Meta-analysis of the Duration of Dual Antiplatelet Therapy in Patients Treated with Second Generation Drug-eluting Stents

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Meta-analysis of the Duration of Dual Antiplatelet Therapy in Patients Treated with Second Generation Drug-eluting Stents

Running title: Antiplatelet duration for second generation DES

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ABSTRACT

The purpose of the study is to evaluate the optimal duration of dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI), especially in the era of second generation drug-eluting stents (DES). The work was conducted between November 2014 and April 2015. All randomized controlled trials (RCTs) comparing short (<12 months) vs. long (⩾12 months) DAPT in patients treated with second generation DES were analyzed. Sensitivity analyses were performed for length of DAPT and type of DES. All-cause death was the primary endpoint, while cardiovascular death, myocardial infarction (MI), stent thrombosis (ST), and major bleeding were secondary endpoints. Results were pooled and compared with random effect models and meta-regression analysis. Eight RCTs with 18,810 randomized patients were included. The studies compared 3 vs. 12 months of DAPT (two trials), 6 vs. 12 months (three trials), 6 vs. 24 months (one trial), 12 vs. 24 months (one trial), and 12 vs. 30 months (one trial). Comparing short vs. long DAPT, there were no significant differences in all-cause death (OR 0.87: 95% CI 0.66-1.44), cardiovascular death (OR 0.95: 95%CI 0.65-1.37), and stent thrombosis (OR 1.20: 95%CI 0.79-1.83), and no differences were present when considering everolimus-eluting and fast-release zotarolimus-eluting stents separately. Shorter DAPT was inferior to longer DAPT in preventing MI (OR 1.35: 95%CI 1.03-1.77). Conversely, major bleeding was reduced by shorter DAPT (OR 0.60: 95%CI 0.42-0.96). Baseline features did not influence these results in meta-regression analysis. In conclusion, DAPT for ⩽6 months is reasonable for patients treated with everolimus-eluting and fast-release zotarolimus-eluting stents, with the benefit of less major bleeding at the cost of increased MI, with similar survival and stent thrombosis rates. An individualized patient approach to DAPT duration should take into account the competing risks of bleeding and ischemic complications after current generation DES.

KEY-WORDS

Dual antiplatelet therapy- Second Generation stent – Aspirin – Clopidogrel – Coronary Disease

INTRODUCTION

Selecting the optimal duration of dual antiplatelet therapy (DAPT) is a challenge for physicians managing patients treated with drug-eluting stents (DES) (1). As the indications for percutaneous coronary intervention (PCI) have expanded, patients are being treated with greater comorbidities and/or complex coronary anatomies. Such patients may theoretically benefit from longer DAPT to prevent ischemic complications including myocardial infraction (MI) and stent thrombosis (ST), although bleeding may be increased (2-5). In this regard, stent thrombosis (ST) rates have been reduced with current second generation DES compared to first generation platforms (6), which may change the risk-benefit equation for prolonged DAPT. In addition, first generation sirolimus-eluting stents and paclitaxel-eluting stents are either no longer manufactured or rarely used, respectively, and DAPT duration data with these devices are thus no longer relevant for current practice. Current evidences suggests a benefit in reduction of MI (both in native vessels and in-stent) for longer DAPT with contrasting data about mortality, but are fraught by including together first and second generation stents and not performing a sensitivity analysis for different types of stent (7-9). We therefore performed an updated meta-analysis to appraise the safety and efficacy of different durations of DAPT in patients treated with second generation DES.

METHODS

The present study was performed according to PRISMA statements (see the Web Appendix for more details) (10).

From November 2014 to April 2015 Pubmed, Cochrane and Google Scholar were searched for the following terms: “dual antiplatelet therapy” and “coronary” and “stent” and “second generation” by two authors (FDA; CM). Citations were first screened independently by two reviewers (GBZ, FDA), with disagreements resolved by consensus. Inclusion criteria were: (i) human studies; (ii) investigating patients undergoing coronary revascularization with PCI and second generation DES; (iii) comparing different length of DAPT: <12 months (“short”) and $\geqslant$12 months (“long”); and (iv) with separate data reported for second generation DES (either in the

manuscript or available from the investigators). In the case of duplicate reporting, the manuscript with the largest sample of patients was selected.

The following data were independently abstracted by two reviewers (GBZ, FDA) on pre-specified electronic forms, with disagreements resolved by consensus: authors, journal, year of publication, location of the study group, type of DES, baseline, angiographic and procedural features, length of DAPT, and definition of bleeding were collected. The corresponding authors of the relevant studies were queried for required quantitative details not in the published manuscripts.

The primary endpoint was all-cause death, while secondary endpoints included cardiovascular death, MI, definite or probable ST, target vessel revascularization (TVR), and major bleeding. Sensitivity analysis were performed for stent type (everolimus-eluting stents [EES] and fast-release zotarolimus-eluting stents [ZES]), and for DAPT duration (≤6 months vs. 12 months; ≤6 months vs. 24 months; 12 months vs. ≥24 months).

