Triple antiplatelet therapy *vs.* dual antiplatelet therapy in patients undergoing percutaneous coronary intervention: an evidence-based approach to answering a clinical query

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT?

- Different strategies have been evaluated for their efficacy in reducing stent thrombosis and restenosis in patients undergoing percutaneous coronary intervention (PCI).
- Triple antiplatelet therapy is one such strategy that has been shown to improve the efficacy outcomes associated with PCI.
- Cilostazol is an antiplatelet agent that is being prescribed as a component of triple-therapy regimen in various centres in our country, and the beneficial effect of cilostazol addition to other antiplatelet regimens has been observed.
- However, the extent of the efficacy is not uniformly in favour of the triple therapy compared with dual therapy.
- Moreover, the use of this agent with bare metal stents (commonly used in developing countries) and drug-eluting stents has not been separately looked into.

WHAT THIS STUDY ADDS

- Triple antiplatelet therapy, with cilostazol as a component, reduces restenosis rates and repeat revascularizations post PCI without any significant increase in bleeding risk.
- The beneficial effect of cilostazol is more evident with drug-eluting stents.
- Its use with bare metal stents needs to be explored further.

AIMS

Outcomes of patients undergoing percutaneous coronary intervention (PCI) with drug-eluting stents (DES) and bare metal stents (BMS) have not been evaluated separately for specific dual and triple antiplatelet agent use. The purpose of this meta-analysis was to determine whether triple antiplatelet therapy (combination of clopidogrel, aspirin and cilostazol) has any advantage in efficacy compared with standard dual antiplatelet therapy (aspirin and clopidogrel) in patients undergoing PCI.

METHODS

Electronic and printed sources were searched till May 2008 for randomized controlled clinical trials (RCTs) of cilostazol in combination with aspirin and clopidogrel. Pooled weighted mean difference (WMD) and pooled odds ratio (OR) with 95% confidence intervals (CIs) were calculated.

RESULTS

A total of four RCTs including 1457 patients with a median follow-up period of 6–9 months were included in the analysis. The rates of major adverse cardiac and/or cerebrovascular events (MACE/MACCE), stent thrombosis and bleeding were not significantly different between triple and dual antiplatelet therapy groups. Pooled analysis showed that cilostazol was associated with significantly decreased incidence of in segment restenosis (ISR) (OR 0.51, 95% CI 0.38, 0.68; $P < 0.00001$), increased minimum luminal diameter (MLD) (WMD 0.16, 95% CI 0.10, 0.22; $P < 0.00001$) for both DES and BMS and also individually. However, the rates of target vessel revascularization (OR 0.45, 95% CI 0.25, 0.83; $P = 0.01$ and late lumen loss (pooled WMD 0.14, 95% CI 0.2, 0.07; $P = 0.001$) were decreased significantly only in the DES group receiving triple therapy.

CONCLUSIONS

Cilostazol appears to be effective in reducing the rates of ISR without any significant benefit for MACE/MACCE.

Review:	Triple Vs Dual antiplatelet therapy in post PCI patients
Comparison:	01 Triple (Aspirin+Clopidogrel+Cilostazol) vs Dual (Aspirin+Clopidogrel)
Outcome:	01 MACE/MACCE frequency

Study or sub-category	Treatment n/N	Control n/N	OR (random) 95% CI	Weight %	OR (random) 95% CI
01 Triple vs Dual antiplatelet therapy in PCI with Bare Metal Stents					
CREST	72/354	67/351		33.23	1.08 [0.75, 1.57]
Chen et al	5/60	14/60		20.40	0.30 [0.10, 0.89]
Subtotal (95% CI)	414	411		53.63	0.63 [0.18, 2.20]

Total events: 77 (Treatment), 81 (Control)

Test for heterogeneity: $Chi^2 = 4.78$, df = 1 (P = 0.03), $I^2 = 79.1\%$

Test for overall effect: Z = 0.72 (P = 0.47)

Study or sub-category	Treatment n/N	Control n/N	OR (random) 95% CI	Weight %	OR (random) 95% CI
02 Triple vs Dual antiplatelet therapy in PCI with Drug Eluting Stents					
DECLARE-Long	7/250	19/250		24.01	0.35 [0.14, 0.85]
DECLARE-DIABETES	6/200	14/200		22.36	0.41 [0.15, 1.09]
Subtotal (95% CI)	450	450		46.37	0.38 [0.20, 0.73]

Total events: 13 (Treatment), 33 (Control)

Test for heterogeneity: $Chi^2 = 0.06$, df = 1 (P = 0.81), $I^2 = 0\%$

Test for overall effect: Z = 2.92 (P = 0.004)

Total (95% CI)	864	861		100.00	0.51 [0.24, 1.08]

Total events: 90 (Treatment), 114 (Control)

Test for heterogeneity: $Chi^2 = 10.77$, df = 3 (P = 0.01), $I^2 = 72.1\%$

Test for overall effect: Z = 1.76 (P = 0.08)

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            0.1  0.2  0.5  1   2    5   10
        Favours treatment    Favours control
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Figure 1

Studies comparing major adverse cardiac event/major adverse cardiac and cerebrovascular event frequencies in triple and dual antiplatelet therapy groups using pooled odds ratio (OR)

Introduction

Recently we were faced with a clinical query regarding the usefulness of triple antiplatelet therapy (cilostazol, aspirin and clopidogrel combination) for patients undergoing percutaneous transluminal coronary angioplasty in our hospital. The underlying logic for off-label use of cilostazol in this setting is that cilostazol has been shown to inhibit vascular smooth muscle proliferation and intimal hyperplasia after endothelial injury, in addition to its antiplatelet effect [1, 2]. As against this, currently used antiplatelet drugs such as aspirin and clopidogrel have no effect on neointimal hyperplasia. More importantly, randomized clinical trials have shown the beneficial effect of cilostazol in reducing long-term major adverse cardiovascular and cerebrovascular events (MACCE) and preventing both angiographic and clinical restenosis in patients [3, 4]. However, the extent of the efficacy is not uniformly in favour of triple therapy *vs.* dual therapy.

