Heliyon 10 (2024) e25264

Contents lists available at ScienceDirect

Heliyon

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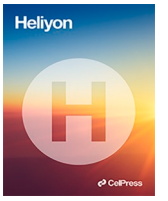

Research article

Efficacy and safety of drug-coated balloon for de novo lesions of large coronary arteries: Systematic review and meta-analysis of randomized controlled trials

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ARTICLE INFO

Keywords:
Drug-coated balloon
Stent
De novo
Coronary artery disease

ABSTRACT

Background: Drug-coated balloon (DCB) is a novel approach to avoiding stent-related complications and has proven effective for the treatment of in-stent restenosis (ISR) and small vessels. However, its role in the treatment of de novo lesions in large vessels is less settled.
Aims: To estimate the efficacy and safety of drug-coated balloon versus stent in the treatment of de novo lesions in large coronary arteries.
Methods: We searched the literature until April 2023. We judged the safety of DCB based on major adverse cardiovascular events (MACEs), cardiac death, all-cause mortality, non-fatal myocardial infarction, target lesion revascularization (TLR), and bleeding event; and efficacy according to late lumen loss (LLL), minimum lumen diameter (MLD). We conducted subgroup analyses according to stent type and whether urgent PCI was required.
Results: A total of 10 RCTs were included. Overall, LLL (mean difference (MD) = −0.19, 95 % confidence interval (CI): −0.32 to −0.06, P = 0.003) was lower in the DCB group than in the Stent arm. This effect was consistent in subgroup analysis regardless of stent type and disease type. In terms of safety indicators, there were no significant differences between DCB and stent. The subgroup analyses found that safety indicators showed no significant differences between DCB and drug-eluting stent (DES), but TLR was lower in the DCB than in the bare metal stent (BMS). Moreover, in ST-elevation myocardial infarction (STEMI), safety indicators and LLL showed no significant differences between DCB and DES, but MLD in the DCB was smaller. While in patients with excluded STEMI, MACE and TLR was lower in the DCB compared with the overall stent.
Conclusions: DCB could be a promising alternative for treating de novo lesions in large coronary arteries with satisfactory efficacy and low risk, superior to BMS and not inferior to DES, with a trend toward lower late lumen loss.

1. Introduction

Percutaneous coronary intervention (PCI) remains the mainstay of treatment for patients with coronary artery disease, and treatment outcomes and prognosis have improved significantly from the initial balloon angioplasty to the implantation of BMS to the

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https://doi.org/10.1016/j.heliyon.2024.e25264
Received 16 September 2023; Received in revised form 22 November 2023; Accepted 23 January 2024
Available online 30 January 2024

use of DES. Stents prevent acute vessel closure following balloon angioplasty [1]; even with second-generation DES, the late occurrence of neo-atherosclerosis and thrombotic events (e.g., stent thrombosis) remains a concern, afflicting 1.0 %–2.5 % of PCI patients [2,3]. Stent-free PCI is a novel approach to avoiding stent-related complications [4], making drug-eluting balloons appealing.

Based on the premise that direct contact of antiproliferative drugs with the vessel wall via a semi-compliant balloon is sufficient to inhibit smooth muscle cell proliferation following adequate pretreatment of the lesion, and attaining lower restenosis rates by leaving no metal behind, DCB is employed to treat coronary artery disease [5,6]. Several clinical trials have demonstrated DCB's efficacy and safety for the treatment of ISR and small vessels, and it is recommended as class IA for treating ISR [7]; however, there is uncertainty about its use in other anatomical settings, such as large vessels and bifurcations, as well as in some specific clinical settings, such as diabetes mellitus, high risk of bleeding, and STEMI. Besides, the use of DCB in large vessel lesions is restricted due to concerns that it may result in acute vessel occlusion. Previous meta-analysis [8,9] have demonstrated that DCB is feasible in large vessel lesions compared to stenting, but some limitations remain (e.g., small number of included studies, inclusion of observational studies, etc.).

Therefore, this meta-analysis aims to explore the efficacy and safety of DCB approaches for de novo lesions in large coronary arteries (reference vessel diameter (RVD) $\geq$ 2.5 mm) in randomized controlled trial.

2. Methods

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Meta-Analysis (PRISMA) statement. The protocol was registered at PROSPERO (registration number: CRD42023439002).

2.1. Search strategy

The PubMed, Embase, Cochrane library database, and the US National Institutes of Health Clinical Trials Registry (http://www.clinicaltrials.gov) were searched for eligible studies published from inception to April 2023. The following key words were used: ("coated balloon "OR" eluting balloon "OR" DCB "OR" DEB "OR" PCB "OR" PEB "OR" PCB "OR" PEB "OR" SCB "OR" SEB") AND ("vessel "OR" artery "OR" Coronary "OR" lesion "OR" narrow "OR" Coronary Disease "OR" stenosis"). No language restrictions were enforced.

2.2. Inclusion and exclusion criteria

Inclusion criteria were: 1) studies with randomized assignment to angioplasty with DCB as experimental strategy; 2) patients with de novo coronary artery diseases; 3) PCI for de novo lesions with lumen diameters $\geq$2.5 mm; 4) stent as control group (BMS or DES). Exclusion criteria were: 1) investigated the efficacy of DCB in ISR; 2) bioabsorbable scaffolds; 3) ongoing studies or irretrievable data; 4) non-randomized study design; 5) absence of a clinical endpoint; 6) therapy of arterial districts besides CAD.

2.3. Data extraction and validity assessment

Data were independently abstracted by two investigators (Jiang and Huang). We imported all of the references from the electronic search into Endnote and removed any duplicates. In the event of disagreement, a third researcher would assist in making the final determination. The data were managed in accordance with the principle of intention-to-treat. The collected information included main study author, publication year, country, sample size, mean age, disease state, the type of DCB and stents, the reference vessel diameter, follow-up duration, and reported outcomes.

2.4. Outcome measures

The safety outcomes: Major adverse cardiovascular events (MACEs), cardiac death, all-cause mortality, non-fatal myocardial infarction, target lesion revascularization (TLR), and bleeding event.

The efficacy outcomes: late lumen loss (LLL), minimum lumen diameter immediately after PCI (MLD1), minimum lumen diameter at follow-up angiography (MLD2).

2.5. Quality assessment

Two evaluators (Jiang and Huang) used the Cochrane Risk-of-Bias Tool for RCTs (RoB 2) and RevMan5.4 to assess the methodological quality of each included study. For quality assessment, the risk of each form of bias was rated as "low risk," "unclear risk," or "high risk" depending on the characteristics of each criterion reported in the study.

2.6. Statistical analysis

RevMan 5.4 software and Stata 14.0 were used for the data analysis of the included studies. Risk ratio (RR) was set as the effect indicator for the dichotomous variable (all safety outcomes), and mean difference (MD) was set as the effect indicator for the continuous variable (all efficacy outcomes). Point estimate values of both effect indicators and corresponding 95 % confidence interval (CI) were calculated. The heterogeneity in studies was assessed through the chi-squared test (Cochran's Q) combined with I2 statistic.

I^2 >50 % were deemed indicative of statistical heterogeneity. In addition, we performed sensitivity analyses to evaluate the effect of included studies on the combined results for outcomes with significant heterogeneity. Considering the differences in the designs, populations, control selection, and treatment effects across studies, a random-effects model was used to synthesize data.

Publication bias was evaluated by creating funnel plots via RevMan 5.4, as well as by conducting Egger's test using Stata 14.0 for outcomes. $P < 0.05$ was suggested as statistically significant publication bias. To further explore other factors associated with outcomes, subgroup analysis were conducted according to stent type (BMS, DES, or Mixed that both had), and disease state (whether urgent PCI was required).

3. Results

3.1. Search results and characteristics of the included studies

A total of 4167 studies were retrieved, as shown in the flow-chart for the selection process in Fig. 1. Following 165 studies remained to be read the full text for further exclusion. Finally, 10 articles [10–19] were included in our meta-analysis, with an overall population of 1468 patients. Among them, 717 (48.8 %) were randomized to a DCB strategy, while 751 (51.2 %) patients to a Stent strategy.7 trials [10,11,14,16–19] involving 1010 patients in the control group with DES, 2 trials [12,13] involving 248 patients in the control group with BMS, and one trials [15] involving 210 patients in the control group with DES or BMS. Four trials [11,14,16,18] included only patients with STEMI, while five trials [10,12,13,15,19] excluded patients with STEMI, and one trial's [17] population had unspecified

