Original Article

Meta-analysis of randomized controlled trials on efficacy and safety of extended thienopyridine therapy after drug-eluting stent implantation

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Background: The potential benefits and risks of extended thienopyridine therapy beyond 12 months after drug-eluting stent (DES) implantation remain unclear.

Methods: Randomized controlled trials (RCTs) were searched in PubMed, EMBASE, the Cochrane Library and China National Knowledge Infrastructure databases. The adverse clinical endpoints were compared between 12 months group (aspirin alone) and >12 months group (additional thienopyridine plus aspirin after 12-month dual antiplatelet therapy). Odds ratios (ORs) with 95% confidence intervals (95% CIs) were used as summary statistics. A random-effect model was used in the meta-analysis process.

Results: Finally, three RCTs incorporating 16,265 participants were included in this meta-analysis. The results indicated that the incidences of myocardial infarction (1.55% *vs*. 2.90%; OR =0.58; 95% CI, 0.40–0.84; P=0.004) and stent thrombosis (0.32% *vs*. 0.98%; OR =0.35; 95% CI, 0.20–0.62; P<0.001) in the >12 months group were significantly lower than the 12 months group. However, compared to the 12 months group, the extended thienopyridine therapy markedly increased the risk of bleeding events (2.09% *vs*. 1.28%; OR =1.64; 95% CI, 1.23–2.17; P<0.001). The risks of stroke (0.78% *vs*. 0.84%; P=0.67) and cardiac death (0.94% *vs*. 0.89%; P=0.61) were similar between the two groups.

Conclusions: The synthesis of available evidence indicates that a regimen of extended thienopyridine therapy beyond 12 months may significantly reduce the risks of myocardial infarction and stent thrombosis but increase the risk of bleeding events in the patients who have received DESs implantation.

Keywords: Drug-eluting stents (DESs); dual antiplatelet therapy; thienopyridine

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Introduction

Coronary artery disease is very common worldwide and is the leading cause of death for males and females in the USA. Percutaneous coronary intervention is one of its major therapeutic strategies. Drug-eluting stents (DESs) have been widely used because they were considered to dramatically reduce the rates of in-stent restenosis or target lesion revascularization compared with bare metal stents (1). Nevertheless, researchers have also raised concerns about the risks of late and very late stent thrombosis (VLST) after DES implantation, since those events may be catastrophic (2-4). Current guidelines recommend that all patients undergoing DES placements should receive dual antiplatelet therapy, usually referred to

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as thienopyridine plus aspirin for 12 months if they are not faced high risk of bleeding (5,6).

However, the optimum duration of thienopyridine therapy is still under debate at present. Concerns over late adverse events have driven studies focused on whether extended thienopyridine therapy can be of clinical benefits. But their findings were not consistent. So far, there have been several relevant meta-analysis performed to address this tissue (7,8). However, the reviewers did not follow strict definitions of the durations, e.g., in Elmariah's meta-analysis (7), some studies included defined 12-month thienopyridine therapy as long-term thienopyridine therapy while 12-month thienopyridine therapy was in the short-term category in some other studies included. When it comes to El-Hayek's analysis (8), thienopyridine therapy of the short course ranged from 3 to 6 months whereas the prolonged therapy varied from 12 to 24 months among the different studies included. Those mentioned above were certain to have influenced the pooled effects. Therefore, to assess the efficacy and safety of extended thienopyridine therapy after DES implantation, we performed a meta-analysis of related randomized controlled trials (RCTs).

Methods

Potential articles were searched in PubMed, EMBASE, the Cochrane Library, and China National Knowledge Infrastructure from their inception to January 4, 2015 with the following terms: "dual antiplatelet therapy, thienopyridine, prasugrel or clopidogrel" and "stent or drug-eluting stent". The reference lists of included studies were searched for any additional studies. Language was restricted to English and Chinese. The literature search process was performed by two investigators independently.