The performance of bare metal stents (BMS) is suboptimal in terms of freedom from restenosis and repeat percutaneous coronary intervention (PCI) in lesions at high risk of restenosis. Another aspect of management of these patients is that BMS are the most commonly used stents in our setting due to poor affordability of drug-eluting stents (DES). Thus there is a great need to prevent neointimal hyperplasia and stent restenosis. Some pharmacological agents have been investigated for their usefulness when added to the standard therapeutic regimen in reducing restenosis rates when used in patients undergoing PCI with BMS. However, this has largely been unsuccessful [4].

Ours is a tertiary care centre, and in recent years increasing attempts have been made to incorporate principles of evidence-based medicine in guiding clinical practice. Such evidence is also used in making policy-related decisions. These practices are based on reports that have shown better therapeutic outcomes associated with evidence-based medicine [5, 6]. In order to provide an

Table 1

Characteristic features of included studies

Study	CREST (2005) [11]		Chen et al. (2006) [9]		DECLARE-Long (2007) [10]		DECLARE-DIABETES (2008) [12]	
Patient characteristics	Age 18–75 years. Having indication for bare metal stent implantation with lesion length ≤30 mm. Reference vessel diameter 2.0–4.0 mm. Diameter stenosis rate range 50–100% determined by coronary angiography		Patients with stable or unstable angina or silent myocardial ischaemia undergoing coronary stent implantation. De novo target-lesion stenosis of >50% but <100% in a native coronary artery that was successfully treated by placement of a bare-metal intracoronary stent		>18 years of age with angina pectoris and/or positive stress test findings and a native coronary lesion. Angiographic eligibility for inclusion was a target lesion with a diameter stenosis >50%, visual reference diameter ≥2.5 mm and length ≥25 mm, and a planned total stent length ≥32 mm		Diabetic patients >18 years of age with angina pectoris or positive stress test and a native coronary lesion. Diameter stenosis >50% and reference diameter ≥2.5 mm	
Type of stent	Bare metal stent		Bare metal stent		Drug-eluting stent		Drug-eluting stent	
Clinical follow-up	6 months		6–9 months		9 months		9 months	
No. of patients for angiographic follow-up	259	267	52	54	250	250	200	200
No. of patients for clinical follow-up	354	351	60	60	250	250	200	200
Study groups	Triple	Dual	Triple	Dual	Triple	Dual	Triple	Dual
MLD (mean ± SD)	1.77 ± 0.68	1.62 ± 0.75	2.14 ± 0.52	1.82 ± 0.36	2.07 ± 0.55	1.93 ± 0.57	2.15 ± 0.52	2.03 ± 0.58
LL (mean ± SD)	0.5 ± 0.6	0.75 ± 0.66	0.81 ± 0.39	1.18 ± 0.54	0.34 ± 0.49	0.51 ± 0.49	0.42 ± 0.5	0.53 ± 0.49
Restenosis rate (%)	22.01	34.46	14	32	6.7	11.2	8	15.6
MACE (n)	67	65	–	–	7	19	6	14
Stent	1	1	–	–	1	1	0	1
Thrombosis (n)	54	56	–	–	9	18	7	16
TVR (n)	3	2	–	–	0	2	1	0
Deaths (n)	13	16	–	–	2	4	3	3
Bleeding (n)	13	16	NM	NM	2	4	3	3

LL, lumen loss; MACE, major adverse cardiac events; MLD, mean lumen diameter; TVR, target vessel revascularization; NM, not mentioned.

Table 2

Quality assessment of studies analysed

Checklist items	Randomization		Baseline comparability			Eligibility criteria specified	Co-interventions identified	Blinding				Withdrawal		Intention to treat analysis
	Truly random	Allocation concealment	No. stated	Presented	Achieved			Assessors	Administration	Participants	Procedures assessed	>80% in final analysis	Reasons stated	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
CREST (2005) [11]	√	√	√	√	√	√	√	√	NS	NS	NS	√	√	√
Chen et al. (2006) [9]	√	√	√	√	√	√	√	√	NS	NS	NS	√	√	√
DECLARE-long (2007) [10]	√	√	√	√	√	√	√	√	NS	NS	NS	√	√	√
DECLARE-DIABETES (2008) [12]	√	√	√	√	√	√	√	√	NS	NS	NS	√	√	√

NS, not specified.

evidence-based answer to the clinical query, which is pertinent to the practice at our centre, we undertook a literature search. During our preliminary literature search we came across 30 studies and, interestingly, on the day of query we also came across a systematic review on the same topic [7]. The main conclusions of the review were that cilostazol was safe and effective in reducing the risk of restenosis and repeat revascularization without any significant increase in bleeding rates and incidence of stent thrombosis (ST). In the above meta-analysis, 23 studies were analysed, of which only three compared the triple therapy (clopidogrel based) with dual therapy. No subgroup analysis specifically addressed our query related to the use of the triple regimen of aspirin, clopidogrel and cilostazol. With this background we undertook a meta-analysis to answer the query raised in cardiology practice.

