - Overalt, MH (1 ² = 20.5%, p = 0.252) -		1.07 (0.42, 2.77) 	100.00 Weight% 0.00 6.96 24.39 19.00 49.64 100.00 0.00 0.00 0.00 0.00 0.00 0.00 0
	Overalt, MH (I ² = 0.9%, p = .) 25 Author (year) Micitya Fukasawa (2018) Jernej Luc "ev (2018) Robert A. Lookstein (2020) Scott D. Trerotola (2020) Moreno-Sánchez, T. (2020) Overalt, MH (I ² = 52.1%, p = 0.080)		0.72 (0.28, 1.89) 	100.00 Weight% 19.27 3.39 28.44 19.85 100.00 Weight% 100.00 Weight% 100.00 Weight% 18.48 61.52 100.00 Weight% 0.05.21 9 73.40 5	Overall, MH (1 ² = 0.0%, p = .) .or Author (year) Chi-Cheng Lai (2014) Jernej Luc (ev (2018) Geet Malexa (2016) Scott O. Trenotola (2020) Moreno-Sanchez, T. (2020) Overall, MH (1 ² = 64.0%, p = 0.025) Author (year) Panagiotis M. Kitrou (2015) Itran, F. G. (2016) Swinnen, J. J. (2019) Overall, MH (1 ² = 0.0%, p = 0.752) Author (year) Panagiotis M. Kitrou (2015) Itran, F. G. (2016) Overall, MH (1 ² = 0.0%, p = 0.752) Overall, MH (1 ² = 0.5%, p = 0.282) - Corentl, MH (1 ² = 20.5%, p = 0.282) - 25 Study HPB DCB		1.07 (0.42, 2.77) Cods Ratio (86% Cr) 6.18 (0.26, 146.76) 8.38 (2.67, 26.33) 1.17 (0.43, 3.17) 4.85 (2.04, 11.52) 1.57 (0.82, 3.00) 2.64 (1.75, 3.97) 120 Cods Ratio (96% Cr) 1.54 (0.85, 4.15) 2.10 (1.20, 3.68) Cods Ratio (95% Cr) 1.54 (0.67, 1.37) 0.99 (0.57, 1.37) 0.90 (0.57	100.00 Weight% 0.00 6.96 24.39 19.00 49.64 100.00 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.000000

Figure 3 Results of direct meta-analysis on primary patency of (A) 3 and 6 months, (B) 9 and 12 months. From top to bottom are the direct meta-analysis results of HPB, DCB, DEB and CtB versus PBA. Thereafter, the forest plot at the bottom comprehensively compares all new types of balloons with PBA. CI, confidence interval; HPB, high-pressure balloon; DCB, drug-coated balloon; DEB, drug-eluting balloon; CtB, cutting balloon.

its cost might be less than CtB (37).

CtB is another type of commonly used balloon. It allows for the regular incision of the vascular intima of AVF. The results from our study demonstrated that CtB was indeed more effective than PBA. Some studies suggested that CtB had a better outcome than that of PBA for AVF stenosis (25-27). However, the CtB and DCB or DEB were never compared head-to-head earlier. In the present study, the

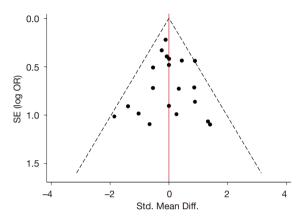


Figure 4 Funnel plot of selected studies. SE, standard error; OR, odds ratio.

SUCRA values of DCB and DEB were larger than that of CtB. These findings suggested that, regarding the patency rate, DCB or DEB was better than CtB.

Both DEB and DCB are new technologies combining PBA with drug delivery. Several studies showed that DEB and DCB effectively treated coronary atherosclerotic lesions (38,39). Four studies investigating the effect of DEB (21-24) and nine studies investigating the effect of DCB were included in our NMA (12,15-21,29). The results demonstrated that both DEB and DCB had a statistically higher patency rate compared with PBA at all time points, which was consistent with the results of several recently published studies (40,41). Meanwhile, both these studies demonstrated that the use of DCB did not cause a significant increase in patient mortality, indicating the high safety of DCB compared with PBA.

Indirect comparisons via NMA demonstrated that DEB had a smaller, but still significant, advantage over DCB in preventing stenosis after 6, 9, and 12 months but not after 3 months. The clinical significance of the difference in primary patency after 6, 9, and 12 months, but not after 3 months, is a subject of debate. The sample size of the study performed by Kitrou was small, leading to confounding results. Theoretically, because of the different