Eligible studies in the analysis should meet all the following criteria. Firstly, it should be a RCT and published in a peer reviewed journal. Secondly, participants should be coronary artery disease patients treated with dual antiplatelet therapy after DES implantation. Besides, the thienopyridine in dual antiplatelet therapy regimen should be clopidogrel or prasugrel. Further, the patients should be randomized to receive aspirin alone (12 months group) or extended dual antiplatelet therapy (>12 months group) after 12-month dual antiplatelet therapy after DES implantation. Moreover, comparison of adverse cardiac events and bleeding events should be made between 12 months group and >12 months group. Ongoing trials, case reports, editorials, reviews and duplicated data were excluded.

Study design, country, number of patients, mean age, stent types, end points, durations of dual antiplatelet therapy, incidences of adverse cardiac events and bleeding events were extracted by two investigators independently. In case of suspicion of double reporting of the same patient populations, data from the main publication were extracted. The clinical endpoints were myocardial infarction, all-cause death, cardiac death, stent thrombosis, stroke, repeat revascularization and bleeding events.

Jadad scale was used to assess the quality of included randomized controlled studies (9,10). A RCT can be awarded a highest score of 5. Funnel plot was used to evaluate the publication bias. All quality assessments of articles were performed by two reviewers. Discrepancies were resolved by contacting a third author.

In this meta-analysis, Cochrane Q-test and I^2 were used to assess the heterogeneity. I^2 values >25%, >50%, >75% were considered evidence of low, moderate, and severe statistical heterogeneity, respectively. To reduce the potential bias, a random-effect model was chosen in the whole study. Odds ratios (ORs) with 95% confidence interval (95% CI) were used as summary statistics. The P value for significance was set at 0.05 and all the P values were 2-tailed. All statistical tests were performed with Review Manager 5.1 software (Cochrane Collaboration, Copenhagen, Denmark).

Results

In the initial database search process (*Figure 1*), a total of 1,587 relevant publications were identified. After title and abstract screening, 1,498 articles were excluded. Finally, four eligible studies were selected after full-text review (11-14). Two studies were from Europe, Australia, New Zealand and North America (12,13). The other two studies were from Asia (11,14). The substudies of included studies were not included (15,16). The types of DESs used in these studies included paclitaxel-eluting, sirolimus-eluting, everolimus-eluting and zotarolimus-eluting stents. The thienopyridines used in the studies were clopidogrel and prasugrel. The patients received both clopidogrel and prasugrel in two studies (12,13) and only received clopidogrel in the other two studies (11,14). However, one of the studies was not enrolled in the analysis process because it was published as an abstract paper and was inferior in quality (14). Finally, the data of three RCTs were used in this meta-analysis (11-13). Totally, 16,265 cases were included in this meta-analysis. Among these patients, about 73.4% of them were

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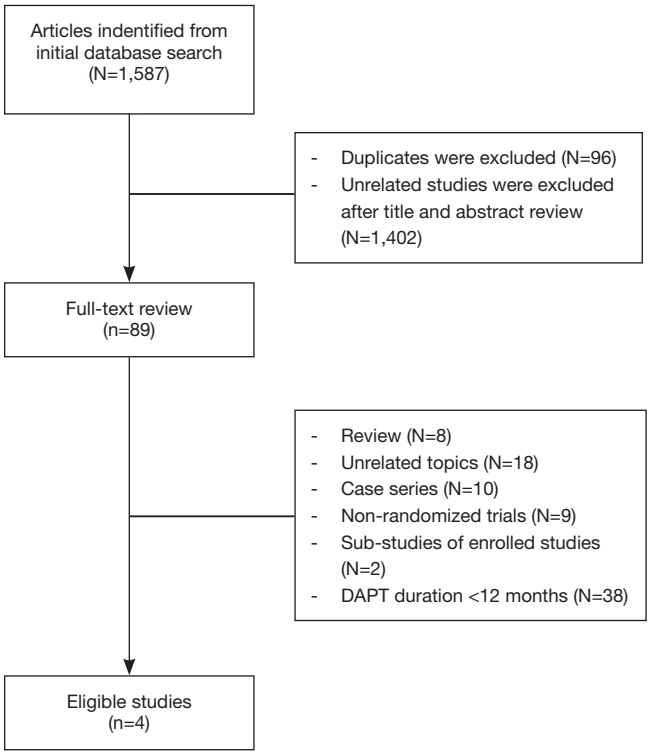

Figure 1 Flow diagram of the systematic review process.

males. There were 8,186 patients in >12 months group and 8,079 cases in 12 months group. The main characteristics of included studies are reported in *Table 1*. According to the funnel plot shown in *Figure S1*, the publication bias was acceptable.

