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Systematic Review

Acute Vessel Closure or Major Adverse Cardiac Events of Drug-Coated Balloons and Stents: A Systematic Review and Meta-Analysis

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Abstract: While the use of drug-eluting stents (DES) has become the first-line strategy for treating coronary artery disease, there are still drawbacks with their use. As our understanding of coronary artery anatomy and physiology evolves, growing evidence supports the use of drug-coated balloons (DCB) not only in the treatment of in-stent restenosis but also in de novo lesions. The aim of this systematic review and meta-analysis is to determine if there is a difference in outcomes when DCBs are used versus when stents are used. PubMed, Cochrane and Web of Science databases were systematically searched. The primary outcome of the meta-analysis was acute vessel closure and the secondary outcomes were stent complications including major adverse cardiovascular events (MACE) and all-cause mortality. Eleven studies with a total of 2349 patients were included. No significant difference was found in terms of acute vessel closure between DCBs and all stents (2.6% vs. 1.0%, OR: 2.13 (0.74–6.44), I^2: 4%, $p = 0.16$). Furthermore, there was no difference in MACE (6.8% vs. 10.1%, OR: 0.53 (0.27–1.04), I^2: 48%, $p = 0.06$), all-cause mortality and target lesion revascularisation. This meta-analysis suggests that the use of DCBs is a safe alternative to stents when treating coronary artery disease.

Keywords: drug-coated balloon (DCB); drug-eluting stent (DES); coronary artery disease (CAD)

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1. Introduction

The initial excitement and optimism for balloon angioplasty to treat coronary artery disease was quickly hampered by the adverse outcomes seen, including 5–10% of patients suffering acute vessel closure [1]. Subsequent generations of stents were developed to mitigate this. Drug-eluting stent (DES) technology continues to evolve and be refined within the field of percutaneous coronary intervention (PCI) with newer generations wielding finer strut designs and less thrombogenic polymers [2]. Whilst DESs have become the default treatment for coronary artery disease, it is apparent that despite successive generations of DESs there remain several established potential disadvantages associated with stents that include anatomical complexities [3,4], thrombotic complications [5] and haemodynamic (shear stress) [6] and more physiological vasomotor disadvantages (including attenuated endothelial function and microvascular dysfunction) [7–9].

Drug-coated balloons (DCB) are semi-compliant angioplasty balloons that can be used to treat coronary artery disease based on the advantage that they transfer a lipophilic, anti-proliferative drug into the vessel wall during balloon inflation without the need for a stent scaffold implant [10,11]. Most commonly, the anti-proliferative drug coating on DCBs is the chemotherapeutic agent Paclitaxel although there are also Sirolimus DCBs available [11].

Currently, the European Society of Cardiology (ESC) guidelines only recommend DCBs in the treatment of in-stent restenosis [12]. However, whilst there is growing evidence supporting the utilisation of DCBs in both de novo small and larger vessels [11,13,14], the RCTs comparing stents with DCBs have relatively small numbers [15–19]. A considerable amount of debate has centred on the risk of acute vessel closure after angioplasty, an area considered to be a major source of potential adverse outcome with DCBs. We hereby present the first meta-analysis combining RCTs of DCBs versus stents, paying particular attention to the rates of acute vessel closure and stent complications.

2. Materials and Methods

We conducted a meta-analysis comparing clinical outcomes with DCBs and stents from randomised controlled trials. This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) [16]. A systematic review of all relevant literature was undertaken to enable this meta-analysis. A systematic search was conducted using PubMed Central (PMC), Web of Science and Cochrane databases from inception to December 2021. The protocol was prospectively registered with OSF: https://doi.org/10.17605/OSF.IO/8G6BZ., accessed 23 November 2022. The search strategy used medical study headings and key words, with our search terms of "randomised" or "randomized", "drug coated balloon" or "drug eluting balloon" and "stent". After removal of duplicates, 2294 records were screened at title/abstract level by four independent researchers (TG, IM, NC and VT). In cases of uncertainty, another independent researcher (VV) adjudicated. Relevant full texts were screened for inclusion by two researchers (TG and NC).