The quality of included studies was independently appraised by two reviewers (GBZ, FDA), with disagreements resolved by consensus. For each RCT we evaluated the risk of bias (low, unclear or high) for random sequence generation, allocation concealment, blinding of patients and physicians, blinding during assessment of follow up, incomplete outcome evaluation, and selective reporting, in keeping with the Cochrane Collaboration approach.

Continuous variables are reported as mean (standard deviation) or median (1^{st}; 3^{rd} quartile). Categorical variables are expressed as n/N (%). Statistical pooling for incidence estimates was performed according to a random-effect model with generic inverse-variance weighting, computing risk estimates with 95% confidence intervals (CI), using RevMan 5.2 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). Small study bias was appraised by graphical inspection of funnel plots. Meta-regression analysis was performed to assess the impact of baseline features on the primary endpoint with Comprehensive Metanalysis (CMA, trial version).

Hypothesis testing for superiority was set at the two-tailed 0.05 level. Hypothesis testing for statistical homogeneity was set at the two-tailed 0.10 level and based on the Cochran Q test, with I^2 values of 25%, 50%, and 75% representing mild, moderate, and severe heterogeneity, respectively (11).

RESULTS

As shown in **Figure 1**, 1'632 publications were found at the initial search, and after abstract evaluation 10 papers were appraised as full texts. Two of these were excluded because separate data for second generation stents was not reported (12,13). Finally, 8 studies with 18,810 randomized patients were included in the present analysis (14-21). With regard to the PRODIGY trial, we limited the analysis to patients randomized to receive ZES or EES (19). Similarly, we included only reported data on second generation DES from the EXCELLENT and DAPT trials. For the DES LATE and SECURITY trials, data specific for second generation stents were provided by the investigators (14,16).

Table 1 shows the main features of the studies. Of the 18,810 patients, 12,510 were treated with EES, 5,768 were treated with fast-release ZES, and 532 were treated with biolimus-eluting stents. The 8 trials compared 3 vs. 12 months DAPT (two trials), 6 vs. 12 months DAPT (three trials), 6 vs. 24 months DAPT (one trial), 12 vs. 24 months (one trial), and 12 vs. 30 months DAPT (one trial). Thebaseline and angiographic features of the included patients are presented in **Table 1 and 2.**

The major results are shown in **Figures 2-7**. Comparing short vs. long DAPT, there were no significant differences in all-cause death (OR 0.87: 95%CI 0.66-1.44), cardiovascular death (OR 0.95: 95%CI 0.65-1.37), ST (OR 1.20: 95%CI 0.79-1.83) or TVR (OR 0.96: 95%CI 0.72-1.27), with no heterogeneity except for TVR. Shorter DAPT compared to longer DAPT was associated with a greater risk of non-fatal MI (OR 1.35: 95% CI 1.03-1.77). Mild heterogeneity was present, and the relationship between DAPT duration and MI was mainly driven by the outcomes from the DAPT trial. The risk of MI was increased with 12 months vs. ≥30 months DAPT (OR 1.61: 95%CI 1.16-2.22), while there was no significant difference in ≤6 months vs. 12 months DAPT (OR 1.27: 0.93-1.74), or for 6 months vs. 24 months DAPT (OR 0.81: 95%CI 0.13-4.87). Conversely, major bleeding was significantly less with shorter compared to longer DAPT (OR 0.60: 95%CI 0.42-0.96), with no heterogeneity present.

The impact of DAPT duration on ischemic and bleeding endpoints was consistent when considered separately for EES and fast-release ZES. By meta-regression analysis, baseline features did not influence the results for all-cause death, MI, ST, or major bleeding (**Table 4**). There was no systematic bias apparent as assessed by funnel plot inspection and with Egger's test which was not significant. (**Figure 8**).

DISCUSSION

The present meta-analysis represents a critical appraisal of the current evidence regarding different DAPT durations in patients receiving second generation DES. The major findings are that shorter DAPT duration was associated with higher rates of total MI, lower rates of major bleeding, and similar rates of ST, cardiovascular mortality and all-cause mortality. These results were consistent for EES and fast-release ZES, and were not dependent on baseline clinical variables. Moreover, to the best of our knowledge, ours is the first meta-analysis to perform a sensitivity analysis for different kinds of second generation stents.

An increased risk of ST with an abbreviated DAPT regimen remains the major concern for interventional cardiologists, due to its ominous impact on prognosis (22-24). In our analysis there was no significant increase in ST with shorter DAPT after implantation of second generation DES. In this regard it should be noted, however, that most ST episodes occur in the first month after stent implantation when all patients are still on DAPT, and that second-generation DES have been demonstrated to have lower rates of late ($\geqslant$1 month) ST compared with first-generation DES (2). However, despite the large number of patients in our study, the 95% confidence interval around the ST point estimate was wide, and we cannot exclude the possibility that short DAPT might be associated with a modest increase risk in ST had more patients been available for inclusion.