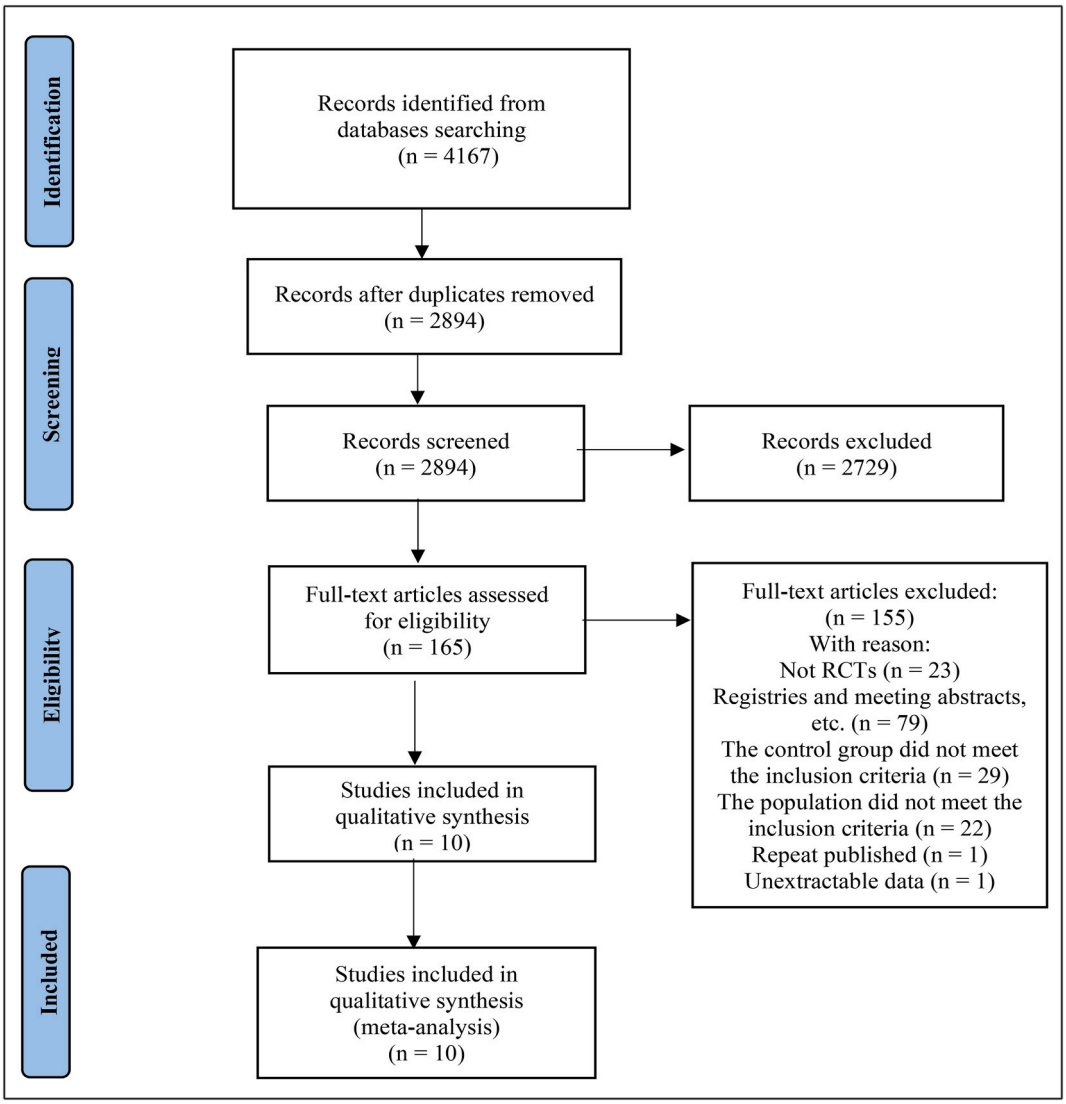

Fig. 1. Study selection flow diagram.

Table 1
The characteristics of the study included.

Study	Year	Country	Population	Reference Vessel Diameter (mm) (DCB/Control)	Number of patient (DCB/Control)	Age (years) (DCB/Control)	Revascularization strategy		Clinical follow-up (months)		Angiographic follow-up (months)	Study
							DCB		Control			
Nishiyama et al.	2016	Japan	CCAD	2.88 ± 0.57/2.72 ± 0.64	30/30	67.30 ± 11.12/70.63 ± 8.97	paclitaxel-coated balloon (SeQuent Please)		everolimus-eluting stents (Xience Prime)		8	8
Gobić et al.	2017	Croatia	STEMI	2.50-4.00	41/37	56.60 ± 13.20/54.30 ± 10.60	paclitaxel-coated balloon (SeQuent Please)		Cobalt-chromium sirolimus eluting stents (Biomime)		6	6
Rissanen et al.	2019	Finland	De novo lesion、with high bleeding risk	2.50-4.00	102/106	77.60 ± 8.40/76.20 ± 8.50	paclitaxel-coated balloon (SeQuent Please)		bare metal stent (Integrity/Omega)		9	NA
Shin ES et al.	2019	Korea	De novo lesion、with high bleeding risk	> 2.80	20/20	57.50 ± 9.20/61.60 ± 9.50	paclitaxel-coated balloon (SeQuent Please)		bare metal stent (Vision)		12	9
Vos MD et al.	2019	Amsterdam	STEMI	3.28 ± 0.52/3.20 ± 0.48	60/60	57.40 ± 9.20/57.30 ± 8.30	paclitaxel-coated balloon (Pantera Lux)		sirolimus-eluting stent (Orsiro/Xience)		9	9
Scheller et al.	2020	Germany	NSTEMI	2.50-3.50	104/106	66.00 ± 11.40/67.00 ± 13.10	paclitaxel-coated balloon ((SeQuentTM Please/SeQuentTM Please Neo)		bare metal stents/new generation limus-eluting DES		9	NA
Hao X et al.	2021	China	STEMI	2.50-4.00	42/42	59.00 ± 11.00/56.00 ± 11.00	Yinyi Biotech Bingo Drug Coated Balloon		DES		12	12
Farah A et al.	2022	Germany	De novo lesion	2.50-2.75	142/179	67.18 ± 10.33/68.42 ± 10.32	paclitaxel-coated balloon (Sequent Please)		paclitaxel-eluting stent ((Taxus Element)/everolimus-eluting stent (Xience)		12	NA
Wang Z et al.	2022	China	STEMI	3.31 ± 0.56/3.43 ± 0.48	92/92	49.20 ± 10.59/49.60 ± 8.820	paclitaxel-coated balloon (VasoguardTM DCB)		Cordimax stent		12	9
Yu X et al.	2022	China	De novo lesion	2.77 ± 0.56/3.01 ± 0.55	84/79	62.60 ± 8.80/64.00 ± 10.50	paclitaxel-coated balloon (Sequent Please)		zotarolimus-eluting stents (Resolute)/everolimus-eluting stents (Xience)/rapamycin-eluting stents (Firehawk)		12	9

Abbreviations: STEMI, ST-segment elevation myocardial infarction; CCAD, chronic coronary artery disease; NA, not available; DCB, drug-coated balloon; DES, drug-eluting stent.

de novo coronary lesions. Study characteristics of included trials are shown in Table 1. Follow-up ranges from 6 months to 12 months.

3.2. Quality assessment

The risk of bias assessment was not high in most of the included studies, as shown in Fig. 2. Several studies did not provide adequate information regarding their allocation concealment procedures, so they were graded as "unclear risk of bias." Due to safety concerns, participants in the majority of studies were not blinded, but the outcome measure was. However, one study, Hao X et al., was assessed to be at high risk of bias due to concerns about the procedure of allocation concealment and the blinding of outcome assessment. In addition to this, Rissanen et al. study had other biases, it was prematurely terminated because of slow recruitment, leading to a smaller sample size than planned. For randomization, reporting bias, and attrition bias, no study presented any obvious one.

3.3. The safety outcomes

3.3.1. Cardiac death

All 10 RCTs, including 1468 patients, measured cardiac death data at the follow-up period, with no significant difference between DCB and stent (RR = 0.58; 95 % CI: 0.24 to 1.40, P = 0.226) (Fig. 3).

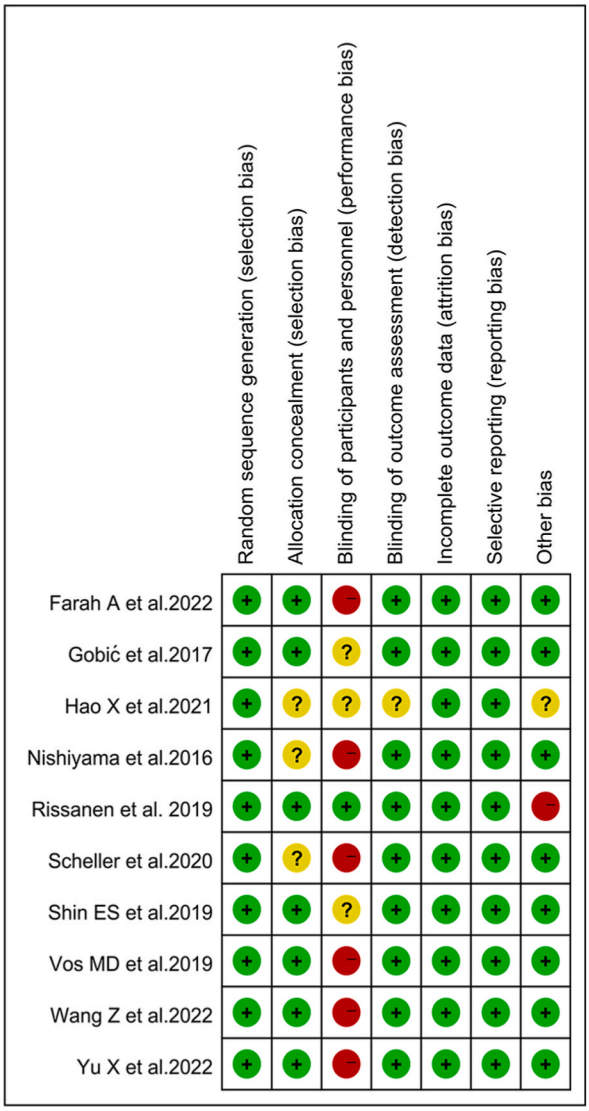

Fig. 2. Evaluation of risk bias of included studies drawn by RevMan5.4.