In order for studies to meet our inclusion criteria, they needed to be randomised study designs using a DCB-only angioplasty versus any type of stent used for the treatment of de novo coronary disease and report clinical outcomes including acute vessel closure and major adverse cardiovascular events (MACE) or any part of MACE. Studies were excluded if they featured a hybrid strategy, e.g., DCBs in conjunction with a stent, the use of bioresorbable scaffolds or any non-randomised study design.

The primary outcome measure was acute vessel closure, defined as clinical or ECG evidence of myocardial ischaemia and/or a critical reduction in blood flow in the vessel dilated leading to either emergency repeat cardiac catheterization, repeat PCI, immediate coronary bypass surgery, or myocardial infarction.

Secondary outcome measures were major adverse cardiovascular events (MACE) and any component of this that was individually reported, including stent thrombosis (defined as definite if confirmed angiographically or pathologically), target lesion revascularisation (TLR), myocardial infarction (MI) and all-cause death.

Data extraction was undertaken by three independent researchers (VT, NC and TG) into a pre-specified excel spreadsheet.

Statistical analysis was conducted using Review Manager 5.3 for MacOS software. The Cochrane Risk of Bias Assessment tool (RoB 2) was used to identify quality of RCTs included in the meta-analysis. Odds ratios (OR) with 95% confidence intervals (CI) were used as summary statistics, with I^2 to quantify heterogeneity. Where heterogeneity was moderate (25–50%) or high (>50%), a random effects model was used. Otherwise, a fixed-effects inverse-variables model was used. Robustness was tested using sensitivity analyses by sequentially removing studies and publication bias was assessed with funnel plots. Statistical significance was set at $p < 0.05$.

3. Results

Of the 2294 studies screened, 70 full texts were assessed for eligibility, with 11 studies included in the analysis, as shown in Figure 1.