Long-term DAPT was associated with a reduction in the rate of total MI, a difference most evident in patients treated with $\geqslant$30 months vs. 12 month DAPT. Given the absence of a major effect on ST, this difference is most likely due to MI arising from non-stent related events due to the progression of atherosclerosis, as shown in the DAPT trial (20). As demonstrated in the

PROSPECT study (25) and in studies with optical coherence tomography (26), despite guideline-based medical treatment, approximately half of adverse events occurring within 3 years after PCI originate from lesions that have not received a stent which often appear angiographically mild, but by intravascular imaging may have severe plaque burden, i.e. a large necrotic core and thin fibrous cap. Prolonged or more potent DAPT may reduce the risk of very late (>1 year) ischemic events from thrombotic events arising from such plaques, especially in patients with acute coronary syndromes, as recently shown with ticagrelor and vorapaxar (27), while bleeding may be an important issue particularly in patients with an indication for oral anti-coagulation (28). It should be highlighted, however, that the MI were not fatal, including both those leading to death and not, and this may explain the neutral effect on survival. Moreover differently from the data of Palmerini et al and Giustino et al (7, 8) no significant difference was reported in stent thrombosis and this may be explained by inclusion of only second generation stents.

Despite the increased risk of MI with shorter DAPT, our meta-analysis found that short-term DAPT is not associated with an increased risk of cardiovascular or all-cause mortality when used after implantation of second generation DES. This finding appears to be independent of the duration of clopidogrel (3 vs. 6 months) and the type of second generation DES implanted (ZES vs. fast-release EES). These results were consistent across differences in numerous baseline variables. These data, applying only to select second generation DES, thus confirm and extend the findings of prior studies from El-Hayek, Giustino and colleagues (7,24). While the reasons for the neutral effect on survival deserve further study, shorter DAPT was strongly associated with reduced rate of major bleeding, the occurrence of which has been strongly associated with mortality (29). These results thus highlight the competing risks and benefits of long-term DAPT, emphasizing the need for an individualized approach to balance the competing risks of bleeding and MI when deciding upon the optimal DAPT duration for each patient.

Our study has several limitations. The trials included used different classifications for severe bleeding. Not all outcome measures were available for second generation DES from the DAPT trial, the largest study among those included. Yet in the overall DAPT study population, 30 months as compared to 12 month DAPT resulted in slightly higher rate of all-cause mortality, so it

is unlikely that our finding of non-inferiority of short DAPT for all-cause mortality would have been altered by inclusion of these missing data. Few patients in the studies we included were treated with ticagrelor and prasugrel, and none with vorapaxar, the use of which may also reduce late MI . Our study also does not apply to patients treated with slow-release ZES or bioresorbable vascular scaffolds, and few patients were treated with metallic DES with bioresorbable polymers consequently limiting evidence on this sample size of population. Moreover, according to evaluation of quality of study (see Table A, online web appendix only) overall risk was low strengthening the results of the present analysis, both from the point of view of allocation concealment, attrition bias and blinding. Time of randomization was quite variable, although all patients were assigned to arm in 30 days. Moreover few patients with left main disease, heart failure, chronic kidney disease were enrolled, no useful inference can be driven on this population: actually due to low number of patients, no meta-regression was performed because it could drive to not reliable results. Finally no data were provided about management of patients with Aspirin Hypersensitivity (30).

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Conflict-of-interest statement

TFL has received research grants unrelated to this project to the institution from Abbott, AstraZeneca, Bayer Health Care, Biosensors, Biotronik, Boston Scientific, Medtronic, Merck, Sharpe and Dhome, Merck, Inc., Roche and Servier, including lecture fees. FDA has received research grants unrelated to this project to the institution from Abbott, Chiesi, Cros nt,Mediserve, including lecture fees.

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FIGURE LEGEND

Figure 1: Selection of the included studies.

Figure 2: All-cause death according to the duration of DAPT.

Figure 3: Cardiovascular death according to the duration of DAPT.

Figure 4: Myocardial infarction according to the duration of DAPT.

Figure 5: Stent thrombosis (definite or probable) according to the duration of DAPT.

Figure 6: Target vessel revascularization according to the duration of DAPT.

Figure 7: Major bleeding according to the duration of DAPT.

Figure 8: Funnel plot analysis of the included studies.

