12- *vs.* >12-Month dual Antiplatelet therapy after Drug-eluting stent implantation: A meta-analysis

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Abstract

Background: The risks and benefits of different duration of dual antiplatelet therapy (DAPT) after drug-eluting stent (DES) implantation remains a matter of debate.

Objectives: To systematically review the risks and benefits of 12-month *vs.* >12-month dual antiplatelet therapy (DAPT) after drug-eluting stent (DES) implantation.

Methods: Randomized controlled trials about duration of DAPT after DES implantation was searched through the PubMed, Cochrane Library, EMbase and Web of Science. No limitations regarding the language of publications.

Results: Six randomized controlled studies involving 25054 patients were included. The results of meta-analysis showed: 12-month DAPT was associated with a lower risk of all-cause mortality (FEM; RR=0.76; 95%CI, 0.63 to 0.92; Z=2.78; P=0.006) and a higher risk of stent thrombosis(FEM; RR=2.48; 95%CI, 1.72 to 3.56; Z=4.88; P<0.00001), myocardial infarction (FEM; RR=1.71; 95%CI, 1.44 to 2.04; Z=6.02; P<0.00001). The rates of stroke, TVR, major bleeding and cardiac mortality had no significant difference between 12-month DAPT and >12-month DAPT.

Conclusion: 12-month dual antiplatelet therapy after drug-eluting stent implantation was associated with a lower risk of all-cause mortality and a higher risk of myocardial infarction and stent thrombosis. The rates of stroke, TVR, major bleeding and cardiac mortality had no significant difference between 12-month DAPT and >12-month DAPT.

Introduction

The American College of Cardiology and American Heart Association(ACC/AHA) guidelines recommend that dual-antiplatelet therapy(DAPT) be administered for at least 12 months after drug-eluting stent(DES) implantation [1], while the European Society of Cardiology and European Association for Cardio-Thoracic Surgery(ESC/EACTS) recommend 6-12 months [2]. Therefore, the optimal duration of dual antiplatelet therapy (DAPT) with aspirin and a P_2Y_{12} inhibitor after drug-eluting stent implantation remains a matter of debate. What would be the safest and shortest DAPA duration after DES implantation?

Methods

In this meta-analysis, S-DAPT was defined as 12-month DAPT after DES implantation; L-DAPT was defined as >12-month (24 months or 30 months or 36 months or 48 months) DAPT after DES implantation. The outcomes included all-cause mortality, cardiac mortality, MI, repeat emergency TVR, stroke, stent thrombosis, major bleeding. MI included Q-wave and non-Q-wave MI. Repeat emergency target vessel revascularization (TVR) was defined as emergency repeat coronary revascularization of any segment of the treated coronary artery within 12 months of stenting. Stroke was defined as acute new neurological deficit ending in death or lasting longer than 24 h, diagnosed as stroke by a physician. The TIMI classification was used to define major bleeding.

We systematically searched MEDLINE, the Cochrane Library, EMbase and Web of Science (from inception up to November 16, 2016)

to identify relevant randomized controlled trials (RCTs) by using the search terms: drug-eluting stent AND dual antiplatelet therapy AND Random. The reference lists of the initially retrieved articles were also reviewed. No limitations regarding the country, time or language of publications.

Data Extraction

Two investigator dependently reviewed the full text of the retrieved articles and reported the results in a structured dataset. Disparities between investigators regarding the inclusion of each trial were resolved by consensus by a third independent investigator. The data's included first author, year, country of publication, study design, S-DAPT and L-DAPT duration, maximum length of follow-up, sample size, outcome measures and endpoints of interest. The assessment of the methodological quality of the included RCTs was followed the recommendations exemplified in the Cochrane handbook for systematic reviews of interventions and summarized in a domain based evaluation of the following components: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting and other bias [3].

Statistical Analysis

We used Review Manager 5.3 to conduct the statistical analysis. The between-study heterogeneity was assessed by the chi-squared test and its extent was quantified by the I^2 statistic (I^2 values of 25%, 50%, and 75% were considered to represent low, moderate and severe statistical inconsistency [4]. Continuous outcomes were analyzed using mean differences (MD) and 95% confidence intervals (CIs). Risk ratio (RR) and 95% CI were calculated by implementing the Mantel-Haenszel fixed effect model (FE) and the Mantel-Haenszel random effect model (RE). A $p<0.05$ was thought to indicate statistical significance in this meta-analysis.