The incidences of myocardial infarction were reported in three studies (11-13). Heterogeneity test results indicated a low heterogeneity among the included studies (I^2=35%). As shown in *Figure 2*, the incidence of myocardial infarction in the >12 months group was significantly lower than the 12 months group (1.55% *vs.* 2.90%; OR =0.58; 95% CI, 0.40–0.84; P=0.004), indicating that the extended thienopyridine therapy reduced the risk of myocardial infarction after DESs implantation in patients with coronary artery diseases.

There were three studies incorporating 16,265 participants were included in the comparison of the risk of stent thrombosis between the 12 months group and >12 months group (*Figure 3*) (11-13). No significant heterogeneity among the studies was found (P=0.30, I^2=18%). The risk of stent thrombosis after DESs implantation was significantly reduced in the >12 months group than the 12 months group (0.32% *vs.* 0.98%; OR =0.35; 95% CI, 0.20–0.62; P<0.001).

As shown in *Figure 4*, three studies reported the death rates (11-13) and two of them incorporating 15,006 participants reported the incidences of cardiac death (11,13). There was no significant heterogeneity among the studies (P>0.05, I^2<50%). The all-cause death rate was higher in the >12 months group than the 12 months group (1.84% *vs.* 1.42%; OR =1.30; 95% CI, 1.02–1.66; P=0.04). There was no statistical difference of cardiac death rates between the two groups (0.94% *vs.* 0.89%, OR =1.12; 95% CI, 0.73–1.71; P=0.61).

Overall, the stroke events were reported in three articles in this analysis. No significant heterogeneity among the studies was found (P=0.69, I^2=0%). There was a similar risk of stroke events between the 12 months group and >12 months group (0.78% *vs.* 0.84%; OR =0.93; 95% CI, 0.66–1.31; P=0.67), indicating that the extended thienopyridine therapy could not further reduce the risk of stroke after DESs implantation in patients with coronary artery diseases (*Figure 5*).

The safety end point mainly analyzed in this study was any bleeding events. As shown in *Figure 6*, three studies incorporating 15,663 participants reported the incidences of bleeding events. There was no significant heterogeneity among the studies (P=0.33, I^2=9%). The extended thienopyridine therapy significantly increased the risk of bleeding in patients with coronary artery diseases after the implantation of DESs (2.09% *vs.* 1.28%; OR =1.64; 95% CI, 1.23–2.17; P<0.001).

In this meta-analysis, the risk of repeat revascularization, definite stent thrombosis, ischemic stroke, major bleeding, minor bleeding and the composite events of these adverse clinical events in patients after DESs implantation were also pooled and analyzed (*Table 2*, *Figures S2–S9*). Random-effect model was used. Global Utilization of Strategies to Open Occluded Arteries (GUSTO) severe bleeding was considered major bleeding in this analysis. The risk of definite stent thrombosis after DESs implantation was significantly reduced in the >12 months group than the 12 months group. However, the extended thienopyridine therapy also markedly increased the risk of major and minor bleeding events (P<0.05). There was no difference in the comparison of repeat revascularization, ischemic stroke and the composite events between the 12 months group than >12 months group (P>0.05).

Discussion

Our meta-analysis demonstrates that in patients treated with DESs, extended thienopyridine therapy beyond 12 months, as compared to aspirin alone, reduced the risk

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Table 1 Main characteristic of eligible studies