Table 1. Duration of dual antiplatelet therapy and stent types in the included studies

Trial and citation	N° patients randomized to second generation DES	Months of DAT	First Generation DES	Cypher	Endeavor/ Resolute	Promus/ Xience	Nobori	Biomatrix	Bleeding's definition	Design of the trial	Timing of enrollement
DAPT, 14 (20)	5967	12 vs. 30	-	11%	13%	47%	-	-	BARC types 3 and 5	Non inferiority	Within 72 hours of PCI
DES LATE, 14 (16)	2137	12 vs 24	73%	-	11%	16%	-	-	TIMI	-	Not detailed
ITALIC, 14 (21)	2031	6 vs. 24*	-	-	-	100% Xience	-	-	REPLACE/GUSTO	Non inferiority	Not detailed
SECURITY, 14 (14) EES ZES	1372 382 809	6 vs. 12	-	-	41,2%	20,1%	26,3%	12,4%	TIMI	Non inferiority	Not detailed
OPTIMIZE, 13 (15)	3119	3 vs. 12	-	-	100% Endeavor	-	-	-	-	Non inferiority	Not detailed
EXCELLENT, 13 (18)	1079	6 vs. 12	-	-	-	100%	-	-	-	Non inferiority	Not known
PRODIGY, ZES 13 (19)	493	6 vs. 24	-	-	100% Endeavor	-	-	-	BARC	Non inferiority	After 30 days
PRODIGY, EES 13 (19)	495	6 vs. 24	-	-	-	100%	-	-	BARC	Non inferiority	After 30 days
RESET, 12 (17)	2117	3 vs. 12	-	.	100% Endeavor	-	-	-	BARC types 2,3,5 and GUSTO	Superiority	After stent implantation

*12 months data available

Table 2. Baseline features of the included patients

Trial and citation	Age (years)	Female	Diabetes mellitus	Ejection fraction	Acute coronary syndrome
DAPT, 14 (20)	62	25 (%)	31 (%)	-	43 (%)
DES LATE, 14 (16)	62	30 (%)	28 (%)	60 (%)	60 (%)
ITALIC, 14 (21)	62	20 (%)	37 (%)	-	-
SECURITY, 14 (14)	65	23 (%)	30 (%)	56 (%)	38 (%)
EES	64	22 (%)	28 (%)	56 (%)	37 (%)
ZES	66	21 (%)	32 (%)	55 (%)	39 (%)
OPTIMIZE, 13 (15)	61	36 (%)	35 (%)	-	32 (%)
EXCELLENT, 13 (18)	63	35 (%)	38 (%)	-	48 (%)
Prodigy, ZES 13 (19)	67	21 (%)	36 (%)	51 (%)	74 (%)
Prodigy, EES 13 (19)	68	21 (%)	26 (%)	50 (%)	77 (%)
RESET, 12 (17)	62	36 (%)	29 (%)	64 (%)	54 (%)

Table 3. Angiographic features of the included patients

Trial and citation	Multivessel disease	Left anterior descending target	Bifurcation target	Class B2/C lesions	Lesion length (median;mm)
DAPT, 14 (20)	-	41 (%)	13 (%)	43 (%)	-
DES LATE, 14 (16)	30 (%)	51 (%)	14 (%)	-	30
ITALIC, 14 (21)	48 (%)	73 (%)	-	-	-
SECURITY, 14 (14)	44 (%)	43 (%)	14 (%)	21 (%)	18
EES	40 (%)	42 (%)	16 (%)	20 (%)	17
ZES	48 (%)	44 (%)	13 (%)	22 (%)	19
OPTIMIZE, 13 (15)	25 (%)	48 (%)	15 (%)	37 (%)	18
EXCELLENT, 13 (18)	51 (%)	52 (%)	10 (%)	53 (%)	23
Prodigy, ZES 13 (19)	73 (%)	57 (%)	-	64 (%)	13
Prodigy, EES 13 (19)	65 (%)	59 (%)	-	68 (%)	13
RESET, 12 (17)	42 (%)	53 (%)	0	67 (%)	20

Table 4. Meta-regression analysis.

	Beta	LCI (95%)	UCI (95%)	P value
All-cause death				
Age*	0.01	-0.10	0.13	0.67
Female gender	-0.01	-0.05	0.04	0.85
Diabetes mellitus	-0.02	-0.09	0.05	0.52
Acute coronary syndrome	-0.02	-0.10	0.14	0.77
Multivessel disease	-0.01	-0.08	0.19	0.65
LAD	-0.03	-0.09	0.04	0.39
Class B2/C lesions	-0.08	-0.13	0.15	0.53
Lesion length**	-0.01	-0.20	0.21	0.84
Myocardial infarction				
Age*	-0.06	-0.18	0.45	0.92
Female gender	-0.01	-0.05	0.02	045
Diabetes mellitus	-0.02	-0.09	0.05	0.52
Acute coronary syndrome	-0.05	-0.03	0.34	0.67
Multivessel disease	-0.01	-0.08	0.21	0.45
LAD	0.01	-0.05	0.08	0.98
Class B2/C lesions	-0.09	-0.17	0.21	0.24
Lesion length**	0.03	-0.04	0.56	0.32
Major bleeding				
Age*	-0.04	-0.15	0.06	0.46
Female gender	0.01	-0.03	0.05	0.59
Diabetes mellitus	0.01	-0.04	0.07	0.52
Acute coronary syndrome	-0.02	-0.10	0.01	0.37
Multivessel disease	-0.01	-0.03	0.02	0.29
LAD	-0.03	-0.10	0.05	0.42
Class B2/C lesions	-0.08	-0.24	0.21	0.37
Lesion length**	-0.02	-0.11	0.31	0.45