Methods
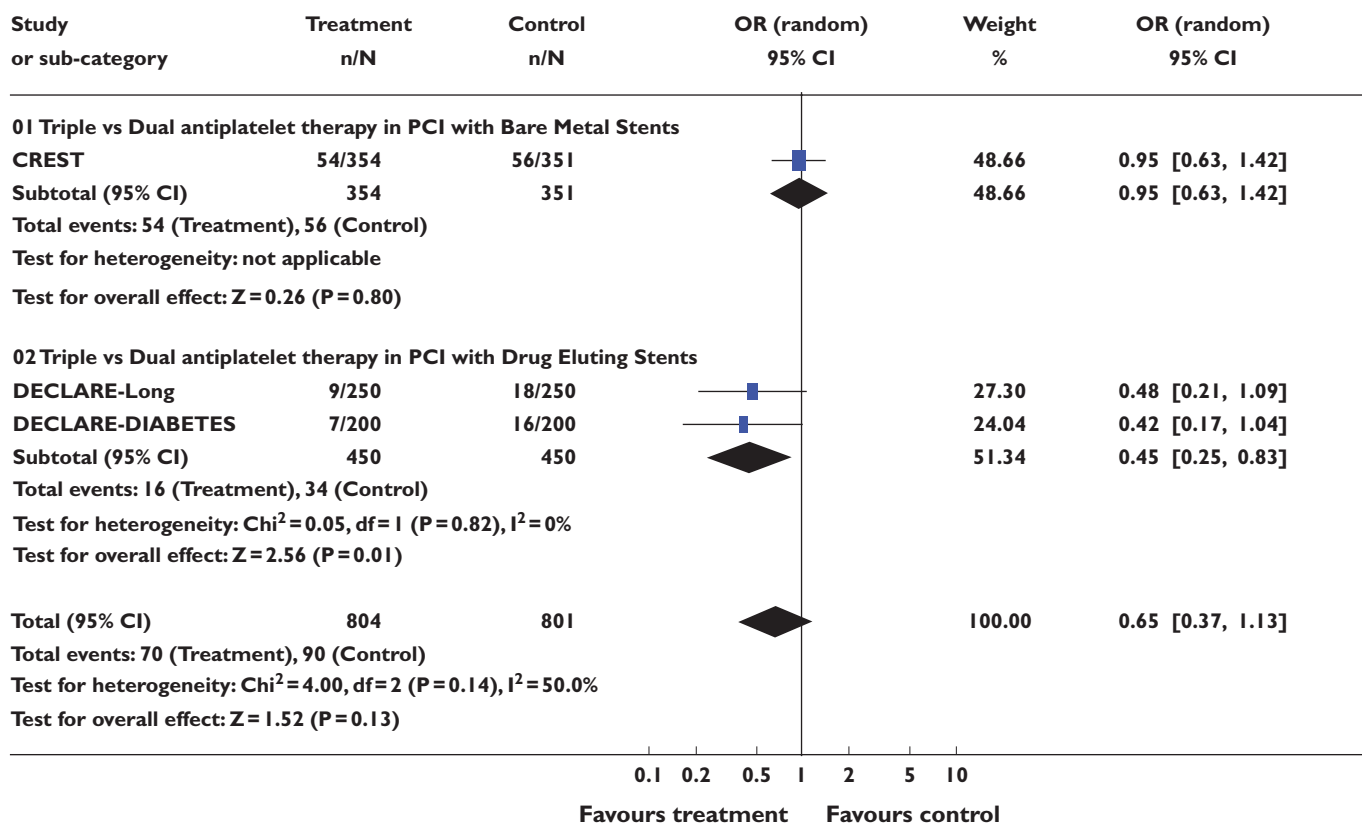
Search strategy and study selection

We systematically searched Medline, Cochrane Central Register of Controlled Trials, and Embsase for all relevant articles up to May 2008. We first entered the medical subjects heading (MeSH) terms and text words, including *cilostazol AND percutaneous coronary intervention AND stents*. Next, we searched using the MeSH terms and text words with *antiplatelet therapy* AND *stents*. Additionally, we entered these terms separately. Boolean logic was used for all searches. Two investigators carried out the search independently. We then combined all the searches and retrieved the relevant articles. Manual search was made by going through the reference lists of the retrieved articles and through Index Medicus and key cardiology journals. Conference abstracts were obtained from conference coverages appearing in journals and other internet-based sources.

Data extraction

Data extraction forms were used to obtain the following information: characteristics of study participants, number of participants, type of intervention (dose, duration), randomization, blinding, study outcomes and duration of follow-up. The data were extracted independently by two investigators and compiled by a third investigator. Differences were removed by consensus.

Randomized controlled trials of cilostazol in combination with aspirin and clopidogrel (triple antiplatelet therapy) in patients undergoing PCI with BMS or DES were included in the study. We planned to include only those randomized controlled clinical trials in which the patients received clopidogrel and aspirin (dual antiplatelet therapy) in the control group. Exclusion criteria were the following: (i) studies that did not meet the inclusion criteria related to antiplatelet therapy, (ii) open label studies, (iii) studies with

Review: Triple Vs Dual antiplatelet therapy in post PCI patients
Comparison: 02 Triple (Aspirin+Clopidogrel+Cilostazol) vs Dual (Aspirin+Clopidogrel)
Outcome: 01 TVR in patients recieving dual or triple antiplatelet therapy

Study or sub-category	Treatment n/N	Control n/N	OR (random) 95% CI	Weight %	OR (random) 95% CI
01 Triple vs Dual antiplatelet therapy in PCI with Bare Metal Stents					
CREST	54/354	56/351		48.66	0.95 [0.63, 1.42]
Subtotal (95% CI)	354	351		48.66	0.95 [0.63, 1.42]
Total events: 54 (Treatment), 56 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.26 (P = 0.80)					
02 Triple vs Dual antiplatelet therapy in PCI with Drug Eluting Stents					
DECLARE-Long	9/250	18/250		27.30	0.48 [0.21, 1.09]
DECLARE-DIABETES	7/200	16/200		24.04	0.42 [0.17, 1.04]
Subtotal (95% CI)	450	450		51.34	0.45 [0.25, 0.83]
Total events: 16 (Treatment), 34 (Control)					
Test for heterogeneity: Chi² = 0.05, df = 1 (P = 0.82), I² = 0%					
Test for overall effect: Z = 2.56 (P = 0.01)					
Total (95% CI)	804	801		100.00	0.65 [0.37, 1.13]
Total events: 70 (Treatment), 90 (Control)					
Test for heterogeneity: Chi² = 4.00, df = 2 (P = 0.14), I² = 50.0%					
Test for overall effect: Z = 1.52 (P = 0.13)					

0.1 0.2   0.5   1   2   5   10

Favours treatment   Favours control

Figure 2

Studies comparing target vessel revascularization frequency in triple and dual antiplatelet therapy groups using pooled odds ratio (OR)

follow-up of <6 months, (iv) studies in which angiographic end-points were not evaluated, and (v) uncontrolled studies.

Study outcomes

The primary end-point evaluated for the present analysis was major adverse cardiac events (MACE) or MACCE. MACE included myocardial infarction (MI), symptom-driven repeat revascularization and death, and MACCE included the components MACE and stroke. Secondary end-points were (i) target vessel revascularization (TVR); (ii) ST, defined as any of the following: angiographic documentation of stent occlusion with or without the presence of thrombus associated with an acute ischaemic event, unexplained sudden death, and MI not clearly attributable to another coronary lesion; (iii) death; (iv) in segment restenosis (ISR); (v) in segment late lumen loss (LL); (vi) in segment minimum luminal diameter (MLD); and (vii) bleeding rates at 6 or 9 months, major bleeding defined as a need for transfusion, a reduction in haemoglobin of $\geq$5 g dl^{-1}, need for surgical intervention, or resulting in hypotension requiring inotropic support.