Study	Collet 2014		Lee 2014		Mauri 2014		Hu 2012	
	12 months	>12 months	12 months	>12 months	12 months	>12 months	12 months	>12 months
DAPT-duration in months	12	29	12	24	12	30	12	36
No. of patients	624	635	2,514	2,531	4,941	5,020	88	94
Age in years (SD)	64.0 (NR)	64.0 (NR)	62.3 (10.1)	62.5 (10.0)	61.6 (10.2)	61.8 (10.1)	NR	NR
Males (%)	503 (81.0)	508 (80.0)	1,749 (69.6)	1,749 (69.1)	3,657 (74.0)	3,778 (75.3)	NR	NR
Hypertension (%)	388 (62.0)	376 (59.0)	1,479 (58.4)	1,423 (56.6)	3,649/4,934 (74.0)	3,796/5,006 (75.8)	NR	NR
Diabetes (%)	222 (36.0)	198 (31.0)	709 (28.2)	709 (28.0)	1,481/4,927 (30.1)	1,556/5,006 (31.1)	NR	NR
STEMI (%)	NR	NR	314 (12.5)	314 (12.4)	511 (10.3)	534 (10.6)	NR	NR
NSTEMI (%)	NR	NR	266 (10.6)	268 (10.6)	767 (15.5)	776 (15.5)	NR	NR
Current smoker (%)	152 (24.0)	147 (23.0)	722 (28.7)	693 (27.4)	1,210/4,893 (24.7)	1,222/4,965 (24.6)	NR	NR
Thienopyridine								
Clopidogrel (%)	562 (90.0)	569 (90.0)	2514 (100.0)	2,531 (100.0)	3,230 (65.4)	3,275 (65.2)	88 (100.0)	94 (100.0)
Prasugrel (%)	53 (9.0)	54 (9.0)	0 (0.0)	0 (0.0)	1,711 (34.6)	1,745 (34.8)	0 (0.0)	0 (0.0)
Primary endpoint	Death, myocardial infarction, stroke, stent thrombosis, urgent revascularization, bleeding		Death, myocardial infarction, stroke, stent thrombosis, repeat revascularization, bleeding		Death, myocardial infarction, stroke, stent thrombosis, bleeding		Cardiac death, myocardial infarction, stent thrombosis, target vessel revascularization	
DES types	Sirolimus, paclitaxel-DES; second generation-DES		Everolimus, zotarolimus, paclitaxel, sirolimus-DES		Everolimus, zotarolimus, paclitaxel and sirolimus-DES		NR	
Country	France		Korea		Europe, Australia, New Zealand and North America		China	
Length of follow up	17 months		42 months		30 months		36 months	
Jadad's score	4		3		3		2	

DAPT, dual antiplatelet therapy; SD, standard deviation; DES, drug-eluding stents; MI, myocardial infarction; STEMI, ST-elevation myocardial infarction; NSTEMI, non ST-elevation myocardial infarction; NR, not reported.

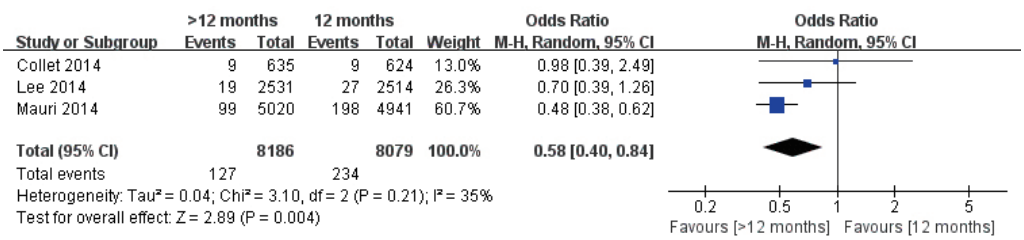

Figure 2 Forest plot illustrating the risk of myocardial infarction: 12 months group *vs.* >12 months group.

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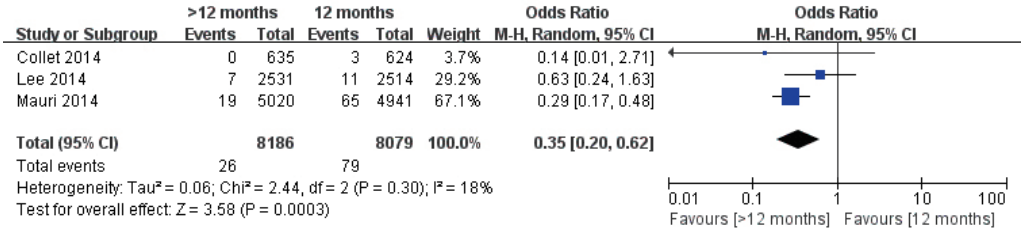

Figure 3 Forest plot illustrating the risk of stent thrombosis: 12 months group *vs.* >12 months group.