Results

The study analysis flow diagram is shown in Figure 1. Of the 1039 citations found in MEDLINE, the Cochrane Library, EMbase and Web of Science, 6 trials met the inclusion criteria and the majority was excluded for reasons presented in Figure 1. Thus, six RCTs were included in the final meta-analysis [5-10].

In Table 1, we list the main characteristics of the included studies that meet our eligibility criteria. All studies [5-10] were published from 2010 to 2016. Their individual sample size ranged from 1259 to 9961 patients. All of the six trials were multi-center studies. Two RCTs evaluated a 12-month versus 30-month DAPT regimen. One RCT evaluated a 12-month versus a 24-month DAPT regimen. One RCT evaluated a 12-month versus a 36-month DAPT regimen. One RCT evaluated a 12-month versus a 48-month DAPT regimen. One RCT evaluated a 12-month versus an 18-30-month DAPT regimen. Data regarding the S-DAPT vs. L-DAPT are presented in Table 2. Data on the quality of the included studies are presented in Table 3.

All-cause mortality

Six RCTs (5-10) in this meta-analysis provided data on the all-cause mortality. No Significant heterogeneity was detected between these studies (Chi²=8.44, df=5; P=0.13; I²=41%). The combined estimate for the all-cause mortality based on the fixed-effects model showed statistically significant difference between the S-DAPT group and the L-DAPT group(24595 patients; FEM; RR=0.76; 95%CI, 0.63 to 0.92; Z=2.78; P=0.006) (Figure 2).

Cardiac Mortality

Four RCTs [5,7-9] in this meta-analysis provided data on the cardiac mortality. No significant heterogeneity was detected between these studies (Chi²=2.93, df=3; P=0.40; I²=0%). The combined estimate for the cardiac mortality based on the fixed-effects model showed no statistically significant difference between the S-DAPT group and the L-DAPT group (20604 patients; FEM; RR=0.93; 95%CI, 0.71 to 1.23; Z=0.50; P=0.61) (Figure 3).
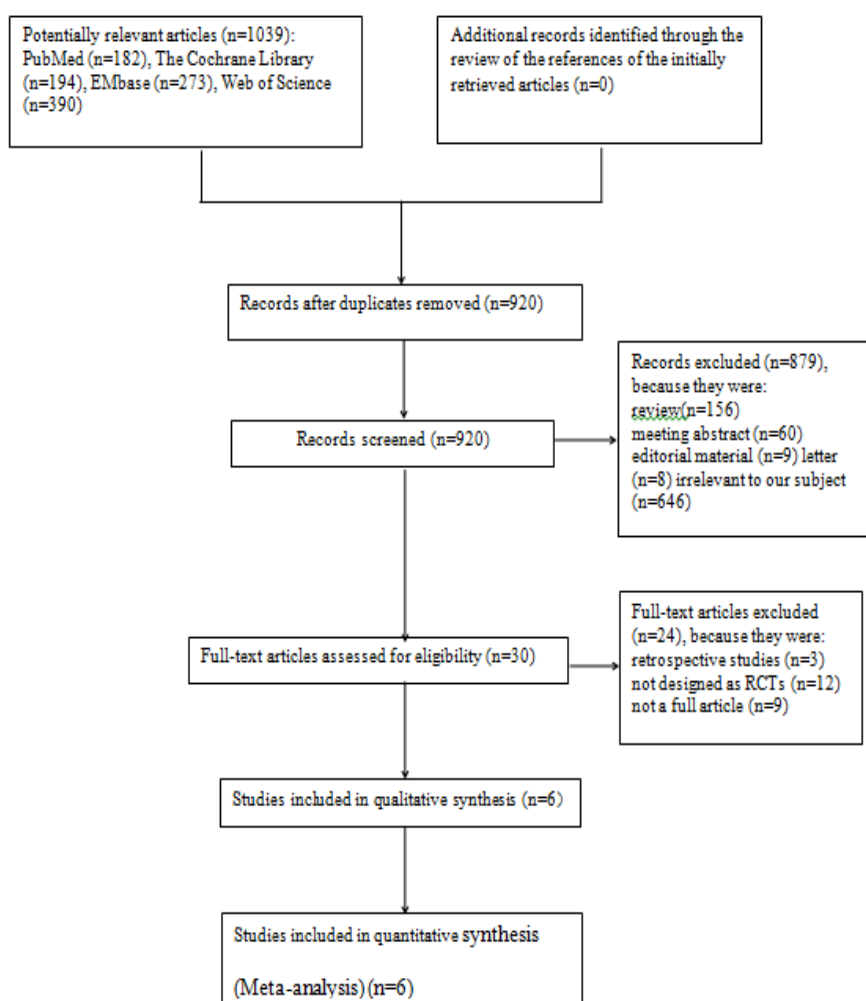