For all the evaluated variables, subgroup analysis was undertaken to compare triple and dual antiplatelet therapy for patients undergoing PCI with BMS or DES.
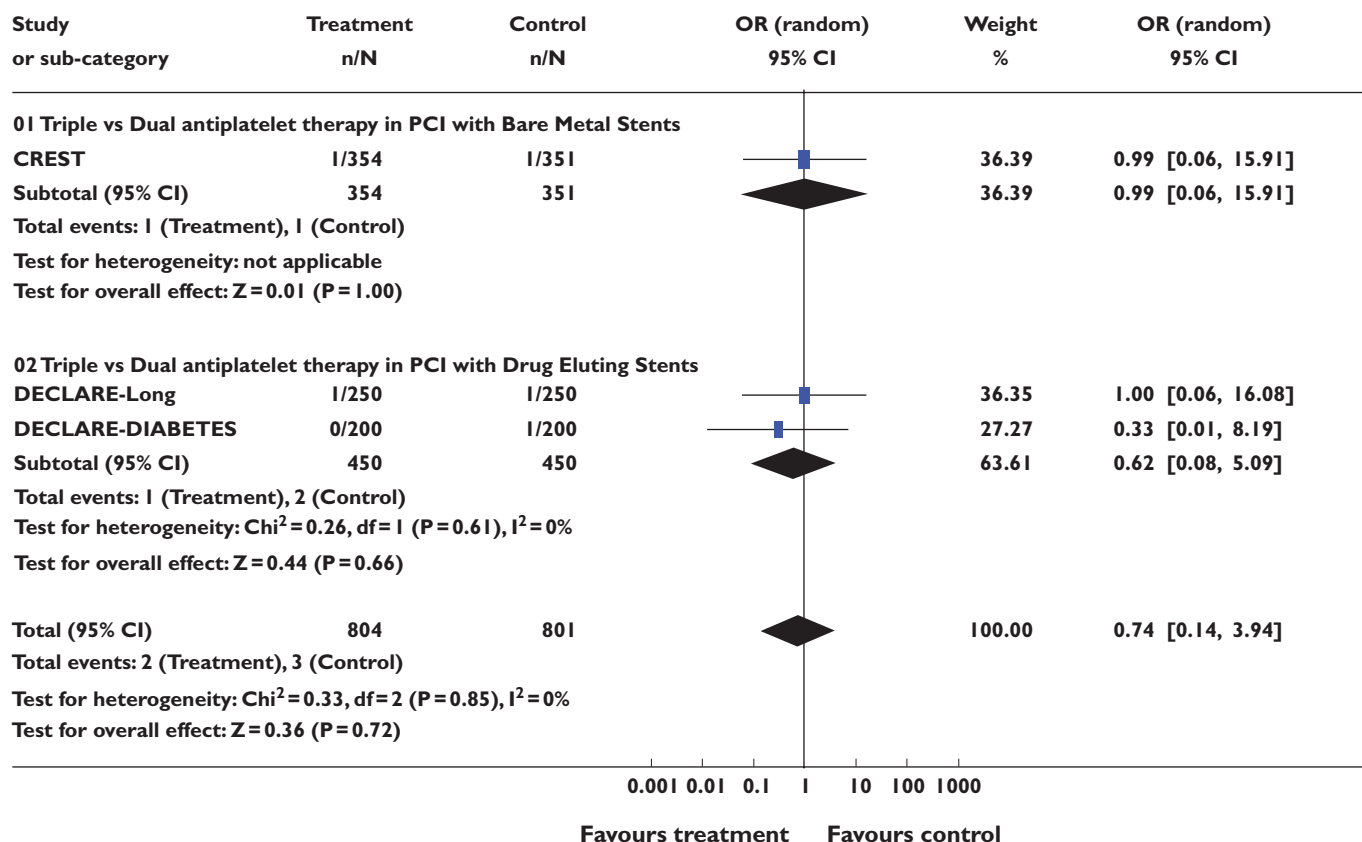
Pertinent data were also extracted for assessment of quality of the studies as described previously by Khan et al. [8]. Briefly, information related to randomization, baseline comparability, blinding, withdrawal and intention-to-treat analysis. Inverted funnel plot was generated for assessment of publication bias.

Analysis

Continuous data were expressed as mean (SD) and weighted mean difference (WMD) was obtained. The data from various studies were pooled and expressed as pooled WMD with 95% confidence interval (CI). Dichotomous data were expressed as odds ratio (OR) with 95% CI. The data were pooled by random effects model in case significant heterogeneity (detected by χ^2 test) was found, otherwise the fixed effects model was used. A P-value <0.05 was considered to be significant. Rosenthal File Drawer's Method was used to evaluate the number of studies with conflicting results that would be required to change the findings

A

Review: Triple Vs Dual antiplatelet therapy in post PCI patients
Comparison: 04 Triple(Aspirin+Clopidogrel+Cilostazol) vs Dual (Aspirin+Clopidogrel)
Outcome: 01 Stent Thrombosis in patients recieving dual or triple antiplatelet therapy

Study or sub-category	Treatment n/N	Control n/N	OR (random) 95% CI	Weight %	OR (random) 95% CI
01 Triple vs Dual antiplatelet therapy in PCI with Bare Metal Stents					
CREST	1/354	1/351		36.39	0.99 [0.06, 15.91]
Subtotal (95% CI)	354	351		36.39	0.99 [0.06, 15.91]

Total events: 1 (Treatment), 1 (Control)

Test for heterogeneity: not applicable

Test for overall effect: Z = 0.01 (P = 1.00)

02 Triple vs Dual antiplatelet therapy in PCI with Drug Eluting Stents					
DECLARE-Long	1/250	1/250		36.35	1.00 [0.06, 16.08]
DECLARE-DIABETES	0/200	1/200		27.27	0.33 [0.01, 8.19]
Subtotal (95% CI)	450	450		63.61	0.62 [0.08, 5.09]

Total events: 1 (Treatment), 2 (Control)

Test for heterogeneity: Chi^2 = 0.26, df = 1 (P = 0.61), I^2 = 0%

Test for overall effect: Z = 0.44 (P = 0.66)

Total (95% CI)	804	801		100.00	0.74 [0.14, 3.94]

Total events: 2 (Treatment), 3 (Control)

Test for heterogeneity: Chi^2 = 0.33, df = 2 (P = 0.85), I^2 = 0%

Test for overall effect: Z = 0.36 (P = 0.72)

0.001 0.01 0.1   1   10 100 1000

Favours treatment   Favours control

Figure 3

(a) Studies comparing stent thrombosis in triple and dual antiplatelet therapy groups using pooled odds ratio (OR). (b) Studies comparing number of deaths in triple and dual antiplatelet therapy groups using pooled OR

of the analysis into statistically nonsignificant results. Revman (Version 4.2) was used for all the analyses.