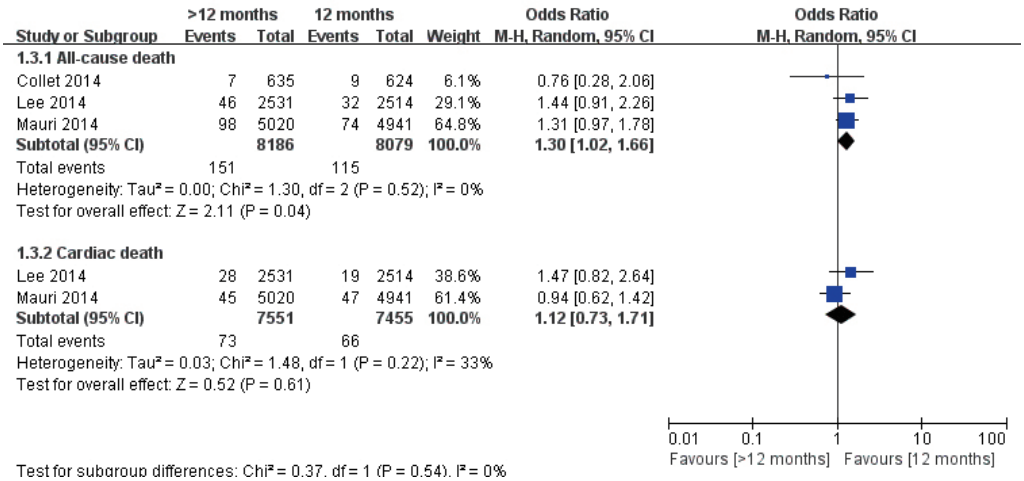

Figure 4 Forest plot illustrating the risk of death: 12 months group *vs.* >12 months group.

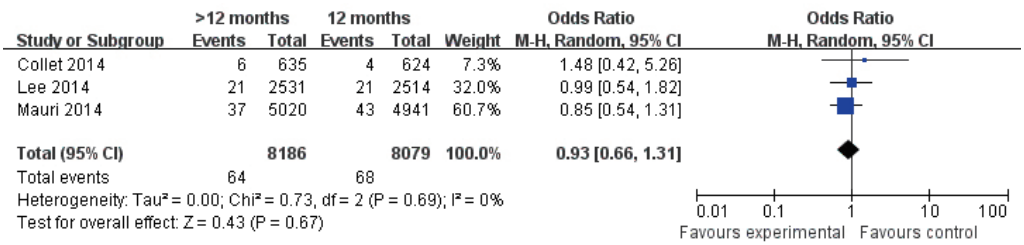

Figure 5 Forest plot illustrating the risk of stroke: 12 months group *vs.* >12 months group.

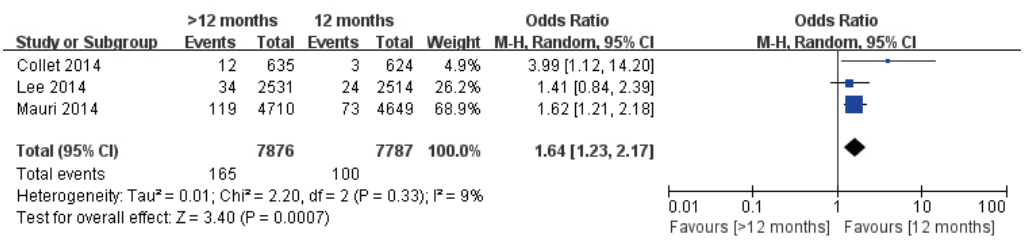

Figure 6 Forest plot illustrating the risk of bleeding events: 12 months group *vs.* >12 months group.