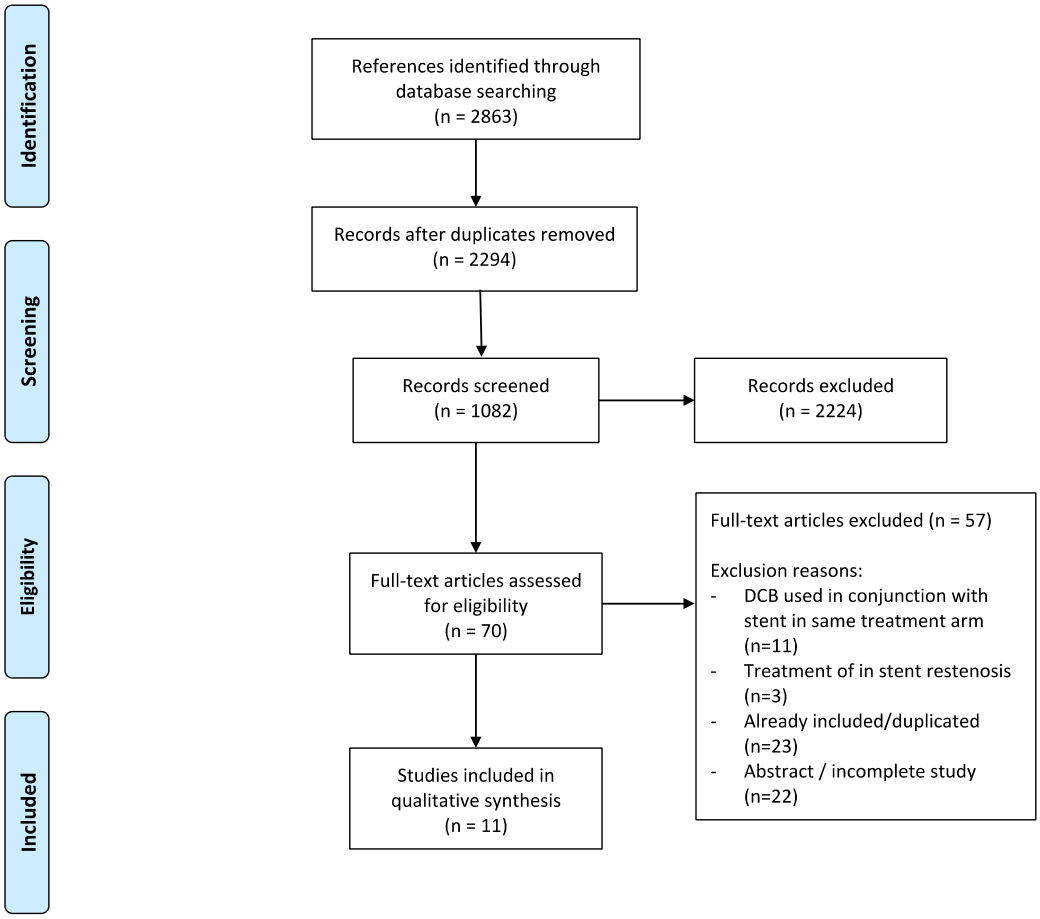

Figure 1. Consort diagram showing literature search and screening process.

The meta-analysis included a total of 2349 patients: 1132 received DCBs and 1110 received stents. The included studies have been summarised in Table 1.

Table 1. Population characteristics of the included studies.

Study ID	Year of Publication	Patients, n DCBs	Patients, n DESs	Clinical Presentation	Age (Mean)	Male Sex n(%)	DCB Used	Stent Used	Follow-Up Time (Months)
Colombo et al. [17]	2015	90	92	Stable/unstable angina Silent ischaemia	65.6	143 (78.6)	In.pact falcon	DES	36
Nishiyama et al. [18]	2016	27	33	Stable angina/silent ischaemia			SeQuent PLEASE	DES	8
Gobic et al. [19]	2017	32	31	STEMI	55.5	46 (72.0)	SeQuent PLEASE	DES	6
Jeger et al. [20]	2018	382	376	All comers	67.8	557 (73.4)	SeQuent PLEASE	DES	36
Shin et al. [21]	2019	20	20	High bleeding risk			SeQuent PLEASE	BMS	9
Rissanen et al. [22]	2019	125	118	High bleeding risk	76.8	131 (62.9)	SeQuent PLEASE	BMS	9
Cortese et al. [23]	2020	118	114	All comers	65.0	170 (73.3)	Elutax SV	DES	6
Scheller et al. [24]	2020	104	106	NSTEMI	66.5	141 (67.1)	SeQuent PLEASE+/-NEO	BMS + DES	9
Wang et al. [25]	2021	92	92	STEMI			Vasoguard DCB	DES	9
Yu et al. [26]	2021	84	79	Stable angina	63.3	118 (72.4)	SeQuent PLEASE	DES	9
Niehe et al. [27]	2022	60	49	STEMI	57.4	104 (87)	Biotronik Pantera Lux	DES	24

DCB = drug coated balloon, DES = drug eluting stent, n = number, STEMI = ST elevation myocardial infarction, NSTEMI = non-ST elevation myocardial infarction, BMS = bare metal stent.

From the studies included, five were all clinical presentations, three included only STEMI patients, a further one included patients with NSTEMI and two included patients with stable coronary disease. The mean age of patients was 64.7. Within the stent arms of the studies, eight studies used DESs, two studies used bare metal stents and one study used a combination of BMS and DES. The median follow-up time was 9 months.

With regards to the primary outcome of acute vessel closure, there were 13 (2.6%) acute vessel closures in the DCB arm compared to 5 (1.0%) in the stent arm using a fixed effects model, odds ratio: 2.13 (0.74–6.44 95% CI) with low heterogeneity in I^2 of 4%. This was not statistically significant (p = 0.16), as shown below in Figure 2.