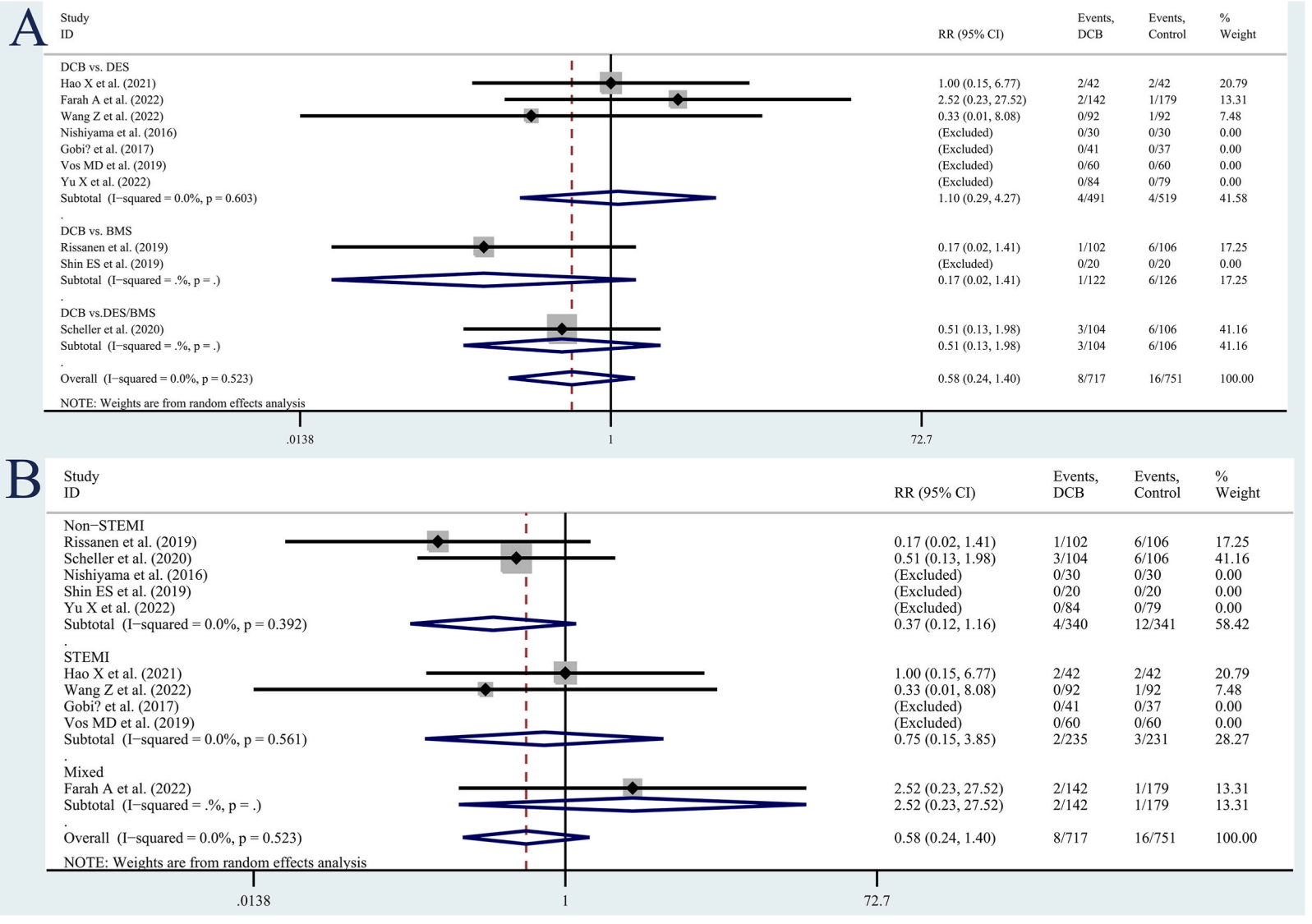

Fig. 3. Forest plot of the effects of DCB compared with control in Cardiac death. (A) Subgroup analysis by the type of stent; (B) Subgroup analysis by the type of disease.

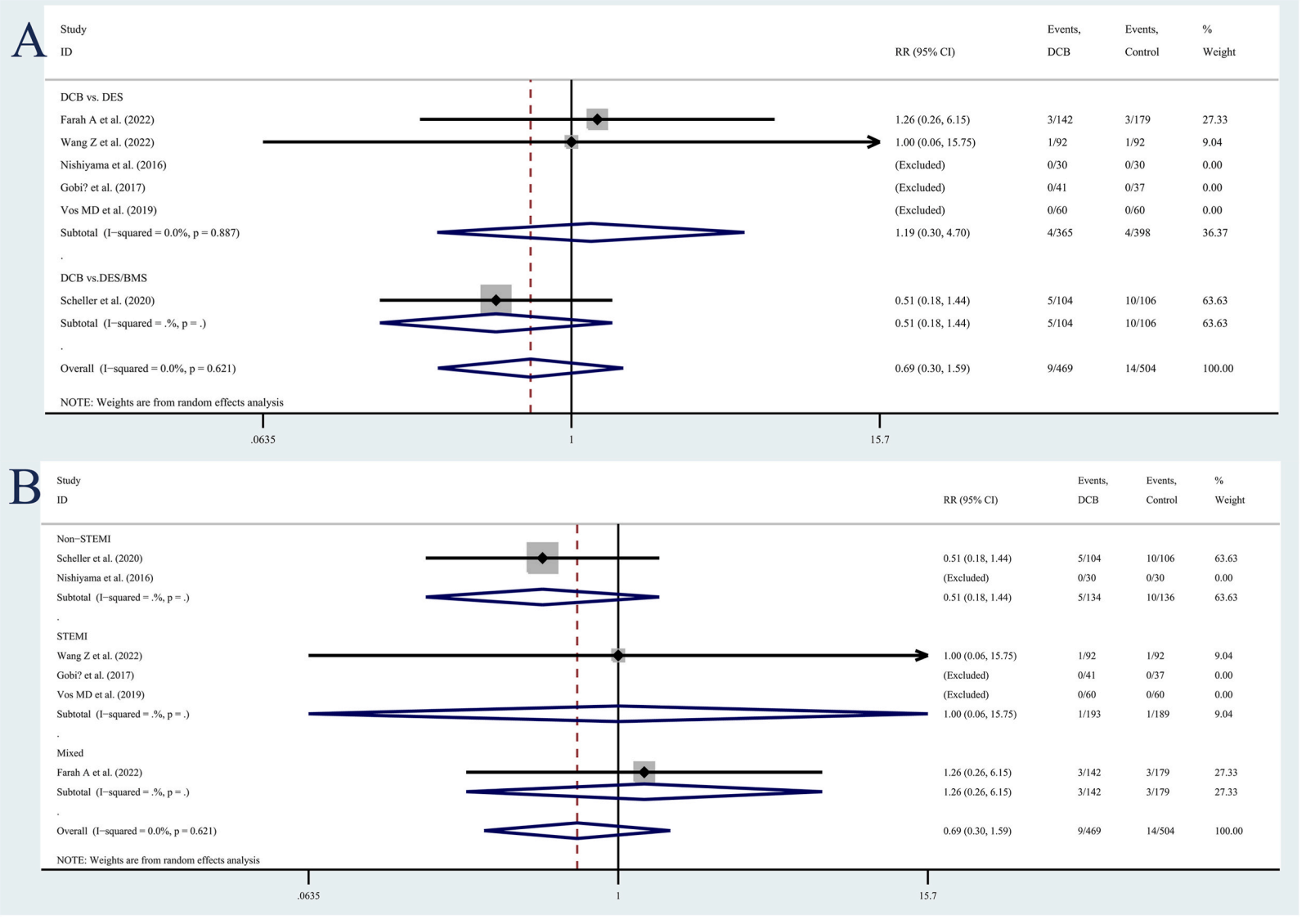

Fig. 4. Forest plot of the effects of DCB compared with control in All-cause mortality. (A) Subgroup analysis by the type of stent; (B) Subgroup analysis by the type of disease.