*increase is for 1 to 10 years

**increase if for 1 to 10mm

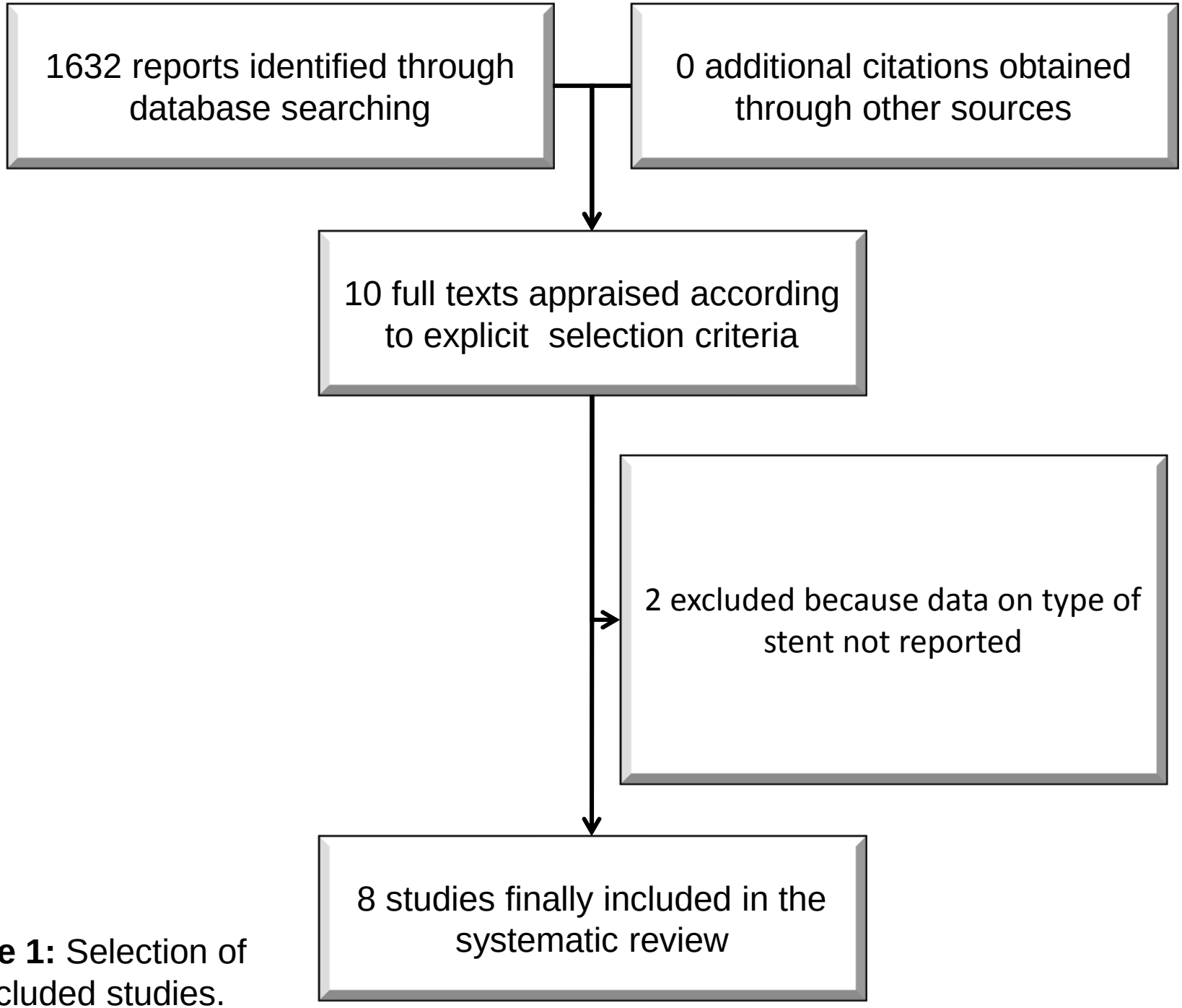

Figure 1: Selection of the included studies.