Figure 1. Flow diagram of the literature search and selection process of the studies.

Table 1. Main characteristics of the studies included in the meta-analysis. S-DAPT *vs.* L-DAPT.

Source/Year [Reference]	Country	Study Design	Definition of short and long duration	Total number in each group	Follow-up Duration
Collet/2014 [6]	France	P, PG, OL, MC	12 *vs.* 18-30 months	624 *vs.* 635	30 months
Park/2010 [10]	South Korea	P, PG, OL, MC	12 *vs.* 24 months	1344 *vs.* 1357	24 months
Hermiller/2016 [7]	International	P, PG, DB, MC	12 *vs.* 30 months	2358 *vs.* 2345	30 months
Mauri/2014 [9]	International	P, PG, SB, MC	12 *vs.* 30 months	4941 *vs.* 5020	30 months
Lee/2014 [8]	Korea	P, PG, OL, MC	12 *vs.* 36 months	2514 *vs.* 2531	24 months
Helft/2015 [5]	International	P, PG, OL, MC	12 *vs.* 48 months	690 *vs.* 695	48 months

P, prospective; PG, parallel group; OL, open label; SB, single-blind; DB, double-blind; MC, multi-center; SC, single-center;

Table 2. Outcome data of the studies included in the meta-analysis. 12-month DAPT *vs.* >12-month DAPT

Source/Year (Reference)	Collet/2014 [6]	Park/2010 [10]	Hermiller/2016 [7]	Mauri/2014 [9]	Lee/2014 [8]	Helft/2015 [5]
all-cause mortality	8 (0.9%) *vs.* 7 (0.8%)	5 (0.7%) *vs.* 10 (1.5%)	26 (1.1%) *vs.* 49 (2.2%)	13 (1.0%) *vs.* 20 (1.5%)	6 (0.6%) *vs.* 11 (1.3%)	32 (1.4%) *vs.* 46 (2.0%)
cardiac mortality	5 (0.5%) *vs.* 3 (0.3%)	3 (0.4%) *vs.* 5 (0.7%)	18 (0.8%) *vs.* 23 (1.0%)	NA	4 (0.4%) *vs.* 7 (0.7%)	19 (0.8%) *vs.* 28 (1.2%)
myocardial infarction	6 (0.7%) *vs.* 4 (0.4%)	1 (0.1%) *vs.* 0	72 (3.2%) *vs.* 48 (2.1%)	7 (0.5%) *vs.* 10 (0.7%)	2 (0.2%) *vs.* 4 (0.4%)	27 (1.2%) *vs.* 19 (0.8%)
stroke	0 *vs.* 4 (0.4%)	6 (0.9%) *vs.* 3 (0.4%)	15 (0.7%) *vs.* 13 (0.6%)	4 (0.3%) *vs.* 9 (0.7%)	5 (0.5%) *vs.* 6 (0.7%)	21 (0.9%) *vs.* 21 (0.9%)
TVR	5 (0.5%) *vs.* 2 (0.2%)	29 (4.4%) *vs.* 21 (3.1%)	NA	26 (1.9%) **vs.** 36 (2.7%)	27 (3.7%) *vs.* 27 (3.7%)	65 (2.8%) *vs.* 81 (3.5%)
Stent thrombosis	3 (0.3%) *vs.* 0	2 (0.3%) *vs.* 2 (0.3%)	16 (0.7%) *vs.* 6 (0.3%)	4 (0.3%) *vs.* 5 (0.4%)	2 (0.2%) *vs.* 3 (0.3%)	11 (0.5%) *vs.* 7 (0.3%)
Major bleeding	0 *vs.* 3 (0.3%)	5 (0.7%) *vs.* 7 (1.0%)	NA	1 (0.1%) *vs.* 3 (0.2%)	2 (0.2%) *vs.* 6 (0.6%)	24 (1.1%) *vs.* 34 (1.4%)