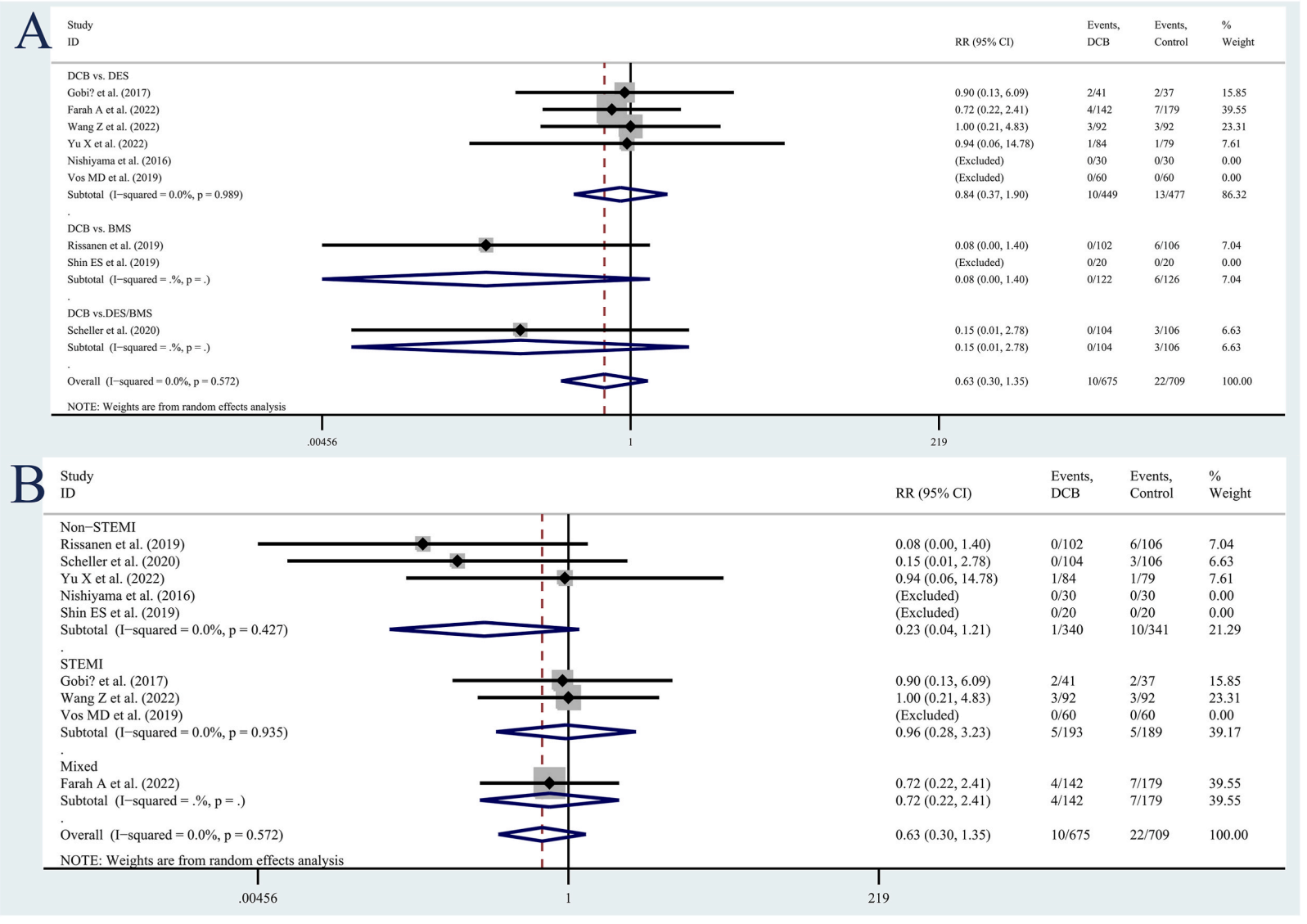

Fig. 5. Forest plot of the effects of DCB compared with control in Non-fatal myocardial infarction. (A) Subgroup analysis by the type of stent; (B) Subgroup analysis by the type of disease.

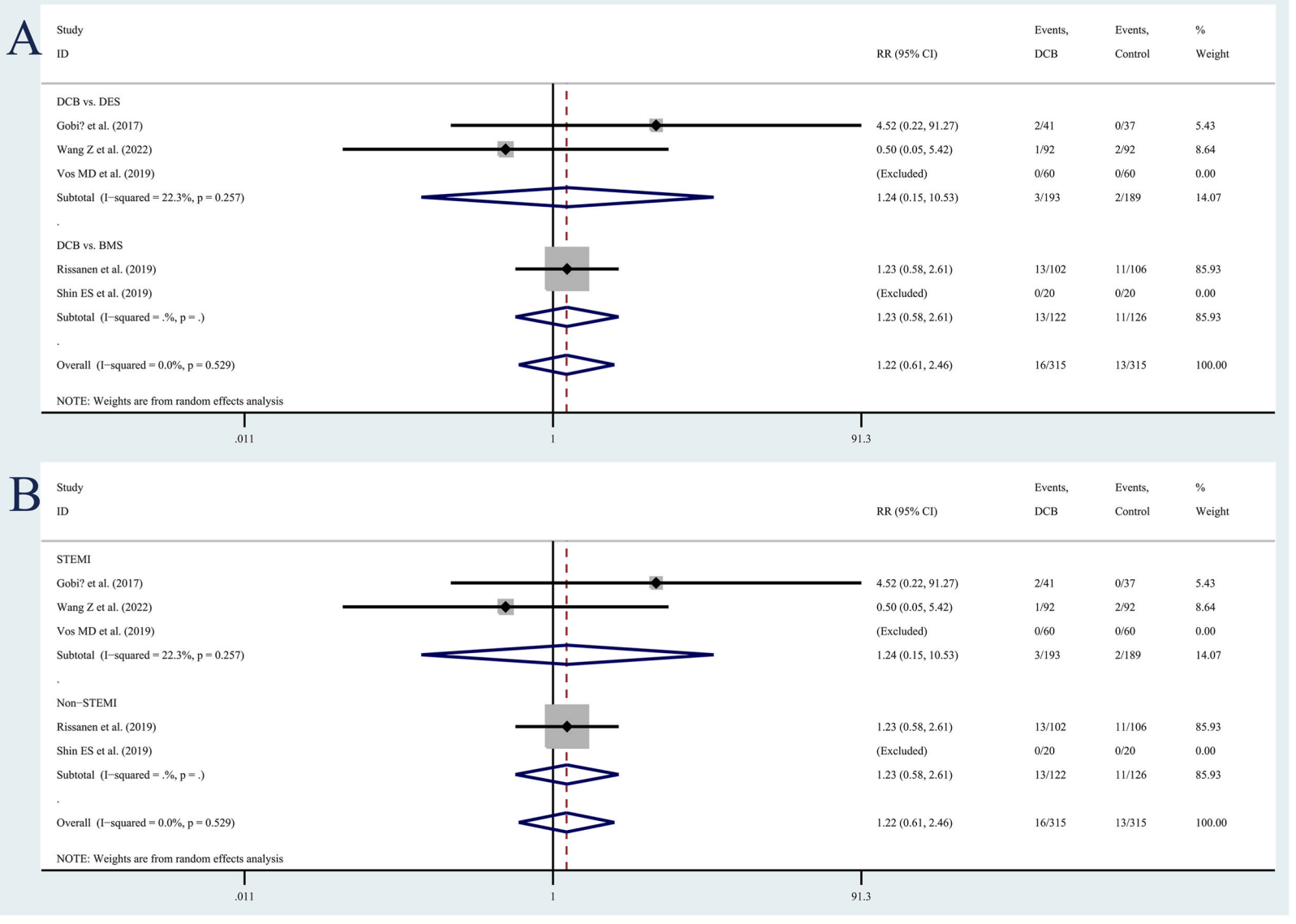

Fig. 6. Forest plot of the effects of DCB compared with control in Bleeding event. (A) Subgroup analysis by the type of stent; (B) Subgroup analysis by the type of disease.

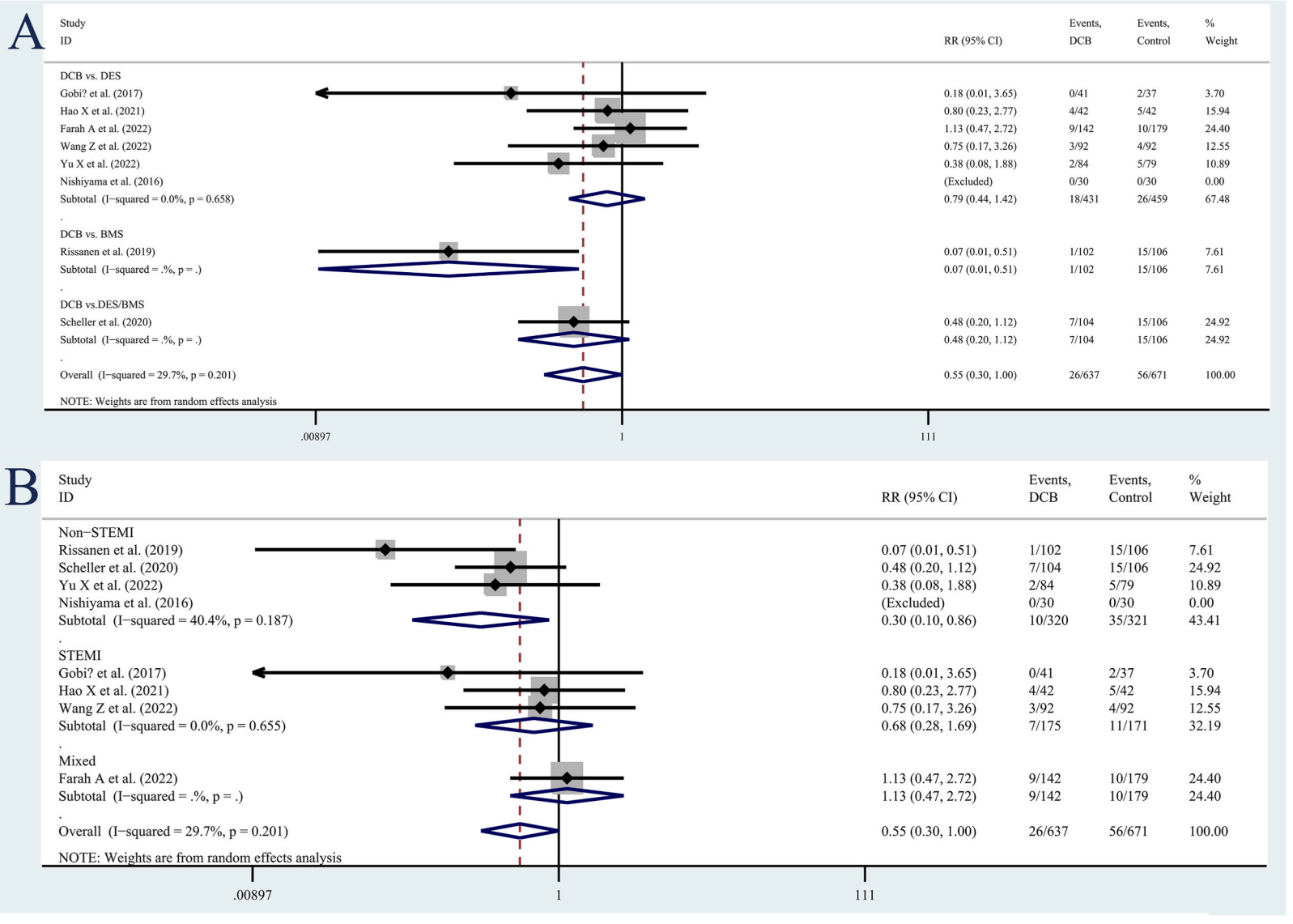

Fig. 7. Forest plot of the effects of DCB compared with control in MACEs. (A) Subgroup analysis by the type of stent; (B) Subgroup analysis by the type of disease.