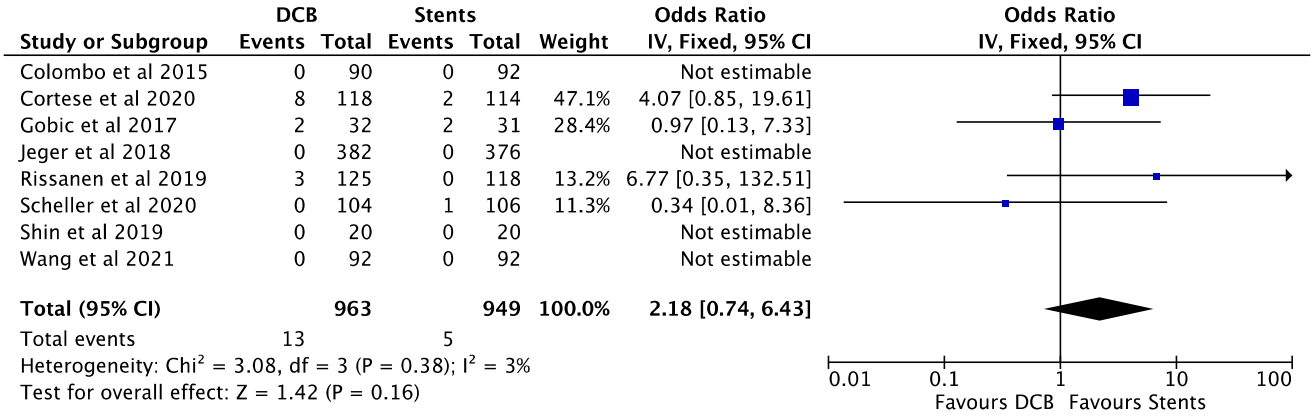

Figure 2. Forest plot of acute vessel closure when comparing DCBs with all stents. DCB, Drug-Coated Balloon; IV, inverse variance; CI, confidence interval.

A sensitivity analysis comparing DCBs with DESs in relation to events of acute vessel closure still did not show a statistically significant difference with event rates of 10 (1.4%) compared to 4 (0.6%) in the DES group (fixed-effects model, odds ratio of 2.37, CI: 0.69–8.21, I^2 of 17% and p-0.17) (Figure 3).

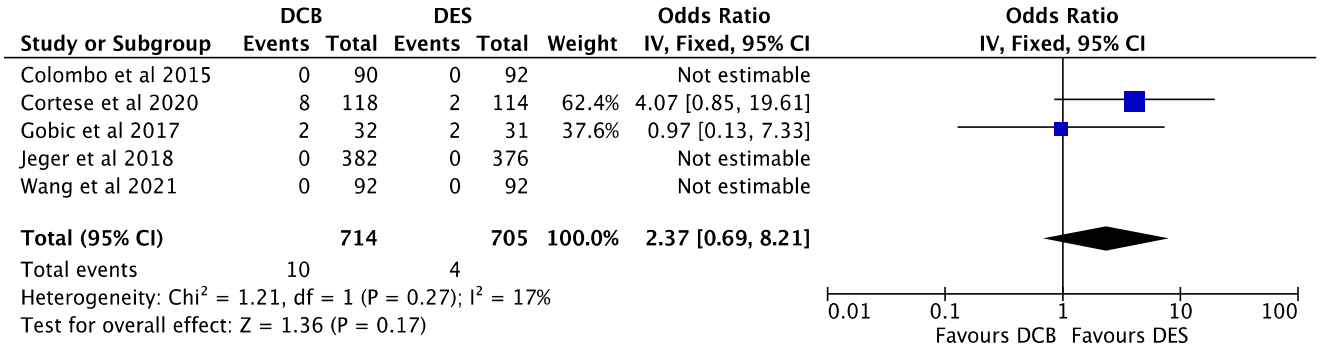

Figure 3. Sensitivity analysis of Acute Vessel Closure, comparing DCBs with DESs (and excluding BMSs). DCB, Drug-Coated Balloon; DES, Drug-Eluting Stent; IV, inverse variance; CI, confidence interval.

The occurrence of MACE was 6.8% in the DCB arm compared to 10.1% in the stent arm using a random effects method (Odds ratio: 0.53, 95% CI: 0.27–1.04, I^2: 48% with a p value of 0.06), as shown in Figure 4.