Table 3. Assessment of the methodological aspects of the included studies.

Source/Year (Reference)	Bias Component (Sequence generation and allocation concealment)	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Quality score
Collet/2014 [6]	Using a computer-generated randomization sequence (1.1; stratified by center)	No	99 patients withdrew consent.	Extensive reporting	did not enroll patients at very high thrombotic burden	High
Park/2010 [10]	According to a pre-established, computer-generated randomization scheme, with stratification on the basis of site and type of drug (sirolimus, paclitaxel, or zotarolimus) in the drug eluting stent.	No	No	Extensive reporting	the rate of the primary end point was lower than expected,	High
Hermiller/2016 [7]	Randomization was stratified by DES/BMS, hospital site, subject complexity, and thienopyridine drug type.	Double-blind	129 patients withdrew consent.	Extensive reporting	tests of interaction on randomized treatment effect between stent groups remain underpowered.	High
Mauri/2014 [9]	Randomization was conducted in a 1.1 ratio. A computer-generated randomization schedule stratified patients according to the type of stent they had received	Single-blind	Almost 1 every 10 screened patients was excluded from the study	Extensive reporting	only patients who were adherent to therapy and who did not have a major adverse cardiovascular or cerebrovascular event, stent thrombosis, or moderate or severe bleeding in the first year underwent randomization, a study design that may have selected for patients who were at lower risk for late adverse events.	High
Lee/2014 [8]	The treatment group assignments were made according to a pre-established, computer-generated randomization scheme that involved stratification on the basis of the site and the type of drug in the drug-eluting stent.	No	Almost 1 every 10 screened patients was excluded from the study	Extensive reporting	the study was an open label trial without a placebo control.	High
Helft/2015 [5]	Patients were randomly assigned to either a short group or long group without further reported details	No	4 patients withdrew consent.	Extensive reporting	only powered to detect major differences in ischemic and bleeding events	High

Myocardial Infarction

Six RCTs [5-10] in this meta-analysis provided data on the rates of myocardial infarction. No Significant heterogeneity was detected between these studies (Chi²=7.23, df=5; *P*=0.20; I²=31%). The combined estimate for the rates of myocardial infarction based on the fixed-effects model showed statistically significant difference between the S-DAPT group and the L-DAPT group(24467 patients; FEM; RR=1.71; 95%CI, 1.44 to 2.04; Z=6.02; *P*<0.00001) (Figure 4).

Stroke

Six RCTs [5-10] in this meta-analysis provided data on the rates of stroke. No significant heterogeneity was detected between these studies (Chi²=3.11, df=5; *P*=0.68; I²=0%). The combined estimate for the rates of stroke based on the fixed-effects model showed no statistically significant difference between the S-DAPT group and the L-DAPT group (24282 patients; FEM; RR=1.04; 95%CI, 0.78 to 1.39; Z=0.29; *P*=0.77) (Figure 5).