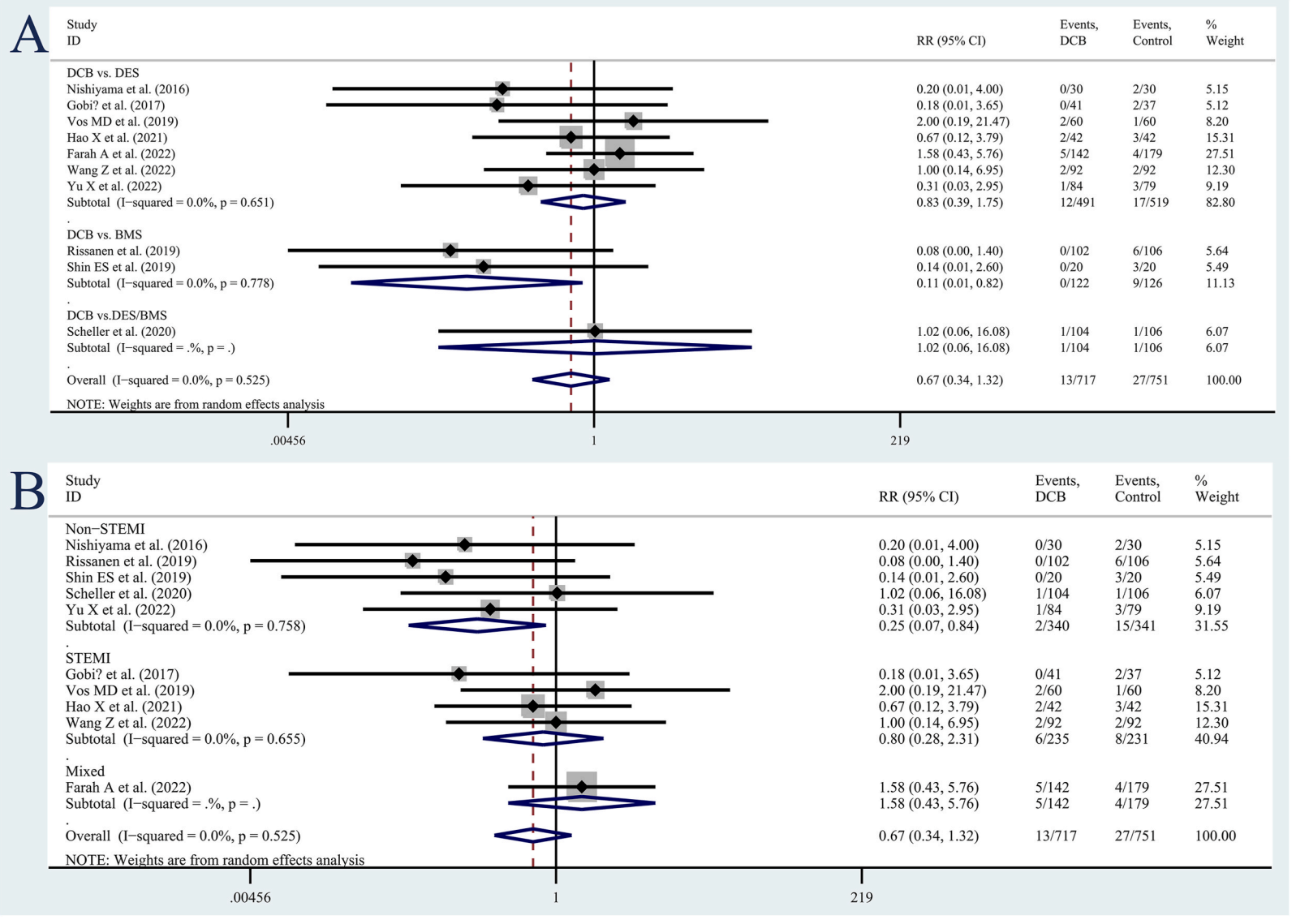

Fig. 8. Forest plot of the effects of DCB compared with control in TLR. (A) Subgroup analysis by the type of stent; (B) Subgroup analysis by the type of disease.

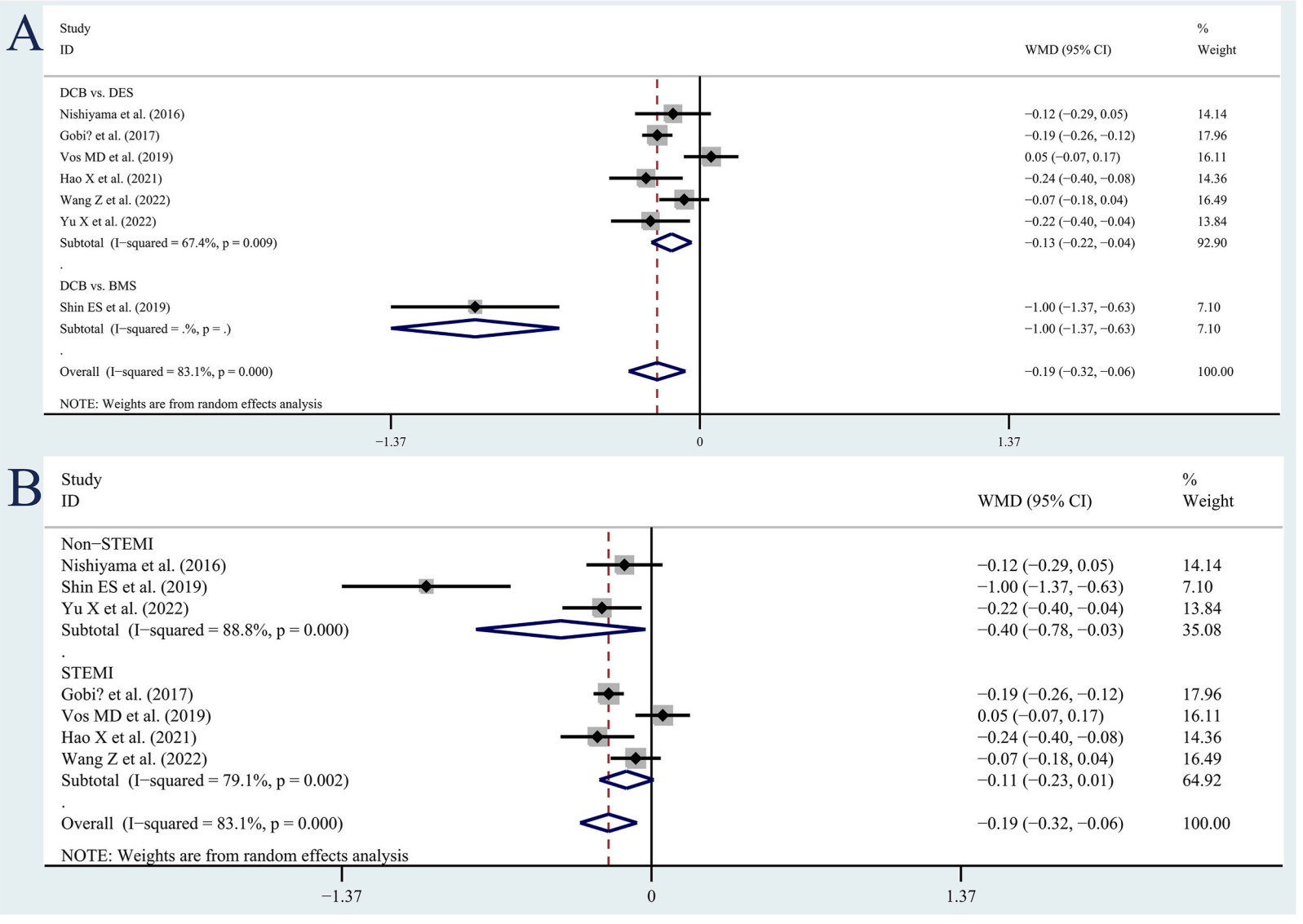

Fig. 9. Forest plot of the effects of DCB compared with control in LLL. (A) Subgroup analysis by the type of stent; (B) Subgroup analysis by the type of disease.