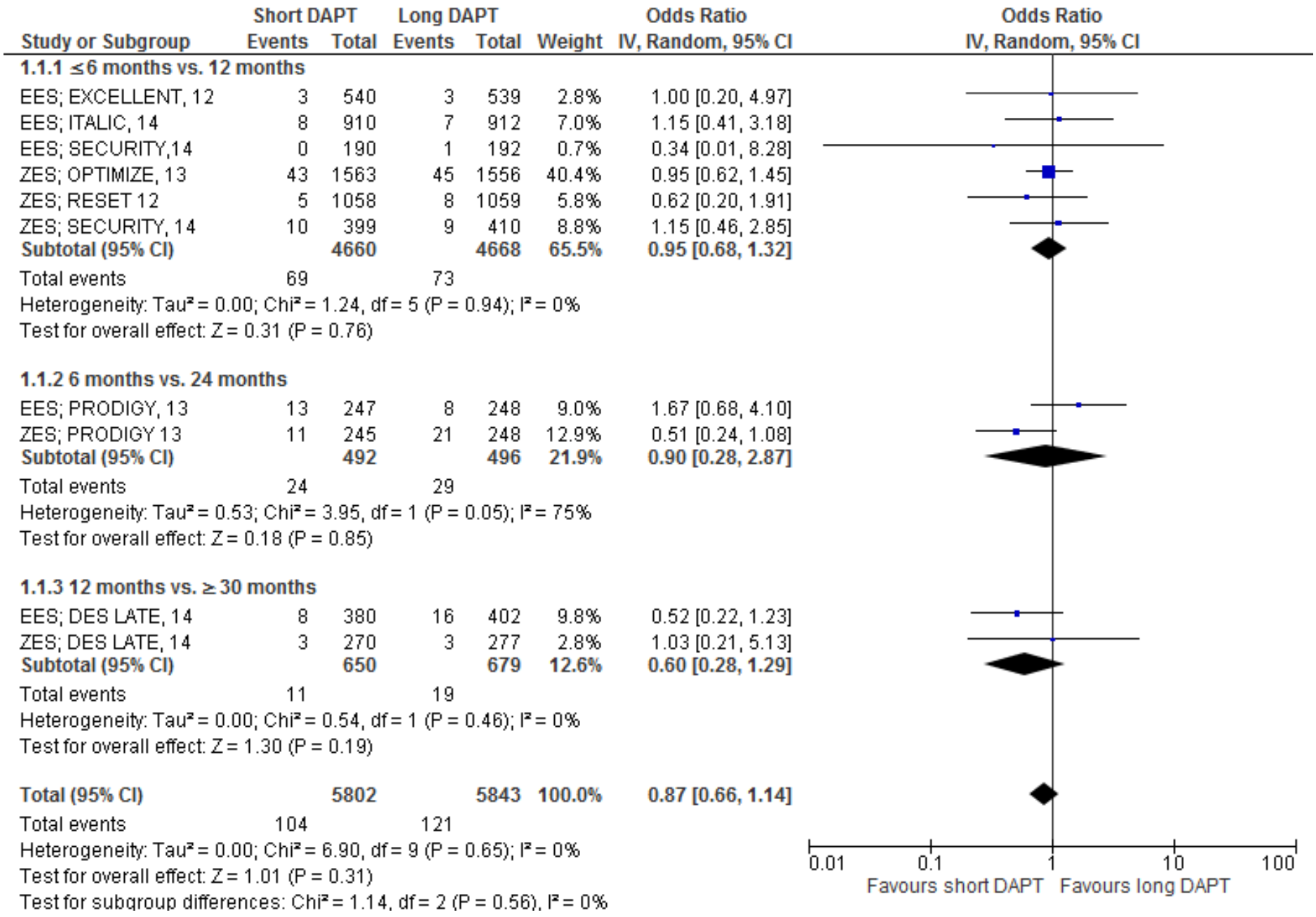

Figure 2: All-cause death according to the duration of DAPT.