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Table 2 Comparison of clinical adverse events between12 months group and >12 months group

Variables	Studies	Participants	Incidences		I^2 (%)	Analysis model	P value	OR (95% CI)
			>12 months group (%)	12 months group (%)				
Death/myocardial infarction/stroke	2	15,006	289/7,551 (3.83)	354/7,455 (4.75)	82	Random-effect	0.570	0.88 (0.57–1.37)
Death/Myocardial infarction	2	6,304	75/3,166 (2.37)	71/3,138 (2.26)	0	Random-effect	0.780	1.05 (0.75–1.46)
Net clinical outcome	2	6,304	119/3,166 (3.76)	102/3,138 (3.25)	0	Random-effect	0.280	1.16 (0.89–1.52)
Definite stent thrombosis	3	16,265	22/8,186 (0.27)	72/8,079 (0.89)	32	Random-effect	0.003	0.34 (0.17–0.69)
Repeat revascularization	2	6,304	89/3,166 (2.81)	74/3,138 (2.36)	0	Random-effect	0.260	1.20 (0.88–1.64)
Ischemic stroke	2	15,006	39/7,551 (0.52)	47/7,455 (0.63)	15	Random-effect	0.440	0.83 (0.52–1.33)
Major bleeding	3	15,663	79/7,876 (1.00)	51/7,787 (0.65)	7	Random-effect	0.030	1.51 (1.03–2.20)
Minor bleeding	2	10,618	86/5,345 (1.61)	50/5,273 (0.95)	0	Random-effect	0.003	1.71 (1.20–2.43)

Net clinical outcome was a composite of any death, myocardial infarction, stent thrombosis, stroke, repeat revascularization and major bleeding events; OR, odds ratio; 95% CI, 95% confidence interval.

of stent thrombosis or myocardial infarction but increased the combined incidence of major and minor bleeds. Nevertheless, there was no statistically significant difference between the two groups in the composite of any death, myocardial infarction, stent thrombosis, stroke, repeat revascularization and major bleeding events.

In our study, we defined the currently recommended 12-month thienopyridine therapy by guidelines as "short-term group" and continued thienopyridine therapy beyond 12 months as "extended group". To our knowledge, this is the first comprehensive meta-analysis to answer whether it is optimal to switch to aspirin alone after 12-month thienopyridine therapy in patients undergoing DESs placement. Moreover, we only included high-quality RCTs and the funnel plot showed no apparent publication bias.

Mainly out of misgivings about VLST and its subsequent cardiovascular complications, some researchers advocate for prolonged use of thienopyridine therapy. Previous studies have shown that VLST, though rare it may be, is associated with high mortality (2). Our study shows extended thienopyridine therapy significantly helps in stent thrombosis or even myocardial infarction but at the cost of increasing bleeding. No statistical difference was detected in the composite of death, myocardial infarction, stent thrombosis, stroke, repeat revascularization and major bleeding events. Thienopyridine therapy does play an important role in the prevention of early stent thrombosis after deployment of a DES. But is it necessary to make it a routine to prolong thienopyridine therapy use for all patients? Our answer is no. To begin with, patients' adherence to extended thienopyridine therapy beyond 12 month itself is a challenge that we cannot neglect. We think identifying patients who are at high risk for VLST and prolonging thienopyridine therapy use for these people may be more cost-effective. Recent studies have suggested that newer second-generation devices can significantly lower incidence of VLST (17,18), which may be explained by improvements of stent structure can result in better stent apposition, superior endothelialization and consequently, reduced platelet aggregation and thrombus formation (19). In other words, the optimal duration of thienopyridine therapy may need to depend upon stent type. Furthermore, while premature thienopyridine therapy discontinuation after DES deployment is known as an independent predictor for stent thrombosis, Mauri *et al.* (13) found an increased risk of stent-related myocardial infarction in both 12 months group and >12 months group during the first three months after discontinuation, which may indicate that not only the thienopyridine therapy duration but also the special condition in the early phase after thienopyridine discontinuation should be considered in VLST.

Our study has several limitations. Firstly, only publications in English and Chinese were considered, which may have left out articles in other languages and the unpublished trials.

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Secondly, although 16,265 patients have been included, there have been only three eligible articles for the synthesis to date, calling for more large-sample multicenter RCTs. Thirdly, different types of DESs or of thienopyridine may have potential effect on clinical outcomes but we have not done the corresponding subgroup analysis as the data was unavailable. Lastly, the RCTs included only enrolled patients free from a major adverse cardiovascular or cerebrovascular event or bleeding in the first year after DESs implantation and it will be inappropriate to extrapolate our findings to populations at high risk for adverse events.