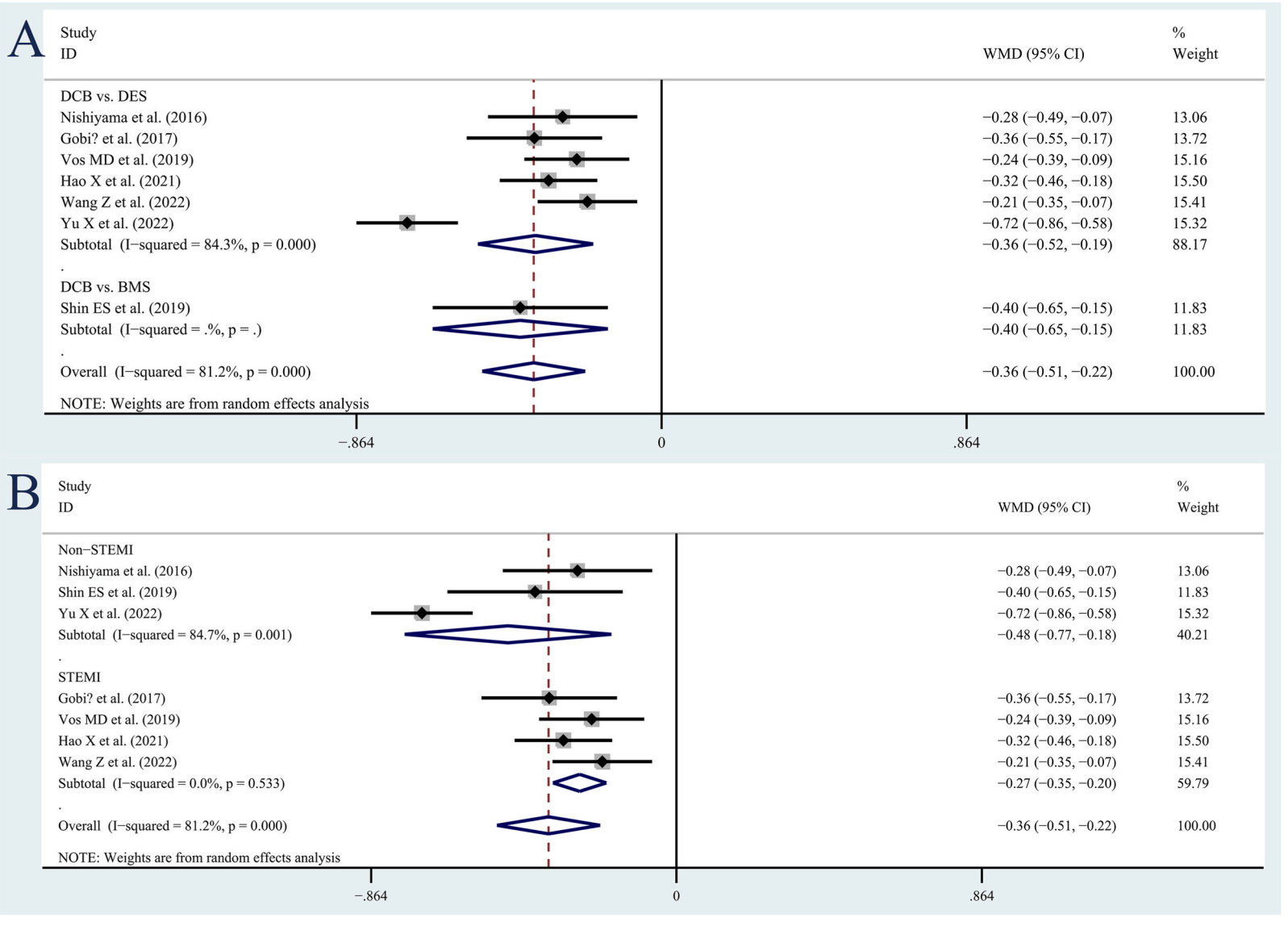

Fig. 10. Forest plot of the effects of DCB compared with control in MLD1. (A) Subgroup analysis by the type of stent; (B) Subgroup analysis by the type of disease.

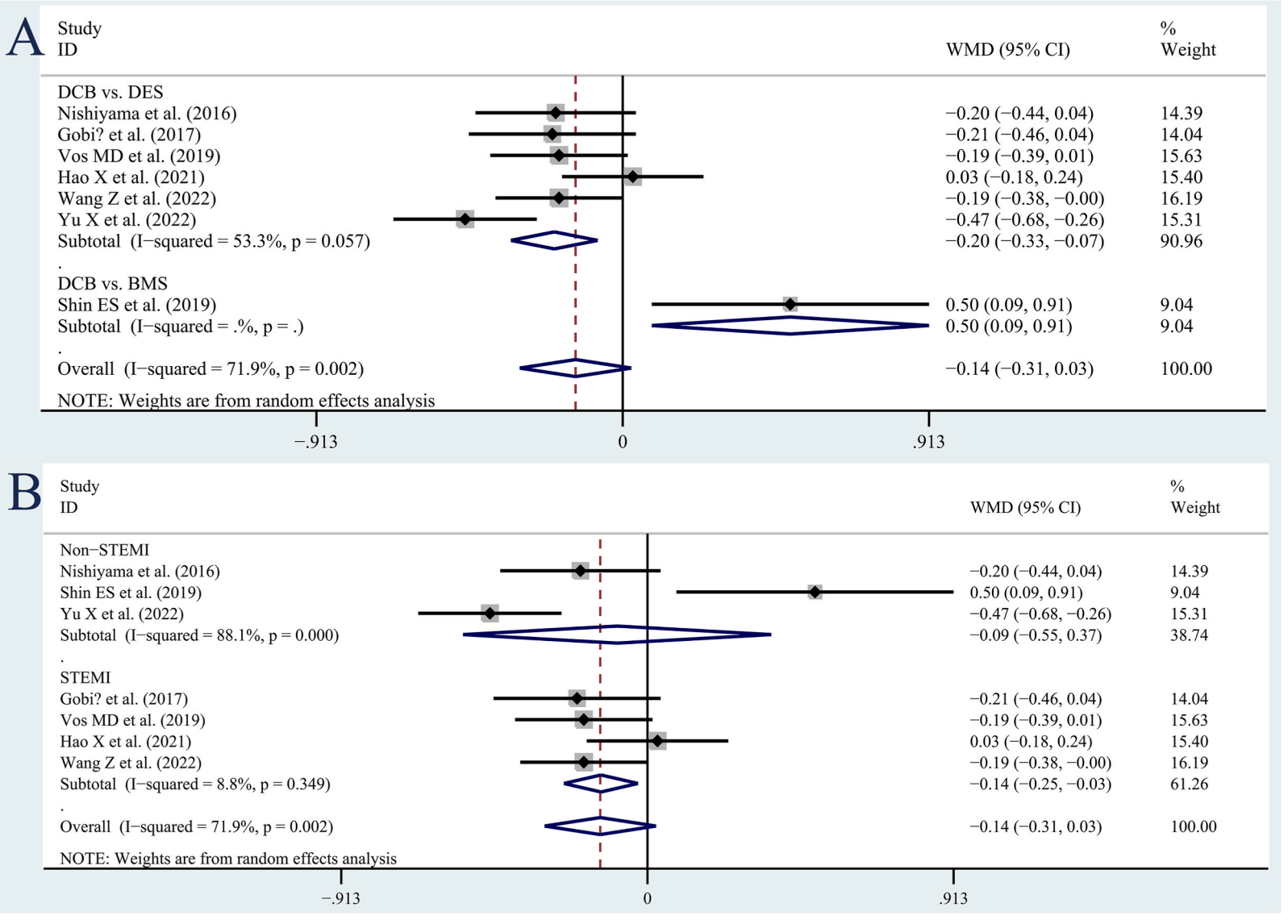

Fig. 11. Forest plot of the effects of DCB compared with control in MLD2. (A) Subgroup analysis by the type of stent; (B) Subgroup analysis by the type of disease.

3.3.2. All-cause mortality

Data for all-cause mortality were available in 6 RCTs, including 973 patients, and found no statistically significant difference in all-cause mortality between DCB and stents (RR = 0.69; 95 % CI: 0.30 to 1.59, P = 0.387) (Fig. 4).

3.3.3. Non-fatal myocardial infarction

The risk of non-fatal myocardial infarction was reported in 9 RCTs, included 1384 patients, indicating no significant difference between DCB and stents (RR = 0.63; 95 % CI: 0.30 to 1.35, P = 0.239) (Fig. 5).

3.3.4. Bleeding event

Bleeding event were recorded in five RCTs with 630 patients, indicated no difference at the follow-up period (RR = 1.22; 95 % CI: 0.61 to 2.46, P = 0.578) (Fig. 6).

3.3.5. Major adverse cardiovascular events (MACEs)

Data for MACEs were available in 8 RCTs, and the results showed no statistically significant difference between DCB and stents (RR = 0.55; 95 % CI: 0.30 to 1.00, P = 0.051) (Fig. 7). Whereas in patients with excluded STEMI, DCB resulted in a significant reduction in MACEs compared with the stent group (RR = 0.30; 95 % CI: 0.10 to 0.86, P = 0.025) (Fig. 7B).

3.3.6. Target lesion revascularization (TLR)

TLR was reported in all ten RCTs. Compared to the DCB group, there was no statistically different for TLR observed in the overall stent group (RR = 0.67; 95 % CI: 0.34 to 1.32, P = 0.243) (Fig. 8), but a higher risk of TLR was found in the BMS group (RR = 0.11; 95 % CI: 0.01 to 0.82, P = 0.031) (Fig. 8A). Further analysis, in patients with excluded STEMI, DCB group exhibited a significant reduction in TLR compared with the stent group (RR = 0.25; 95 % CI: 0.07 to 0.84, P = 0.025) (Fig. 8B).