Results

Thirty hits were obtained when the combined MeSH terms were used. From the initial search, 26 studies were considered as potentially eligible. These were further evaluated for eligibility. Four were found to be eligible for inclusion in this meta-analysis. Twenty-two were excluded because they did not meet the inclusion criteria. The study characteristics of the four included studies are shown in Table 1. The included studies satisfied most of the criteria for quality assessment (Table 2).

MACE/MACCE, TVR, ISR and MLD were reported in all the studies, for a total population of 1725 patients. One study [9] did not report stent thrombosis and deaths, therefore these end-points were evaluated for 1457 patients.
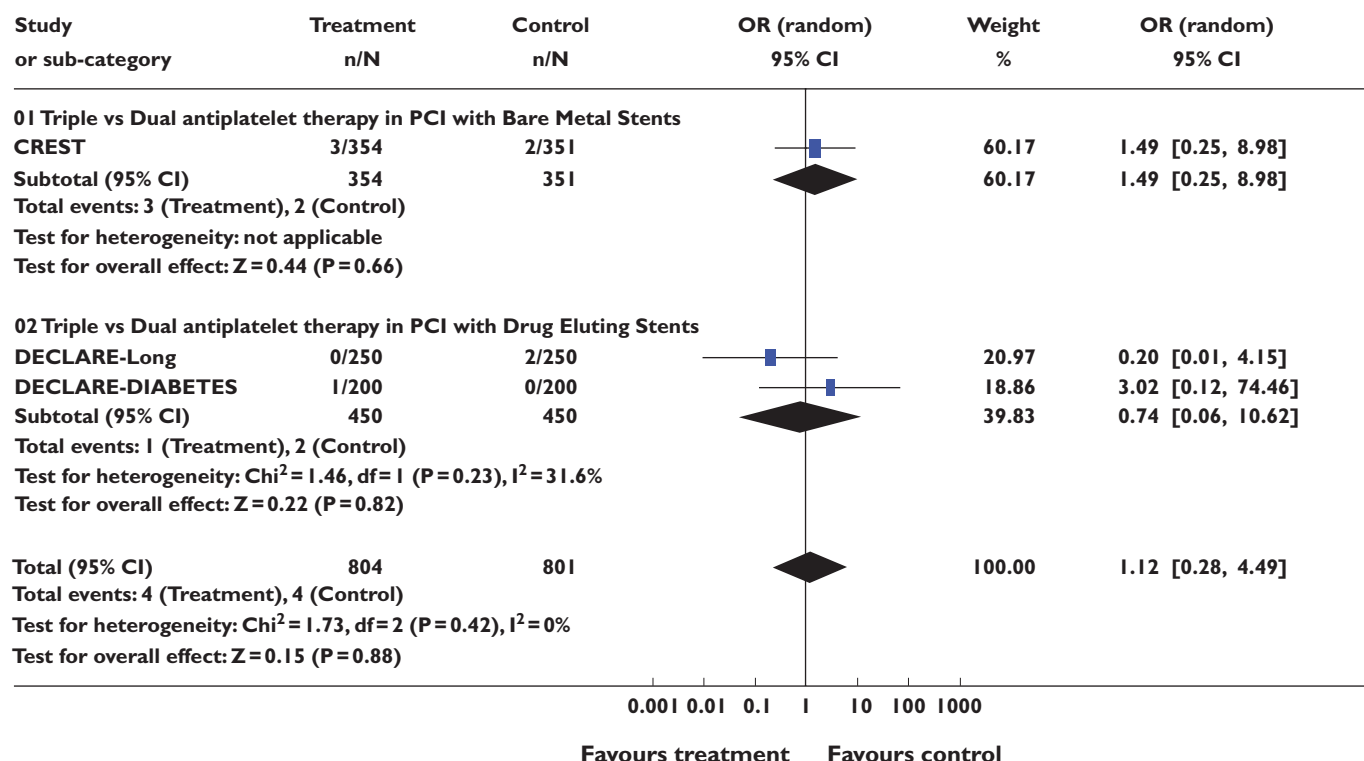
MACE/MACCE

Four studies [9–12] including 1725 patients were included for this analysis. There was no difference in the incidence of MACE/MACCE between the triple therapy and dual therapy groups (pooled OR 0.51, 95% CI 0.25, 1.03; P = 0.06). However, on subgroup analysis there was a significant difference between the two groups favouring the triple drug therapy in patients undergoing PCI with DES (OR 0.38, 95% CI 0.38, 0.72; P = 0.003) (Figure 1).

Target vessel revascularization

Four studies [9–12] including 1725 patients were included for this analysis. There was no difference in the incidence of TVR between triple and dual antiplatelet therapy for the combined analysis of BMS and DES (pooled OR 0.75, 95% CI 0.53, 1.04; P = 0.08). However, when the DES were considered alone, there were significant differences between the two groups favouring triple drug therapy in patients with

B

Study or sub-category	Treatment n/N	Control n/N	OR (random) 95% CI	Weight %	OR (random) 95% CI
01 Triple vs Dual antiplatelet therapy in PCI with Bare Metal Stents					
CREST	3/354	2/351		60.17	1.49 [0.25, 8.98]
Subtotal (95% CI)	354	351		60.17	1.49 [0.25, 8.98]

Total events: 3 (Treatment), 2 (Control)
Test for heterogeneity: not applicable
Test for overall effect: Z = 0.44 (P = 0.66)

02 Triple vs Dual antiplatelet therapy in PCI with Drug Eluting Stents					
DECLARE-Long	0/250	2/250		20.97	0.20 [0.01, 4.15]
DECLARE-DIABETES	1/200	0/200		18.86	3.02 [0.12, 74.46]
Subtotal (95% CI)	450	450		39.83	0.74 [0.06, 10.62]

Total events: 1 (Treatment), 2 (Control)
Test for heterogeneity: Chi^2 = 1.46, df = 1 (P = 0.23), I^2 = 31.6%
Test for overall effect: Z = 0.22 (P = 0.82)

Total (95% CI)	804	801		100.00	1.12 [0.28, 4.49]

Total events: 4 (Treatment), 4 (Control)
Test for heterogeneity: Chi^2 = 1.73, df = 2 (P = 0.42), I^2 = 0%
Test for overall effect: Z = 0.15 (P = 0.88)

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         0.001 0.01  0.1   1   10  100 1000
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Favours treatment   Favours control

Figure 3

Continued

DES placement (pooled OR 0.45, 95% CI 0.25, 0.83; $P = 0.01$) (Figure 2).