Conclusions

In summary, a meta-analysis of the published RCTs indicates that when compared to aspirin alone, a regimen of extended thienopyridine therapy beyond 12 months may significantly reduce the risks of myocardial infarction and stent thrombosis but increase the risk of bleeding events in the patients who have received DESs implantation.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Supplementary

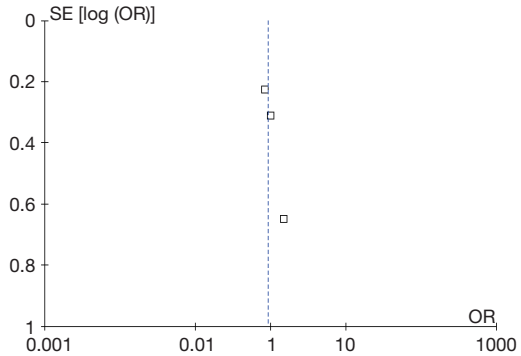

Figure S1 Funnel plots of the included studies.

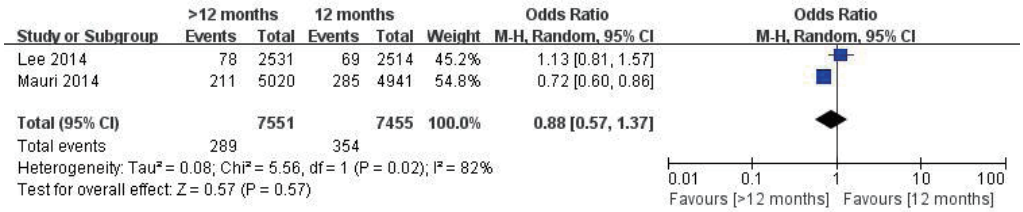

Figure S2 Forest plot illustrating the risk of death/myocardial infarction/Stroke: 12 months group *vs.* >12 months group.

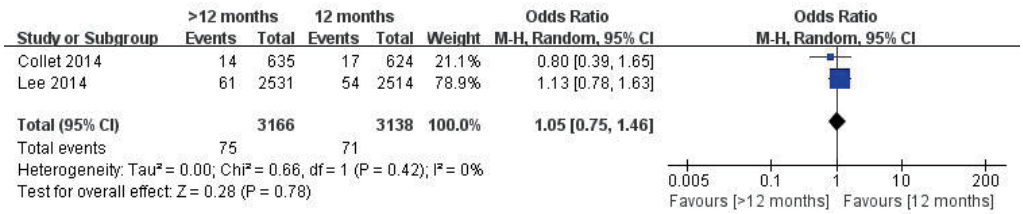

Figure S3 Forest plot illustrating the risk of death/myocardial infarction: 12 months group *vs.* >12 months group.

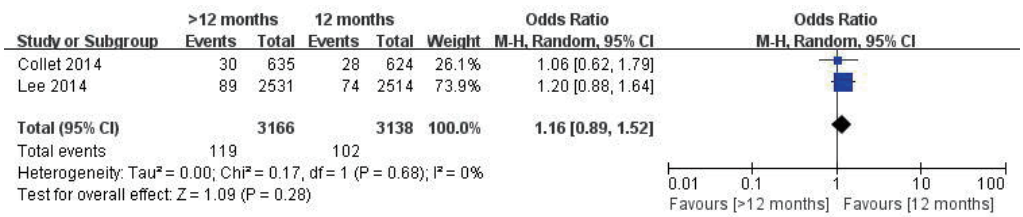

Figure S4 Forest plot illustrating the risk of net clinical outcome: 12 months group *vs.* >12 months group. Net clinical outcome was a composite of any death, myocardial infarction, stent thrombosis, stroke, repeat revascularization and major bleeding events.