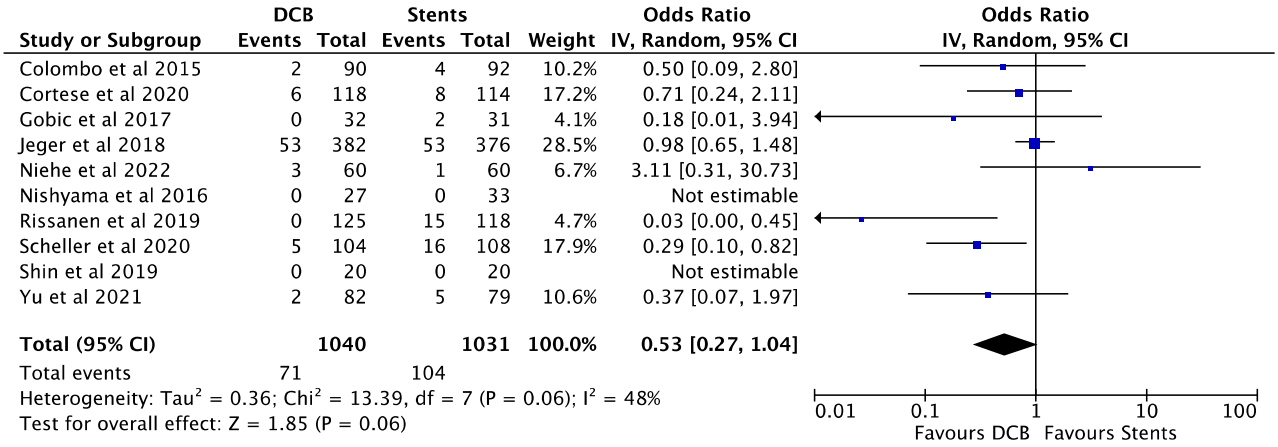

Figure 4. Forest plot of major adverse cardiovascular events, comparing DCBs with all stents. DCB, Drug-Coated Balloon; IV, inverse variance; CI, confidence interval.

A sensitivity analysis removing the BMS studies still showed no statistically significant difference (8.3% compared to 9.3%), odds ratio: 0.91, CI: 0.66–1.24, $p = 0.55$ (Supplementary Figure S1). A further subgroup analysis of MACE by presentation (including both elective and STEMI patients) showed no statistically significant difference between DCBs and stent-in electives, the odds ratio was 0.37 (CI: 0.07–1.97), $p = 0.24$ (Figure 5) and in STEMI patients, OR: 0.83 (0.07–10.65), $p = 0.89$ (Figure 6).

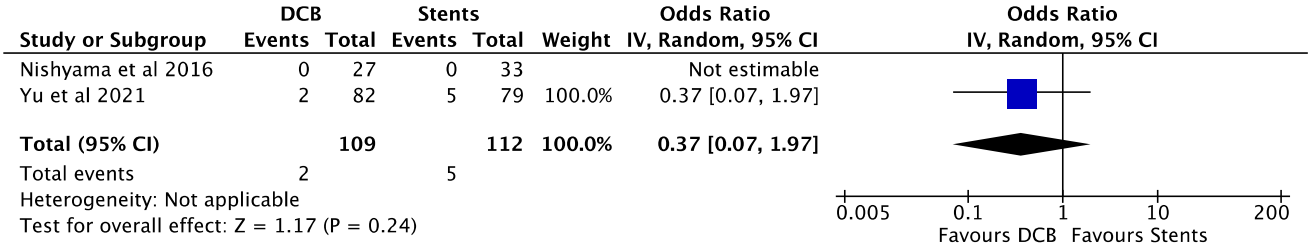

Figure 5. Forest plot of major adverse cardiovascular events in elective patients. DCB, Drug-Coated Balloon; IV, inverse variance; CI, confidence interval.

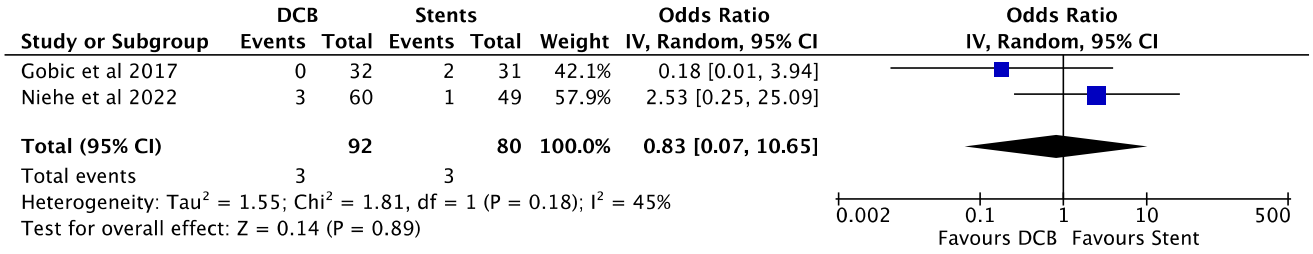

Figure 6. Forest plot of major adverse cardiovascular events in STEMI patients. DCB, Drug-Coated Balloon; IV, inverse variance; CI, confidence interval.