3.4. The efficacy outcomes

3.4.1. Late lumen loss (LLL)

There were 7 RCTs with 729 patients reporting angiographic results, all of which used DES as the control group, except the Shin ES et al. study [13], which used BMS as the control group. Compared to overall stent group, the LLL in the DCB group was considerably lower (MD = −0.19, 95 % confidence interval (CI): −0.32 to −0.06, P = 0.003) (Fig. 9). However, $I^2 = 83.10$ % indicates that there was great heterogeneity among these studies. A sensitivity analysis was performed by sequentially excluding studies one by one, and the results showed that the aforementioned outcome indicators were relatively stable (Supplementary Fig. 1).Excluding the Shin ES et al. study, which used BMS as the control group; the DCB group still resulted in a significant reduction in LLL compared with the DES group (MD = −0.13, 95 % confidence interval (CI): −0.22 to −0.04, P = 0.006) (Fig. 9A). Meanwhile, in patients with excluded STEMI, the DCB group exhibited a statistical reduction in LLL compared with the stent group (MD = −0.40, 95 % confidence interval (CI): −0.78 to −0.03, P = 0.036), but this result was not shown in the STEMI patient (Fig. 9B).

3.4.2. Minimal lumen diameter immediately after PCI (MLD1)

The results showed that MLD1 in DCB group was smaller than that in stent group with a heterogeneity (MD = −0.36, 95 % confidence interval (CI): −0.51 to −0.22, P < 0.001, $I^2 = 81.2$ %, P < 0.001) (Fig. 10). A sensitivity analysis was performed showed that the aforementioned outcome indicators were relatively stable (Supplementary Fig. 2).

3.4.3. Minimal lumen diameter at follow-up angiography (MLD2)

The results showed that MLD2 in the DCB group was smaller than that in the stent group with heterogeneity (MD = −0.14, 95 % confidence interval (CI): −0.31 to 0.03, P = 0.097, $I^2 = 71.9$ %, P = 0.002) (Fig. 11). Sensitivity analyses were performed and found that heterogeneity decreased from the previous study after culling the Shin ES et al. study [13], which used BMS as the control group (Supplementary Fig. 3). However, MLD2 still was smaller in the DCB group than in the DSE group (Fig. 11A).

3.5. Subgroup analysis

To further compare the safety and efficacy of DCB to stent, data were sorted and analyzed according to stent type and disease type. In the subgroup where DES was the control group, the results showed that the risk of the safety outcomes in patients receiving DCB strategy was similar to that of DES strategy, but for the efficacy outcomes, the advantage of DCB in reducing LLL was still observed. In the subgroup where BMS was the control group, for the safety outcomes, we found that the risk of TLR was lower in patients receiving the DCB strategy. For the efficacy outcomes, only 1 study provided the angiographic outcomes, which could not be calculated the combined effect size. Furthermore, In the subgroup of patients with STEMI who all used DES as the control group, the safety indicators and LLL showed no statistically significant differences between DCB and DES, but MLD in the DCB was smaller. While in subgroup of patients with excluded STEMI, we found that the risk of MACE and TLR was lower in the DCB compared with the overall stent, and the LLL in the DCB group was smaller. The detailed description results were shown in the form below (Tables 2 and 3).

3.6. Publications bias

Publication bias was assessed by funnel plots for cardiac death. The funnel plots showed that the points were relatively evenly distributed on both sides of the midline line according to a visual inspection (Supplementary Fig. 4). The absence of bias was also confirmed by Egger's test (P = 0.906 for Cardiac death and P = 0.393 for LLL) (Supplementary Figs. 5–6).

4. Discussion

The main findings of our meta-analysis can be summarized as follows: (1) DCB had a significant decrease in LLL compared to the overall stent (including BMS and DES), but no statistically significant difference was detected in safety outcomes; (2) As compared to DES, DCB showed no statistically difference in safety outcomes, whereas MLD and LLL were smaller in DCB group; (3) As compared to BMS, DCB significantly reduces the risk of TLR; (4) In STEMI patients, the safety outcomes and LLL showed no statistically difference between DCB and DES; (5) While in patients with excluded STEMI, the incidence of MACEs and TLR was lower in the DCB group compared with the overall stent.

As coronary large vessels supply blood to a wider area and contain more smooth muscle fibers, it is widely accepted that they are more susceptible to elastic retraction, which can lead to acute vascular occlusion [20], and stenting is frequently the best strategy. There were many issues arising from the stent itself [21], such as higher restenosis rates due to endothelial overgrowth from BMS [22], late stent thrombosis due to delayed healing and persistent inflammatory process from DES [23], increased risk of hemorrhage from the requisite prolonged dual antithrombotic therapy (DAPT), and rarely mentioned allergic reactions to coronary stents that may play a role in ISR or stent thrombosis [24]. Therefore, the notion of "leaving nothing behind" is particularly alluring for the treatment of de novo coronary lesions [25]. Anatomical subgroup analysis of retrospective and prospective observational studies [26–28] initially suggested that the application of DCB was feasible in large vessel disease. In our study, there was no significant difference in safety outcomes for DCB compared to DES. However, a meta-analysis published by Lin et al. [8] reported an increased TLR in the DCB compared to the DES, which may be included in observational studies, increasing the possibility of confounding bias. The use of DCB should have been subjected to greater scrutiny and required reasonable security assurances.

Given that DES is the mainstay of treatment for large coronary arteries, we compared the safety and efficacy between DCB and DES in subgroup analysis, which showed no significant differences in safety outcomes. However, in terms of efficacy outcomes, it was observed that MLD1 was smaller in the DCB than in the DES, and it presented similar results in MLD2. First, similar to POBA, DCB is not effective in counteracting acute passive vascular elastic recoil [14]. Second, it might be attributed to the treatment allocation, wherein the operator preferred stenting when the target vessel lesion was larger. But for LLL, the DCB was lower and even showed late lumen enlargement (LLE). LLL was calculated by post-procedure MLD minus follow-up MLD, which was considered a marker of poor remodeling [29].

The mechanism of late lumen enlargement has not been elucidated, Yamamoto et al. [29] assessed by intravascular ultrasound (IVUS) to show a significantly decrease in mean plaque volume among those in the larger and moderate LLE groups, but not in the group without lumen enlargement. Additionally, balloon delivery of paclitaxel may cause plaque regression. As Elgendy et al. [30] mentioned, the long-term antiproliferative effect of the coating drug promotes the physiological healing of blood vessels, producing positive reconstruction and potential lumen enlargement. Ahmad WAW et al. [31] found that, paclitaxel-coated balloons showed a higher anti-restenosis effect than sirolimus-coated balloons in coronary de-novo lesions, with positive remodeling more frequently observed in the paclitaxel group. In our study, LLL and MLD were used as efficacy outcomes. LLL, a direct angiographic measure of neointimal hyperplasia, is the most commonly used surrogate endpoint for DCB in coronary heart disease trials [32]. Failure of DES is mainly due to neointimal hyperplasia [33], whereas DCB could not induce a vasoproliferative cascade reaction in the absence of metallic foreign body implantation, and the mechanism of vessel diameter change is more complex. Lang et al. [32] assessed the

Table 2
Summary effect sizes for outcomes with DCB vs. the control treatment in subgroup analysis by stent type.

Outcomes	DCB vs. DES			DCB vs. BMS			Overall		
	N	RE Effect Sizes (95 % CI)	P	N	RE Effect Sizes (95 % CI)	P	N	RE Effect Sizes (95 % CI)	P
The safety outcomes									
Cardiac death	7	1.10 (0.29, 4.27)	0.887	2	0.17 (0.02, 1.41)	0.102	10	0.58 (0.24, 1.40)	0.226
All-cause mortality	5	1.19 (0.30, 4.70)	0.804	NA	NA	NA	6	0.69 (0.30, 1.59)	0.387
Non-fatal myocardial infarction	6	0.84 (0.37, 1.90)	0.676	2	0.08 (0.00, 1.40)	0.084	9	0.63 (0.30, 1.35)	0.239
Bleeding event	3	1.24 (0.15, 10.53)	0.845	2	1.23 (0.58, 2.61)	0.594	5	1.22 (0.61, 2.46)	0.578
MACEs	6	0.79 (0.44, 1.42)	0.436	1	0.07 (0.01, 0.51)	0.009	8	0.55 (0.30, 1.00)	0.051
TLR	7	0.83 (0.39, 1.75)	0.618	2	0.11 (0.01, 0.82)	0.031	10	0.67 (0.34, 1.32)	0.243
The efficacy outcomes									
LLL	6	−0.13 (−0.22, −0.04)	0.006	1	−1.00 (−1.37, −0.63)	<0.001	7	−0.19 (−0.32, −0.06)	0.003
MLD1	6	−0.36 (−0.52, −0.19)	<0.001	1	−0.40 (−0.65, −0.15)	0.002	7	−0.36 (−0.51, −0.22)	<0.001
MLD2	6	−0.20 (−0.33, −0.07)	0.002	1	0.50 (0.09, 0.91)	0.018	7	−0.14 (−0.31, 0.03)	0.097

Abbreviations: RE, random effects; CI, Confidence Interval; RR, Risk Ratio; NA, not available; N, number of included studies.

Table 3
Summary effect sizes for outcomes with DCB vs. the control treatment in subgroup analysis by disease type.