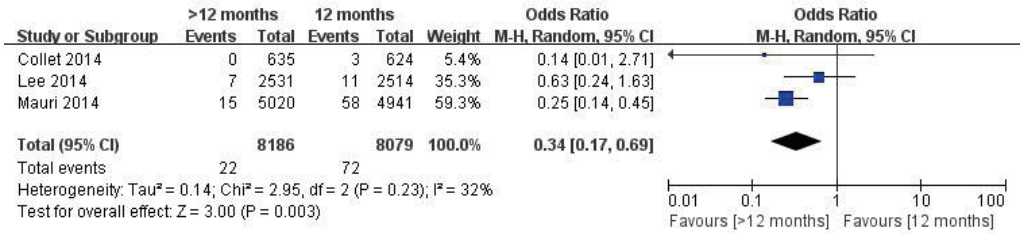

Figure S5 Forest plot illustrating the risk of definite stent thrombosis: 12 months group *vs.* >12 months group.

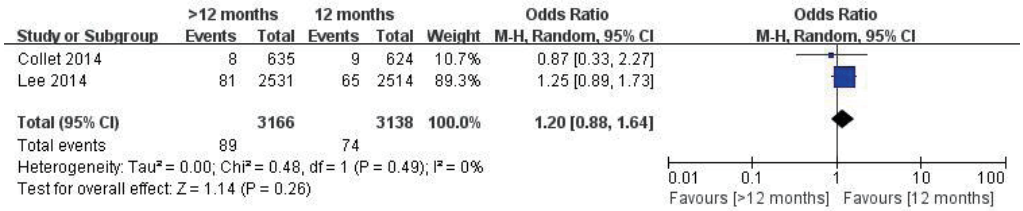

Figure S6 Forest plot illustrating the risk of Repeat revascularization: 12 months group *vs.* >12 months group.

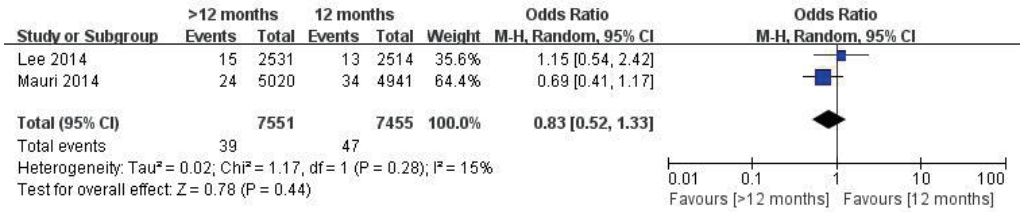

Figure S7 Forest plot illustrating the risk of ischemic stroke: 12 months group *vs.* >12 months group.

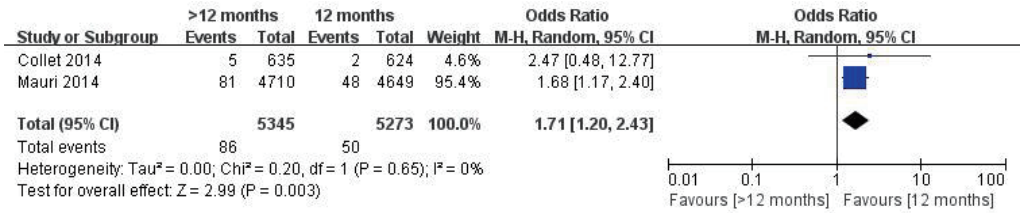

Figure S8 Forest plot illustrating the risk of major bleeding: 12 months group *vs.* >12 months group.

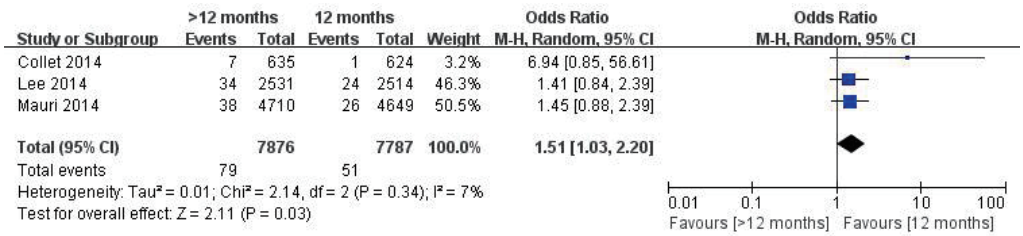

Figure S9 Forest plot illustrating the risk of minor bleeding: 12 months group *vs.* >12 months group.