Stent Thrombosis

Six RCTs [5-10] in this meta-analysis provided data on the stent thrombosis. No Significant heterogeneity was detected between these studies (Chi²=8.68, df=5; *P*=0.12; I²=42%). The combined estimate for the rates of stent thrombosis based on the fixed-effects model showed statistically significant difference between the S-DAPT group and the
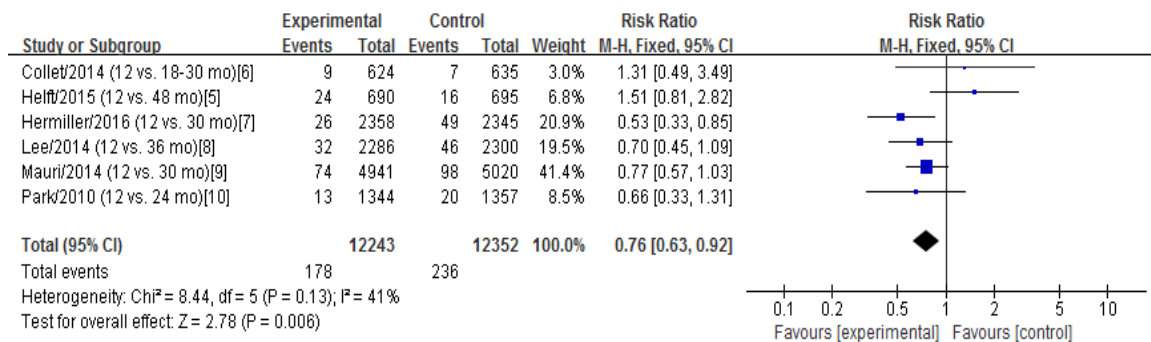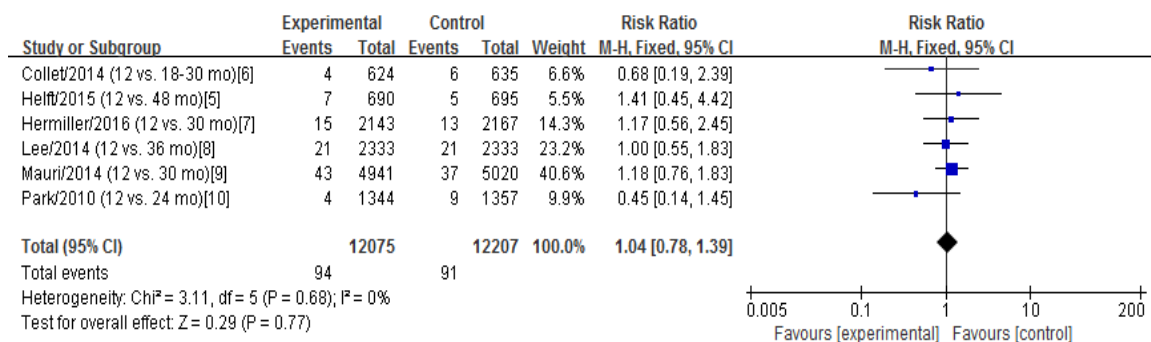
Figure 2. The all-cause mortality. forest plot showing the comparison of S-DAPT vs. L-DAPT. The size of each square represents the proportion of information provided by each study. The vertical line depicts the point of "no difference" between the two groups, and the horizontal lines correspond to the 95% confidence intervals (CIs). Diamonds represent the risk ratio (RR) for all studies.
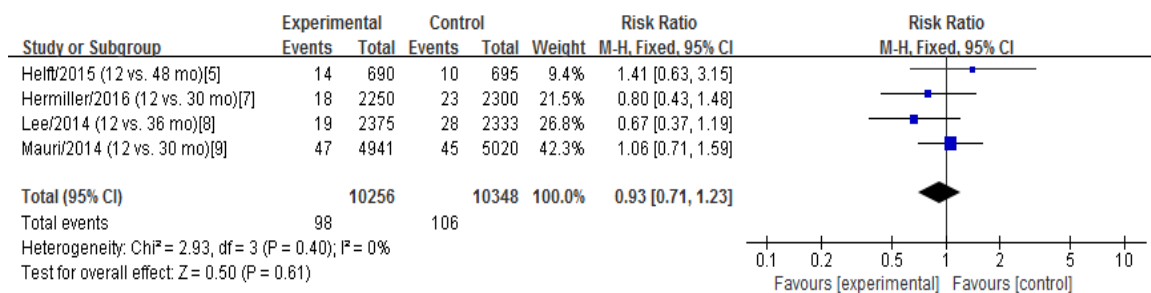
Figure 3. The cardiac mortality. forest plot showing the comparison of S-DAPT vs. L-DAPT. The size of each square represents the proportion of information provided by each study. The vertical line depicts the point of "no difference" between the two groups, and the horizontal lines correspond to the 95% confidence intervals (CIs). Diamonds represent the risk ratio (RR) for all studies.
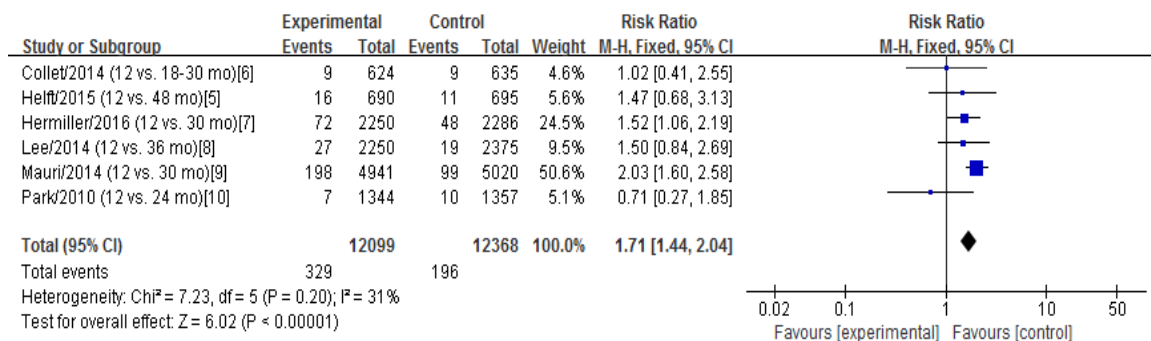
Figure 4. The rates of myocardial infarction. forest plot showing the comparison of S-DAPT vs. L-DAPT. The size of each square represents the proportion of information provided by each study. The vertical line depicts the point of "no difference" between the two groups, and the horizontal lines correspond to the 95% confidence intervals (CIs). Diamonds represent the risk ratio (RR) for all studies.