Stent thrombosis and deaths

Three studies [10–12] including 1457 patients were included for this analysis. There was no difference in the incidence of stent thrombosis between triple and dual antiplatelet therapy for the combined analysis (pooled OR 0.75, 95% CI 0.14, 3.62; $P = 0.68$). The same studies were analysed for mortality. There was no difference in mortality during the follow-up periods between triple and dual antiplatelet therapy (pooled OR 1.00, 95% CI 0.29, 3.45; $P = 0.99$). Similar results were seen on subgroup analysis (Figure 3a,b).

In segment restenosis

Four studies [9–12] including 1725 patients were included for this analysis. The pooled OR of angiographic restenosis at 6 months was 0.51 (95% CI 0.38, 0.68; $P = 0.00001$), which was statistically significant in favouring triple therapy. Similar results were observed on subgroup analysis (Figure 4).
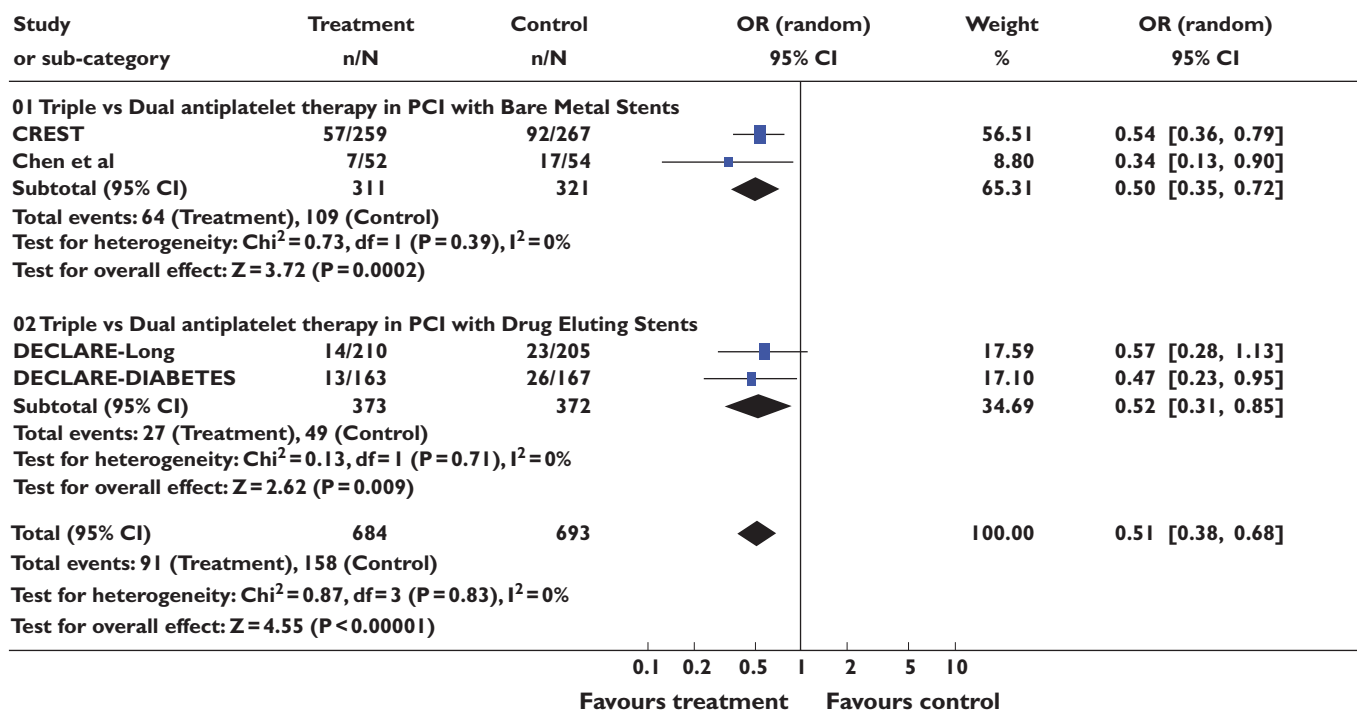
Minimum luminal diameter

Four studies [9–12] including 1725 patients were included for this analysis. There was a significant difference in the MLD at the end of 6 months between the triple therapy and dual therapy groups with pooled WMD = 0.16 (95% CI 0.10, 0.22; $P < 0.00001$). The MLD in the BMS and DES followed a similar trend. For BMS group pooled WMD was 0.21 (95% CI 0.11, 0.31; $P < 0.0001$) and pooled WMD for DES group was 0.13 (95% CI 0.05, 0.21; $P < 0.001$).

Late lumen loss

Four studies [9–12] including 1725 patients were included for this analysis. The pooled WMD of late LL was −0.37 (95% CI −0.74, 0.01; $P = 0.05$), which was not statistically significant in favouring triple therapy. However, for the DES the triple therapy resulted in significantly less late LL with a pooled WMD −0.14 (95% CI −0.21, −0.07; $P = 0.001$), whereas for the BMS pooled WMD −0.59 (95% CI −1.41, −0.22; $P = 0.00001$), triple therapy was found to be beneficial in preventing late LL in both DES and BMS stented patients.