There was no significant difference between the DCB and stent strategies with regards to all-cause mortality (4.5% in DCBs compared to 5.2% in stents) with an odds ratio of 0.86 (0.53–1.38), I^2 0% (fixed effects) and $p = 0.52$, as shown in Figure 7.

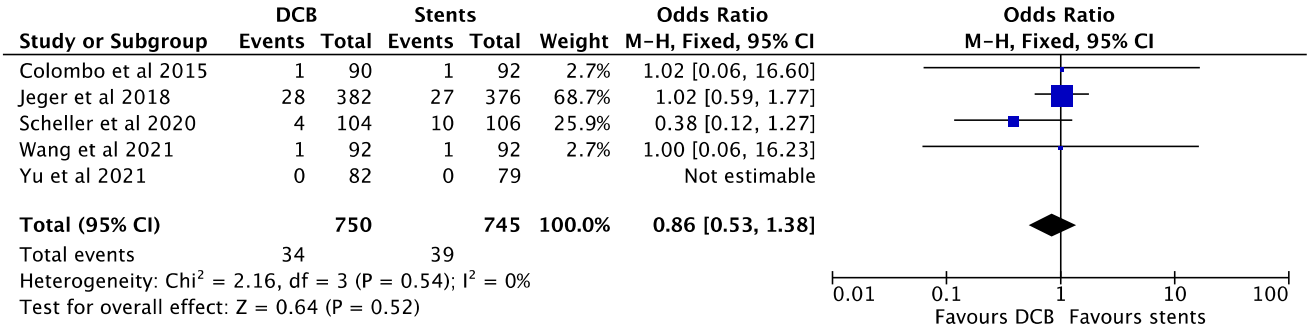

Figure 7. Forest plot for all-cause mortality. DCB, Drug-Coated Balloon; M-H, Mantel-Haenszel method; CI, confidence interval.

Finally, there was no difference found in target lesion revascularisation (TLR) rates, with 5.1% TLRs in the DCB group compared to 4.8% in the stent group (OR: 1.06, 95%CI 0.73–1.52, I^2: 6%, $p = 0.76$), as shown in Figure 8.