Figure 5. The rates of stroke. forest plot showing the comparison of S-DAPT vs. L-DAPT. The size of each square represents the proportion of information provided by each study. The vertical line depicts the point of "no difference" between the two groups, and the horizontal lines correspond to the 95% confidence intervals (CIs). Diamonds represent the risk ratio (RR) for all studies.

L-DAPT group(24125 patients; FEM; RR=2.48; 95%CI, 1.72 to 3.56; Z=4.88; *P*<0.00001) (Figure 6).

TVR

Four RCTs [5-6,8,10] in this meta-analysis provided data on the rates of TVR. No significant heterogeneity was detected between these studies (Chi²=1.41, df=3; *P*=0.70; I²=0%). The combined estimate for the rates of TVR based on the fixed-effects model showed no statistically significant difference between the S-DAPT group and the L-DAPT group (9980 patients; FEM; RR=0.85; 95%CI, 0.68 to 1.06; Z=1.45; *P*=0.15) (Figure 7).

Major Bleeding

Four RCTs [5-6,8,10] in this meta-analysis provided data on the rates of major bleeding. No Significant heterogeneity was detected between these studies (Chi²=3.07, df=3; *P*=0.38; I²=2%). The combined estimate for the rates of major bleeding based on the fixed-effects model

showed no statistically significant difference between the S-DAPT group and the L-DAPT group(9956 patients; FEM; RR=0.68; 95%CI, 0.43 to 1.07; Z=1.67; *P*=0.09) (Figure 8).

Publication bias

Six studies [5-10] were included in this meta-analysis. Assessment of publication bias using a funnel plot was presented in Figure 9.

Discussion

This meta-analysis included six randomized controlled studies involving 25054 patients. The main results of this meta-analysis are as follow:

1) 12-month DAPT was associated with a lower risk of all-cause mortality.