Review:	Triple Vs Dual antiplatelet therapy in post PCI patients
Comparison:	03 Triple (Aspirin+Clopidogrel+Cilostazol) vs Dual (Aspirin+Clopidogrel)
Outcome:	01 In segment restenosis rate in patients recieving dual or triple antiplatelet therapy

Study or sub-category	Treatment n/N	Control n/N	OR (random) 95% CI	Weight %	OR (random) 95% CI
01 Triple vs Dual antiplatelet therapy in PCI with Bare Metal Stents					
CREST	57/259	92/267		56.51	0.54 [0.36, 0.79]
Chen et al	7/52	17/54		8.80	0.34 [0.13, 0.90]
Subtotal (95% CI)	311	321		65.31	0.50 [0.35, 0.72]
Total events: 64 (Treatment), 109 (Control)					
Test for heterogeneity: Chi² = 0.73, df = 1 (P = 0.39), I² = 0%					
Test for overall effect: Z = 3.72 (P = 0.0002)					
02 Triple vs Dual antiplatelet therapy in PCI with Drug Eluting Stents					
DECLARE-Long	14/210	23/205		17.59	0.57 [0.28, 1.13]
DECLARE-DIABETES	13/163	26/167		17.10	0.47 [0.23, 0.95]
Subtotal (95% CI)	373	372		34.69	0.52 [0.31, 0.85]
Total events: 27 (Treatment), 49 (Control)					
Test for heterogeneity: Chi² = 0.13, df = 1 (P = 0.71), I² = 0%					
Test for overall effect: Z = 2.62 (P = 0.009)					
Total (95% CI)	684	693		100.00	0.51 [0.38, 0.68]
Total events: 91 (Treatment), 158 (Control)					
Test for heterogeneity: Chi² = 0.87, df = 3 (P = 0.83), I² = 0%					
Test for overall effect: Z = 4.55 (P < 0.00001)					

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        0.1  0.2   0.5    1    2    5   10
        Favours treatment      Favours control
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Figure 4

Studies comparing in-segment restenosis rates in triple and dual antiplatelet therapy groups using pooled odds ratio (OR)

Bleeding

Three studies [10–12] including 1457 patients were included for this analysis. There was no significant difference in bleeding episodes between the two groups (pooled OR 0.77, 95% CI 0.41, 1.44; $P = 0.42$) (Figure 5).

Publication bias

Funnel plot was constructed using the OR values obtained from MACE/MACCE. From the funnel plot the possibility of publication bias in the analysis could not be ruled out (Figure 6).
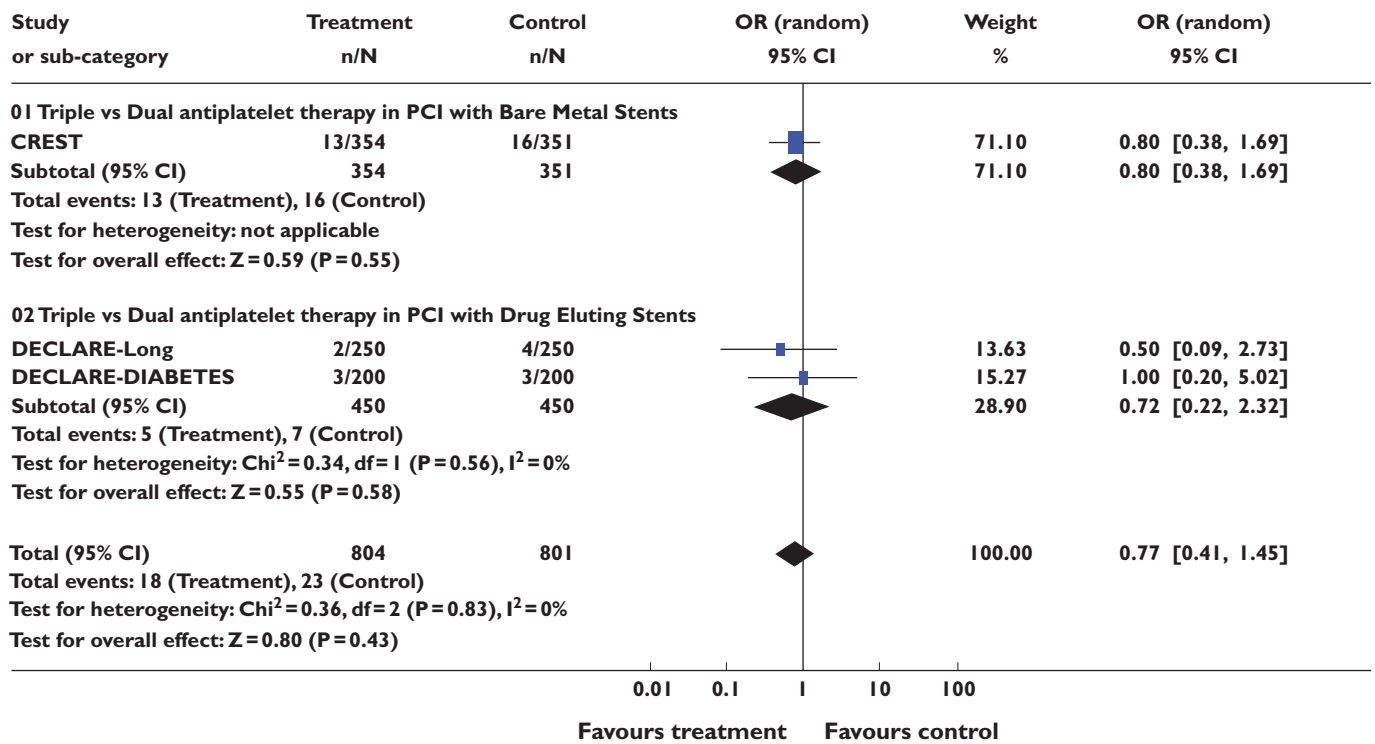
Discussion

The results of our study showed that addition of cilostazol does not significantly decrease the incidence of MACE or MACCE for the overall analysis of PCI with either DES or BMS. However, there was a significant reduction in MACE with triple therapy in the subgroup of studies that included patients who had undergone PCI with DES. Whereas MACE was consistently reduced with triple therapy in the two studies done in patients with DES, results were conflicting in case of BMS. In the CREST study [10], the incidence of MACE was more in the triple therapy

group. The lesions and patient characteristics in DECLARE DIABETES [11] and DECLARE-Long [12] were different from those of Chen *et al.* [9] and the CREST study [10]. In the former, patients were either diabetic or had long lesions. It is likely that the benefits of triple therapy are more pronounced in patients with long lesions and in diabetics. Despite a higher event rate (18.3–23.3%) in the control groups in patients who underwent PCI with BMS, triple therapy with cilostazol failed to show any beneficial effect. This is surprising, since the drugs used to coat the DES are aimed to do precisely what cilostazol was used for.