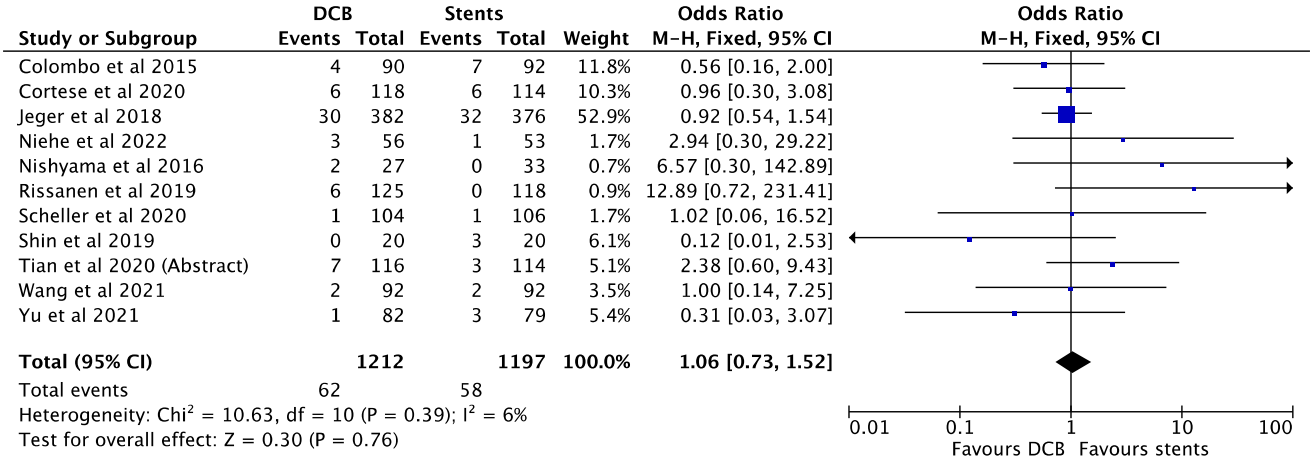

Figure 8. Forest plot for target lesion revascularisation. DCB, Drug-Coated Balloon; M-H, Mantel-Haenszel method; CI, confidence interval.Funnel plots for acute vessel closure, MACE and TLR showed no significant publication bias (Supplementary Figure S2a–c).

4. Discussion

This meta-analysis of 2349 patients from 11 RCTs demonstrated that there is no significant difference between DCBs and stents in the rates of acute vessel closure (2.6% vs. 1.0%, Odds Ratio: 2.13, 95%CI 0.74–6.44, I^2 4%, p 0.16). Additionally, it was found that DCBs and stents have similar rates of MACE (6.8% vs. 10.1%, Odds ratio: 0.53, 95% CI: 0.27–1.04, I^2 48%, p 0.06), all-cause mortality (OR 0.86, 95%CI 0.53–1.38, I^2 0%, p 0.52) and target lesion revascularisation (OR 1.06, 95%CI 0.73–1.52, I^2 6%, p 0.76).

The risk of acute vessel closure was a key driving factor in the development of coronary stents, as early reports of occurrence were as high as 8.3% prior to the development of stents [1]. However, with improvements in angiographic imaging quality, additional intracoronary imaging tools, better understanding of coronary dissections and operator experience, it is apparent which vessels can safely be treated without a stent implantation strategy. Furthermore, whilst the early landmark stent trials showed a reduction in long-term clinical outcomes with stents compared to balloon angioplasty, Benestent reported no difference in acute vessel closure or any in-hospital event between the balloon angioplasty/stent groups [28]. Acute stent thrombosis is also a recognised complication with any stent, although newer antiplatelet regimens combined with improved drug-eluting stent development have reduced this rate to about 1% within 30 days [29]. Despite this, the risk of acute vessel closure remains a concern amongst interventionalists when not implanting

a stent. Individually, all of the randomised controlled trials included in this meta-analysis would not be adequately powered to detect a difference in acute vessel closure rate between the two study arms.

Our meta-analysis shows no difference in the rates of acute vessel closure between DCBs and any stent strategy, even when completing a subgroup analysis for DCBs compared to DESs. DCBs have never been shown to be associated with an increased risk of acute vessel closure when compared to DESs; however, given the concern about acute vessel closure with balloon angioplasty only, we felt it important to explore this risk. A subtle difference in terminology may help this discussion, as although stents were developed for acute vessel closure, this was specifically to bailout those cases that were apparent at the time of the procedure (vessel threatening dissections and flow limiting recoil). However, if a PCI result is deemed safe angiographically, there are no data to suggest that stent implantation reduces subsequent acute vessel closure within the first 24 h. Indeed, the acute vessel closure rate was higher in the stent arm of the trial by Benestent et al. [28]. The mechanisms associated with acute stent thrombosis are identified as platelet aggregation and activation in response to the stent, procedural/lesion specific factors such as small vessel size, multiple stents, coronary dissection, geographic miss, stent malapposition, under expansion of the stent, stent design and bifurcation lesions [30]. Early acute vessel closure was reduced by the introduction of dual-antiplatelet therapy [31].

Whilst stents were introduced to overcome the acute complications of balloon angioplasty, the early long-term composite outcomes were found to be superior when compared to balloon angioplasty. This was driven by a reduction in target lesion revascularisation and instigated the evolution of stents to form the mainstay of coronary intervention. Despite this, stents were not shown to reduce mortality. Benestent reported a reduction in composite endpoints with stents due to the reduced need for revascularisation [28]. Similarly, the STRESS study reported lower rates of revascularisation with stents but no reduction in death or myocardial infarction [32]. This meta-analysis shows that in current day angioplasty trials, there is no difference in major adverse cardiovascular events when comparing a DCB to a stent strategy, and again when adjusting for a DCB compared with a DES strategy. Furthermore, we identified no reduction in target lesion revascularisation rates between the two strategies.