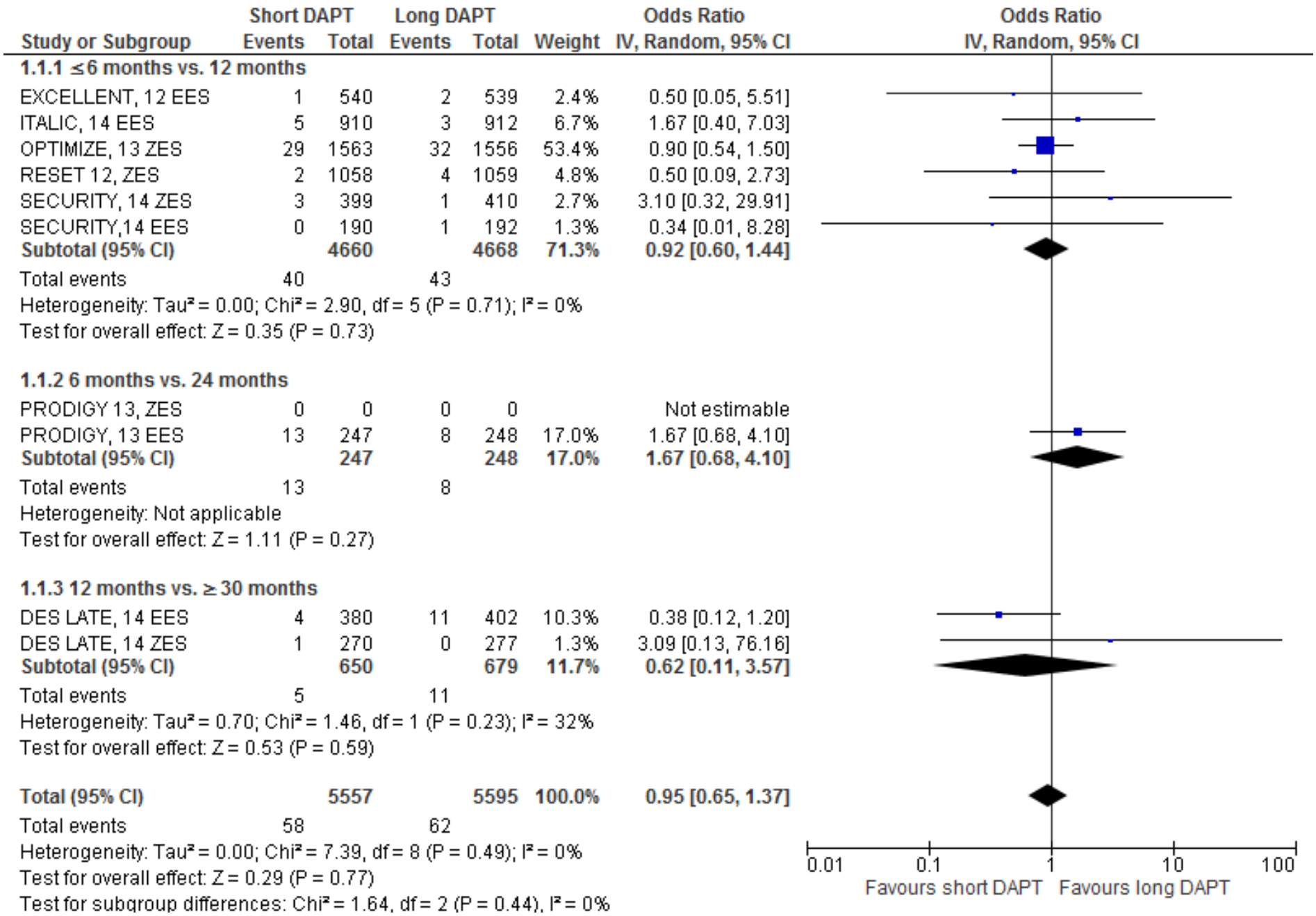

Figure 3: Cardiovascular death according to the duration of DAPT.