As against the primary end-point, triple antiplatelet therapy significantly reduced restenosis rates overall as well as in subgroups of studies of BMS and DES. The antiproliferative properties of cilostazol may have contributed to this beneficial effect. Restenosis rates have largely been reduced by the DES. Addition of pharmacological agents with the aim of reducing restenosis rates in patients undergoing PCI with BMS has shown conflicting results [4]. As against this, cilostazol has consistently shown reduction in restenosis rates. The results of the previous meta-analysis showed that cilostazol reduced the restenosis rate and repeat revascularization in patients undergoing PCI after acute coronary syndrome. Many of the studies analysed had used BMS and it is known that BMS
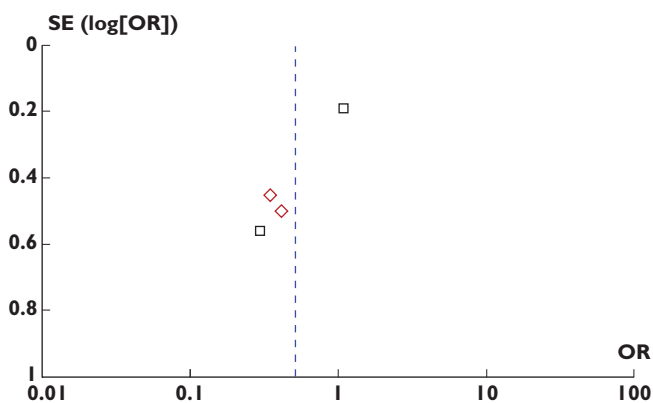
Review: **Triple Vs Dual antiplatelet therapy in post PCI patients**
Comparison: **06 Triple (Aspirin+Clopidogrel+Cilostazol) vs Dual (Aspirin+Clopidogrel)**
Outcome: **01 Bleeding rates in patients recieving dual or triple antiplatelet therapy**

Study	Treatment	Control	OR (random)	Weight	OR (random)
or sub-category	n/N	n/N	95% CI	%	95% CI
01 Triple vs Dual antiplatelet therapy in PCI with Bare Metal Stents					
CREST	13/354	16/351		71.10	0.80 [0.38, 1.69]
Subtotal (95% CI)	354	351		71.10	0.80 [0.38, 1.69]
Total events: 13 (Treatment), 16 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.59 (P = 0.55)					
02 Triple vs Dual antiplatelet therapy in PCI with Drug Eluting Stents					
DECLARE-Long	2/250	4/250		13.63	0.50 [0.09, 2.73]
DECLARE-DIABETES	3/200	3/200		15.27	1.00 [0.20, 5.02]
Subtotal (95% CI)	450	450		28.90	0.72 [0.22, 2.32]
Total events: 5 (Treatment), 7 (Control)					
Test for heterogeneity: Chi² = 0.34, df = 1 (P = 0.56), I² = 0%					
Test for overall effect: Z = 0.55 (P = 0.58)					
Total (95% CI)	804	801		100.00	0.77 [0.41, 1.45]
Total events: 18 (Treatment), 23 (Control)					
Test for heterogeneity: Chi² = 0.36, df = 2 (P = 0.83), I² = 0%					
Test for overall effect: Z = 0.80 (P = 0.43)					

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        0.01   0.1    1    10   100
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Favours treatment   Favours control

Figure 5

Studies comparing bleeding frequency in triple and dual antiplatelet therapy groups using pooled odds ratio (OR)

Figure 6

Funnel plot. Assessing publication bias using odds ratio (OR) of major adverse cardiac event/major adverse cardiac and cerebrovascular event frequency of the included studies. Triple vs Dual antiplatelet therapy in PCI with Bare Metal Stents (□); Triple vs Dual antiplatelet therapy in PCI with Drug Eluting Stents (◇)

is associated with an increased incidence of restenosis. Our subgroup results concur with the previous meta-analysis done by Biondi-Zoccai et al. [7] and support that addition of cilostazol in patients with BMS reduces rest-enosis rates. However, in that meta-analysis 13 out of 23 studies analysed used ticlopidine as a part of an antiplatelet regimen. In our analysis we did not include studies that used ticlopidine.

Stent thrombosis was not shown to be significantly reduced by the use of cilostazol in either of the stent groups. Similar results were seen in the study done by Biondi-Zoccai et al. [7]. Stent thrombosis is of special concern with DES, and cilostazol was not shown to affect the incidence significantly. These data should be interpreted cautiously, since stent thrombosis has an event rate of 1% at 1 year [13] and there is an incremental risk of stent thrombosis of 0.2–0.5% per year thereafter [14, 15]. The maximum follow-up period of the pooled studies was 9 months, hence the results of our meta-analysis do not reflect long-term events. Cilostazol was found to be safe considering the low bleeding risk. In our analysis there was no significant difference between the dual and triple therapy groups. An increased incidence of major and minor bleeding events was observed in patients receiving abciximab and cilostazol [16]. However, cilostazol use was associated with a significantly increased incidence of gastrointestinal disturbance and rash when used in combination with aspirin and clopidogrel [12].

Keeping in tune with the standard practice of our Drug Information Unit, which received the query, we framed our evidence-based answer as follows: 'though triple therapy significantly reduces restenosis rates compared to dual therapy when given to patients with DES and/or BMS, there is no significant reduction in MACE/MACCE and stent thrombosis rate. However, for patients with long lesions and patients receiving DES, triple antiplatelet therapy significantly reduces incidence of MACE. There is no significant difference in bleeding rates, target vessel revascularization and mortality in the two groups'.

It is well known that systematic reviews are associated with limitations, and the results obtained with these methods should be analysed accordingly. In our study publication bias could not be ruled out. The numbers of patients analysed were too low to reflect the data on the whole population. Clinical events such as stent thrombosis, bleeding and death were low in all the studies.

In conclusion, evidence needs to be generated for the use of the triple therapy regimen in patients undergoing PCI with BMS who have long lesions or who are diabetic. More evidence is needed for the effect of triple therapy on long-term follow-up.

Competing interests

None declared.

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