2) 12-month DAPT was associated with a higher risk of myocardial infarction and stent thrombosis.
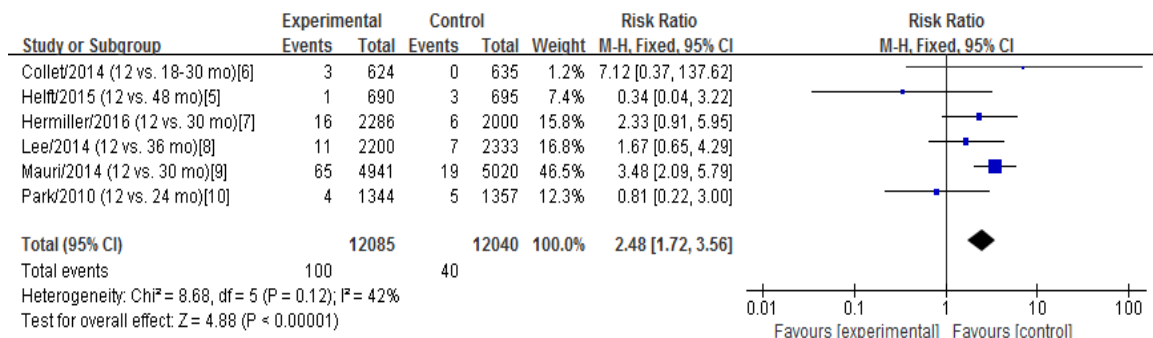
Figure 6. The rates of stent thrombosis. forest plot showing the comparison of S-DAPT vs. L-DAPT. The size of each square represents the proportion of information provided by each study. The vertical line depicts the point of "no difference" between the two groups, and the horizontal lines correspond to the 95% confidence intervals (CIs). Diamonds represent the risk ratio (RR) for all studies.
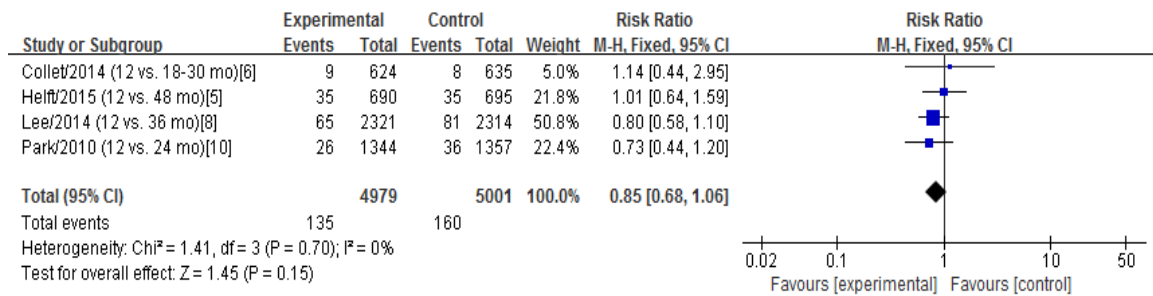
Figure 7. The rates of TVR. forest plot showing the comparison of S-DAPT vs. L-DAPT. The size of each square represents the proportion of information provided by each study. The vertical line depicts the point of "no difference" between the two groups, and the horizontal lines correspond to the 95% confidence intervals (CIs). Diamonds represent the risk ratio (RR) for all studies.
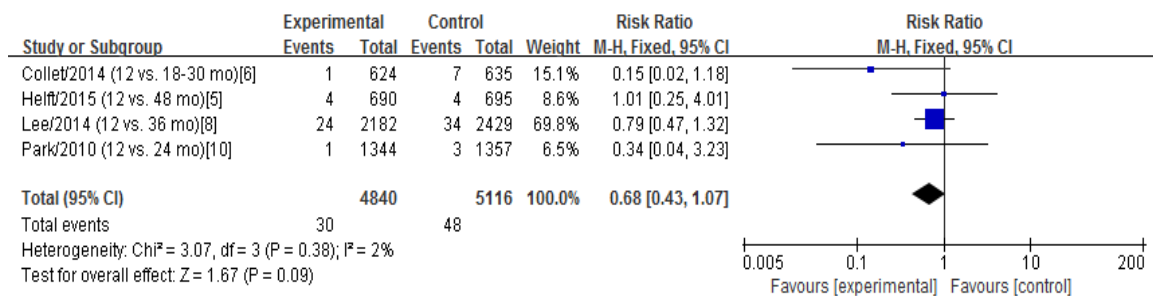
Figure 8. The rates of major bleeding. forest plot showing the comparison of S-DAPT vs. L-DAPT. The size of each square represents the proportion of information provided by each study. The vertical line depicts the point of "no difference" between the two groups, and the horizontal lines correspond to the 95% confidence intervals (CIs). Diamonds represent the risk ratio (RR) for all studies.
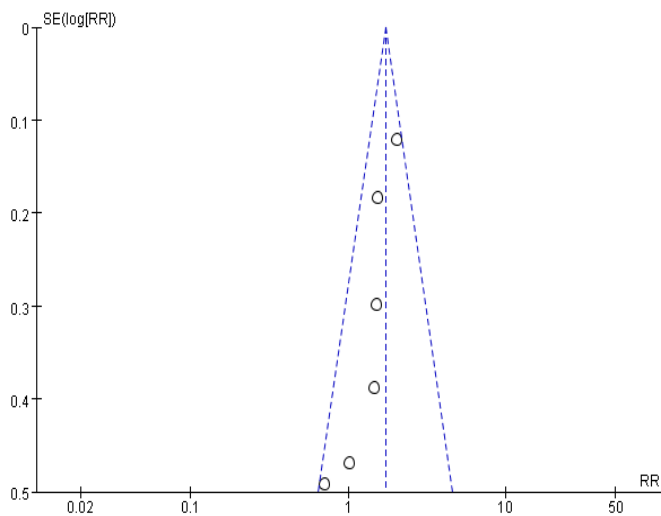
Figure 9. Funnel plot.