DCB	1.15 (0.28, 5.11)	0.70 (0.22, 2.16)	0.62 (0.34, 0.82)	0.97 (0.33, 2.95)
0.65 (0.15, 2.98)	DEB	0.58 (0.10, 3.38)	0.54 (0.14, 1.97)	0.82 (0.16, 4.48)
1.74 (0.41, 7.53)	2.68 (0.39, 17.40)	HPB	0.91 (0.30, 2.62)	1.40 (0.50, 4.11)
1.79 (0.83, 3.89)	2.75 (0.78, 9.49)	1.02 (0.26, 4.14)	РВА	1.56 (0.62, 4.34)
0.94 (0.25, 3.81)	1.45 (0.26, 8.20)	0.54 (0.14, 2.24)	0.52 (0.17, 1.76)	CtB
DCB	1.26 (0.30, 6.37)	0.35 (0.08, 0.37)	0.53 (0.23, 0.74)	0.65 (0.15, 2.51)
1.00 (0.15, 5.76)	DEB	0.28 (0.04, 1.61)	0.42 (0.10, 1.39)	0.51 (0.08, 2.85)
2.41 (0.41, 14.01)	2.40 (0.30, 21.94)	НРВ	1.52 (0.41, 5.51)	1.85 (0.49, 6.78)
2.07 (0.74, 6.31)	2.07 (0.53, 9.69)	0.88 (0.18, 4.13)	PBA	1.23 (0.35, 4.15)
1.81 (0.33, 10.85)	1.81 (0.24, 16.36)	0.76 (0.16, 3.70)	0.87 (0.20, 3.91)	CtB

■3 months ■6 months ■9 months ■12 months

Figure 5 ORs of the effect of different balloons in NMA (3, 6, 9 and 12 months). Results are the ORs in the column-defining treatment compared with the ORs in the row-defining treatment. For the results of 6 and 12 months, ORs higher than 1 favor the column-defining treatment. For the results of 3 and 9 months, ORs lower than 1 favor the row-defining treatment. To obtain ORs for comparisons in the opposite direction, reciprocals should be taken (e.g., the OR for DCB compared with PBA is 1/0.62=1.61). DCB, drug-coated balloon; DEB, drug-eluting balloon; HPB, high-pressure balloon; PBA, plain balloon angioplasty; CtB, cutting balloon; OR, odds ratio; NMA, network meta-analysis.

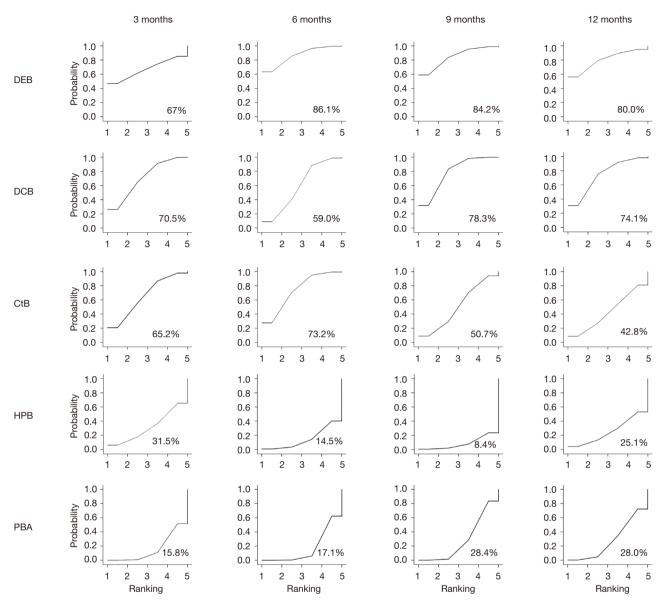


Figure 6 Ranking of treatment strategies. The curves show the cumulative probability to be the best treatment in terms of primary patency rates at follow-up. DEB, drug-eluting balloon; DCB, drug-coated balloon; CtB, cutting balloon; HPB, high-pressure balloon; PBA, plain balloon angioplasty.

manufacturing processes, the effect of DEB should be better than that of DCB. A study performed by Buszman *et al.* also demonstrated that the new-generation balloons could result in homogeneous and circumferential coatings, which was caused by a proprietary dipping process applied in these balloons. It led to the preferential deposition of the paclitaxel-iopromide formulation in the folds of the balloon (42). Prospective studies with larger sample sizes should be conducted. Also, the mechanism underlying the inhibition of vascular intimal proliferation by DEB and DCB should be further investigated.

Limitations

In the present study, we retrieved all unpublished data and contacted authors for supplementary materials. A substantial amount of information was still not available to the public. Nonetheless, the present study represented a comprehensive synthesis of data currently available. Moreover, we could not obtain relevant data about the costs of different balloons. Future studies should consider both cost and efficacy. Finally, the patient inclusion criteria of different RCTs were not completely consistent. Therefore, an RCT performed by our center may be needed to analyze different balloons comprehensively.

Conclusions

The results demonstrated that the short-term and longterm outcomes of new balloons (DEB, DCB, CtB, and HPB) were superior to those of PBA. DEB was the most effective strategy for treating AVF stenosis because it showed the lowest risk of stenosis compared with other treatment strategies. DCB could be the second selection in terms of patency rates while CtB may be the third. In our study, HBP was relatively less effective than other balloons. However, HPB was better for resistant lesions than other balloons because of higher burst pressure.

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