Outcomes	STEMI			Non-STEMI			Overall		
	N	RE Effect Sizes (95 % CI)	P	N	RE Effect Sizes (95 % CI)	P	N	RE Effect Sizes (95 % CI)	P
The safety outcomes									
Cardiac death	4	0.75 (0.15, 3.85)	0.728	5	0.37 (0.12, 1.16)	0.088	10	0.58 (0.24, 1.40)	0.226
All-cause mortality	3	1.00 (0.06, 15.75)	1.000	2	0.51 (0.18, 1.44)	0.203	6	0.69 (0.30, 1.59)	0.387
Non-fatal myocardial infarction	3	0.96 (0.28, 3.23)	0.947	5	0.23 (0.04, 1.21)	0.083	9	0.63 (0.30, 1.35)	0.239
Bleeding event	3	1.24 (0.15, 10.53)	0.845	2	1.23 (0.58, 2.61)	0.594	5	1.22 (0.61, 2.46)	0.578
MACEs	3	0.68 (0.28, 1.69)	0.407	4	0.30 (0.10, 0.86)	0.025	8	0.55 (0.30, 1.00)	0.051
TLR	4	0.80 (0.28, 2.31)	0.676	5	0.25 (0.07, 0.84)	0.025	10	0.67 (0.34, 1.32)	0.243
The efficacy outcomes									
LLL	4	−0.11 (−0.23, 0.01)	0.071	3	−0.40 (−0.78, −0.03)	0.036	7	−0.19 (−0.32, −0.06)	0.003
MLD1	4	−0.27 (−0.35, −0.20)	<0.001	3	−0.48 (−0.77, −0.18)	0.001	7	−0.36 (−0.51, −0.22)	<0.001
MLD2	4	−0.14 (−0.25, −0.03)	0.014	3	−0.09 (−0.55, 0.37)	0.701	7	−0.14 (−0.31, 0.03)	0.097

Abbreviations: RE, random effects; CI, Confidence Interval; RR, Risk Ratio; N, number of included studies.

correlation between surrogate endpoints and clinical endpoints, and noted that MLD/%DS (percentage diameter stenosis) should be considered a more appropriate surrogate endpoint for coronary artery disease when comparing DCB with DES. Therefore, further RCTs using different outcome endpoints are still needed to demonstrate the benefit of DCB for de novo lesions in large coronary arteries.

It is important to note the potential technical complexity added by the use of DCB. DCB is designed to deliver an antiproliferative drug and is not intended to be used to prepare lesions; consequently, lumen predilatation generates microdissection, which is necessary for optimal drug up-take [6,34]. As suggested in the DCB Consensus [34], after lesion preparation, residual stenosis, TIMI (Thrombolysis In Myocardial Infarction) flow grade, and severity of dissection, become critical for determining the suitability of DCB treatment. Shin et al. [13] demonstrated that fractional flow reserve (FFR)-guided DCB treatment was superior to BMS. In the REVELATION trial [14], there was no significant difference between DCB and DES in terms of FFR assessed at 9 months. Using intracoronary physiology, FFR to guide the use of DCB-only in large coronary arteries is safe and effective, and the recommended FFR threshold of 0.80 may be a reasonable risk predictor. Considering the impact of acute recoil and dissection on physiological assessment, Yamamoto et al. [35] conducted a study that demonstrated a significant decrease in FFR and instantaneous wave-free ratio (iFR) 15 min after DCB treatment in the bailout stenting group, and that serial physiological assessment after DCB is essential. In addition, intravascular imaging techniques, such as IVUS/optical coherence tomography (OCT), which provide real-time assessment of vessel size, lumen area, dissection, etc. to optimize PCI protocols, lack standardized evidence-based guidelines.

Subgroup analyses were conducted in line with the urgency of PCI, found that there was no statistically significant difference in safety outcomes between patients with STEMI who had DCB therapy and those who received DES treatment, whereas the MLD was lesser in the DCB group, which could be attributable to the treatment allocation itself, as previously mentioned. Similar to Li et al. [36], whereby they showed that among the setting of STEMI, the risk of MACEs in DCB group was comparable to that in the stent. In a recently largest cohort study [37] assessing the safety of DCB-only compared with DES for STEMI, there was no difference in all-cause mortality nor in any of the secondary outcome, and the median vessel diameter was >3 mm in both groups. The predominant mechanism of acute total lumen occlusion in STEMI is rupture of vulnerable coronary atheromatous plaque [38], resulting in a dramatic reduction or interruption of coronary blood supply and the need for emergency restoration of perfusion. Nevertheless, following balloon dilatation during PCI, quite a few infarct-related lesions still contain residual thrombus, which can result in a reduction in coronary flow [39,40], a phenomenon referred to as "no-reflow" [41]. Hence, a" deferred stenting" strategy has been proposed, and its viability and safety has been substantiated in pertinent study [42]. For that, DCB emerges as a possible option due to its ability to restore coronary blood flow, facilitate wall repair, and avoid the potential hazards linked with stent implantation. It is worth highlighting that STEMI caused by plaque rupture is frequently accompanied by varying degrees of thrombotic burden; optimal lesion preparation is necessary prior to the adherence of drug-coated surfaces to sick endothelial cells in DCB procedures, and in the presence of thrombus, this may beinappropriate due to the inhibition of drug delivery to the vessel wall [43]. Hence, rigorous patient selection and adequate target vessel lesion preparation are even more crucial.

In terms of patients who could be treated with elective PCI (excluding STEMI), the incidence of MACEs and TLR was lower in the DCB compared with the stent. Unlike STEMI due to plaque rupture, the mechanism of superficial plaque erosion is probably often associated with non-ST-elevation myocardial infarction NSTEMI [44], whereas the majority of CAD is caused by stable plaques, and there is little possibility of predicting which plaque may lead to a future cardiovascular event [38], and fortunately with optimum medical therapy, progression from stable coronary artery disease to acute coronary syndromes is rare [45]. The COURAGE trial [46], which randomly selected 2287 patients for the comparison of PCI and no-PCI treatment, there were no significant differences in the primary outcomes between the two groups, even over a five-year period. Even more, the timing of invasive strategies (IS) for NSTEMI is still under debate, with a treatment based on antithrombotic drugs and statins that passivate plaque serving as a condition for delaying percutaneous coronary intervention [47]. In the study by Kite et al. [48], early IS in patients with NSTEMI did not reduce repeat re-vascularization, etc., in the context of optimal drug therapy compared to a delayed IS.

These benefits prompted us to think about the intensity of intervention required for this particular patient, with stronger

interventions not necessarily yielding better results. To begin with, in the coronary arteries as a whole, there are usually multiple areas of atherosclerosis, and in the context of optimal medicine treatment, the drugs are effective for the coronary arteries as a whole, whereas stenting tends to be in the individual segments that are considered to be the most severely affected. Moreover, during stent placement, the stent presses against the wall and squeezes the thrombus and plaque at the lesion; this mechanical compression has the potential to cause the dislodgement of thrombus and plaque fragments, resulting in distal microvasculature and even a no-reflow phenomenon. Additionally, DCB avoids prolonged and persistent inflammation resulting from residual stent, while also decreasing late stent thrombosis and avoiding loss of vasomotor function. From an alternative standpoint, individuals are exposed to an enhanced risk of bleeding events when receiving dual antiplatelet therapy (DAPT) following percutaneous coronary intervention [49].

Although there had been meta-analysis of the use of DCB-only strategies in large coronary lesions, the number of included studies was quite small and the sample sizes were not large enough, limiting the ability to detect differences between DCB and stent groups. In our meta-analysis, we comprehensively assessed the impact of DCB-only strategies on angiographic and clinical outcomes in large coronary lesions, identified sources of heterogeneity by quantitative analysis, and provided new evidence-based medical evidence. Furthermore, we only included randomized studies to minimize possible selection bias.

There are some limitations in this study. First, the 10 studies included had a follow-up duration ranging from 6 to 12 months, and the shorter follow-up time does not provide an adequate indication of the long-term safety of the DCB strategy. Second, different baseline risk distributions, types of stents/DCBs used, and different antiplatelet regimens may have influenced the validity of our results, but perhaps the most important difference was in the different intervention strategies. Thirdly, due to the limited number included, specific patient subgroups could not be further evaluated, potentially limiting the applicability to a broader population of patients with vascular disease. Finally, the definition of MACEs varied among the studies include, and there may have been some heterogeneity, however, our study design employed a random-effects model rather than a fixed-effects model to estimate the effect, as the former measure yielded a more conservative result [50].

5. Conclusion

This study found that DCB could be a promising alternative for treating de novo lesions in large coronary arteries with satisfactory efficacy and low risk, superior to BMS and not inferior to DES. We also found that when used in STEMI patients, DCB appeared to be safe and effective, whereas in elective percutaneous coronary intervention patients (excluding STEMI), it showed more positive effects. Moreover, a trend toward lower late lumen loss in the absence of stenting may be more favorable for outcomes. Further studies are imperative in order to validate that approach.

Data availability statement

Data included in article/supp. material/referenced in article.

Funding

No funds, grants, or other support was received.

Protocol and registration

This systematic review and meta-analysis strictly followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement and elaboration for standardized reporting. The protocol of this study was registered in PROSPERO with the registration number CRD 42023439002.

CRediT authorship contribution statement

Jin-Li Jiang: Data curation, Formal analysis, Writing – original draft. **Qiao-Juan Huang:** Methodology, Project administration, Supervision, Validation. **Meng-Hua Chen:** Conceptualization, Project administration, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e25264.

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