3) The rates of stroke, TVR, major bleeding and the cardiac mortality had no significant difference between the 12-month DAPT and >12-month DAPT.

Optimal DAPT duration is critical for balancing the risk of ischemic and bleeding complications after DES implantation. Elmariah, *et al.* [11] founded that patients' mortality was no significant difference between short term of DAPT and long term of DAPT after DES implantation. Giustino, *et al.* [12] confirmed that all-cause mortality was numerically higher with long term of DAPT without reaching statistical significance. However, in this meta-analysis, we found that the short term of DAPT was associated with a lower risk of all-cause mortality (FEM; RR=0.76; 95%CI, 0.63 to 0.92; Z=2.78; *P*=0.006). While the cardiac mortality between the short DAPT and long DAPT had no significant difference (FEM; RR=0.93; 95%CI, 0.71 to 1.23; Z=0.50; *P*=0.61).

Recently, trials demonstrated that Prolonged DAPT reduced stent-related and non-stent-related adverse ischemic events following PCI [13]. American guidelines recommend at least 12 months of DAPT after DES implantation in order to reduce the rates of late and very late stent thrombosis. In this meta-analysis ,results showed that short term of DAPT (12 months) was associated with a higher risk of stent thrombosis(FEM; RR=2.48; 95%CI, 1.72 to 3.56; Z=4.88; *P*<0.00001), as well as myocardial infarction (FEM; RR=1.71; 95%CI, 1.44 to 2.04; Z=6.02; *P*<0.00001).

The definition of major bleeding complications varies widely across clinical studies. In this meta-analysis, we adopted the TIMI major bleeding scale. The results showed that the major bleeding between 12-month DAPT and >12-month DAPT after drug-eluting stent implantation had no significant difference (FEM; RR=0.68; 95%CI, 0.43 to 1.07; Z=1.67; *P*=0.09).

The results of this meta-analysis confirm and extend the previous reports [14-21]. However, this meta-analysis has several limitations. First, not all included studies provided data on all outcomes. Second, four trials included in the meta-analysis were open label, potentially introducing performance bias. Third, all of the patients included in the meat-analysis were treated with clopidogrel as adjunctive therapy to aspirin. It remains unclear whether results would have differed with the other kind of P_2Y_{12} inhibitor, especially in patients with acute coronary syndrome.

Conclusion

In conclusion, 12-month dual antiplatelet therapy after drug-eluting stent implantation was associated with a lower risk of all-cause mortality and a higher risk of myocardial infarction and stent thrombosis. The rates of stroke, TVR, major bleeding and cardiac mortality had no significant difference between 12-month DAPT and >12-month DAPT. Further research is required to determine the duration of DAPT after DES implantation in patients with ACS.

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