Despite multiple generations of DESs, potential concerns about the need for prolonged antiplatelet therapy, late and very late stent thrombosis [31] as well as persistent attenuated physiology remain. Consequently, there is a need to investigate the need to always implant a DES and to find alternative treatment strategies. Bioresorbable vascular scaffolds (BVS) were developed combining the benefit of a stent in the short term and the benefits of not having a stent in the long term. Unfortunately, studies demonstrated worse patient outcomes with BVSs and their use is currently not recommended [33–37]. Whilst the practice of utilising DCB only angioplasty is variable and expanding, with an increasing number of RCT and registry data [14,18,24,26,28,35], DCB use is not included in the guidelines outside of the treatment of in-stent restenosis [12].

Despite this, the indications for DCB angioplasty will continue to increase, with the Basket Small-2 trial showing non-inferiority when comparing DCBs with DESs [20]. A meta-analysis by Li M et al. [36] assessed the outcomes of patients with small-vessel coronary artery disease treated with DCBs versus DESs. They included four RCTs with 1227 patients and found no difference in MACE, target vessel revascularisation (TVR) and death while also demonstrating a non-significant trend of a lesser risk of MI in the DCBs group. Sanchez et al. performed a meta-analysis of five randomised trials looking at DCB versus DESs for small-vessel coronary artery disease with a mean follow up of 10 months [37]. DCB use was associated with a similar risk of TVR, TLR and all-cause death, with a trend towards a lower risk of MI and vessel thrombosis. With increasing registry data supporting the safety of DCBs in larger vessel size [11,14], there remain patients and lesion characteristics that may benefit from a DCB strategy, such as calcific disease, diffuse disease, significant size mismatch, bifurcation lesions and high-bleeding-risk patients.

This meta-analysis is the first to date comparing DCBs with stents for all-comers with all coronary vessel sizes. DCB-only angioplasty is not associated with a higher rate of acute occlusions and furthermore, there was no difference in major adverse cardiovascular events. A bail-out stenting rate of 15% indicates that only a minority of patients need a stent acutely for safety reasons.

5. Limitations

The duration of follow-ups for the studies was relatively short, with a median follow-up time of 9 months (the studies ranged from six months to up to three years). However, as our primary outcome was that of acute vessel closure, the duration of follow-up has less importance. Whilst we have not used patient-level data, the large number of patients included in the analysis strengthens the analysis, combined with a low level of heterogeneity across our studies, which has strengthened our statistical findings. Finally, some studies included BMSs in their comparison arm, which whilst appropriate at the time of the study's conception is now a treatment strategy not in routine clinical use. However, our sensitivity analysis showed no change in the outcome when removing BMSs from the analysis.

6. Conclusions

The unresolved persistent disadvantages to the implantation of a permanent stent scaffold structure including procedural complexity, particularly for bifurcation lesions, endothelial dysfunction and mandated dual anti platelet therapies, mean that careful consideration and evolutions in practice are important. This meta-analysis investigated the safety profile of DCBs for acute vessel closure and MACE. We confirm through meta-analysis of RCTs comparing DCBs to stents that the rate of acute occlusions is not significantly different between stents and DCBs and that there is no difference in major adverse cardiovascular events.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/biomed2040035/s1, Figure S1: Sensitivity Analysis of major adverse cardiovascular events in DCB compared to DES; Figure S2: Funnel plots for acute vessel closure (a), major adverse cardiovascular events (b) and target lesion revascularisation (c).

Author Contributions: T.G. and N.C. executed the systematic review and meta-analysis and wrote the first draft. I.M., V.T. and J.R. executed the systematic review and amended the manuscript. S.E. planned and designed the study, supervised the systematic review and meta-analysis and made amendments to the manuscript. V.S.V. planned and designed the study, supervised the systematic review and meta-analysis and made amendments to the manuscript. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: Ethical review and approval were waived for this study as this is a meta-analysis of already published data.

Informed Consent Statement: Patient consent was waived as this is a meta-analysis of already published data.

Data Availability Statement: All data are available from the corresponding author on request.

Conflicts of Interest: The authors declare no conflict of interest.

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