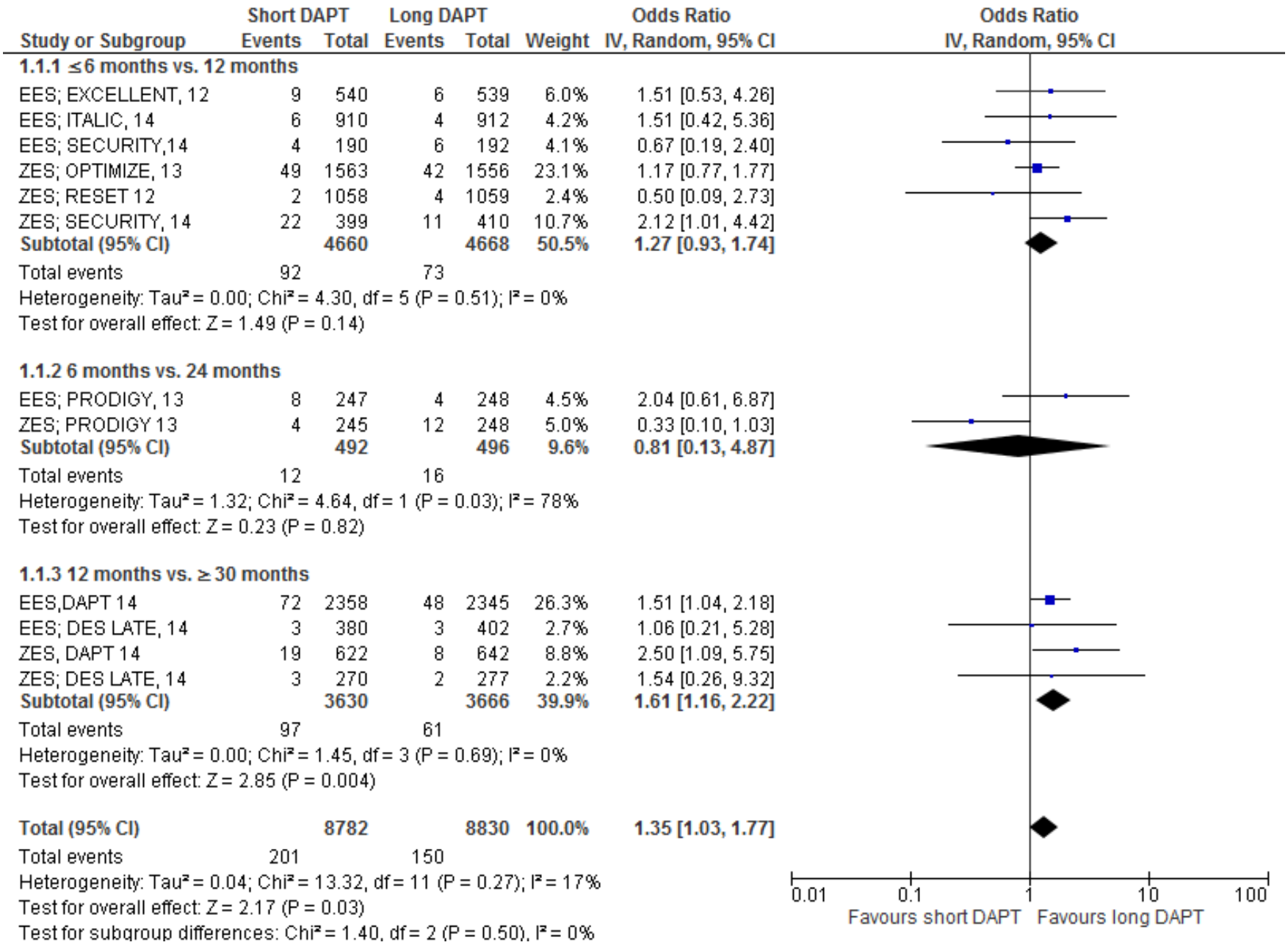

Figure 4: Myocardial infarction according to the duration of DAPT.

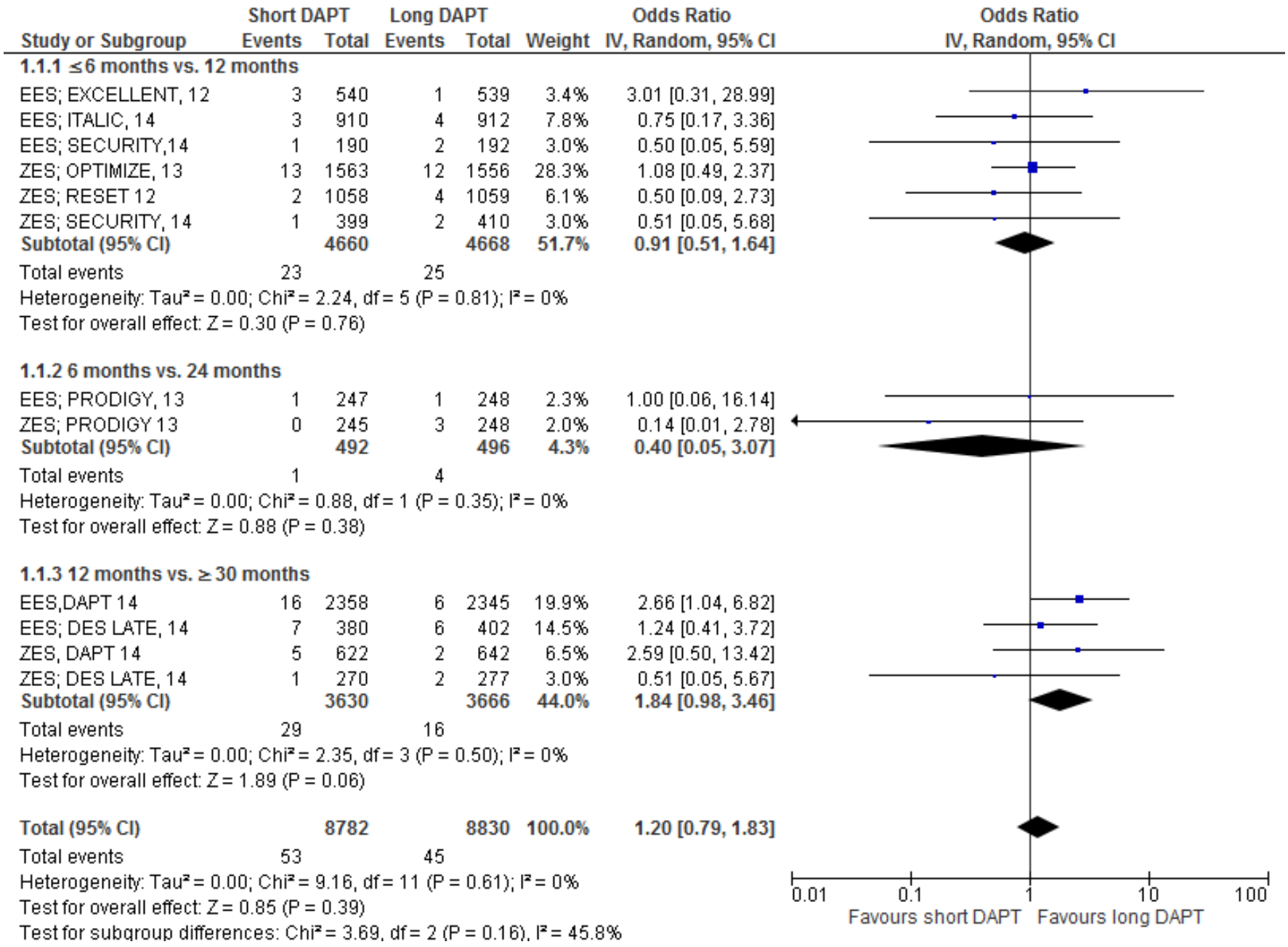

Figure 5: Stent thrombosis (definite or probable) according to the duration of DAPT

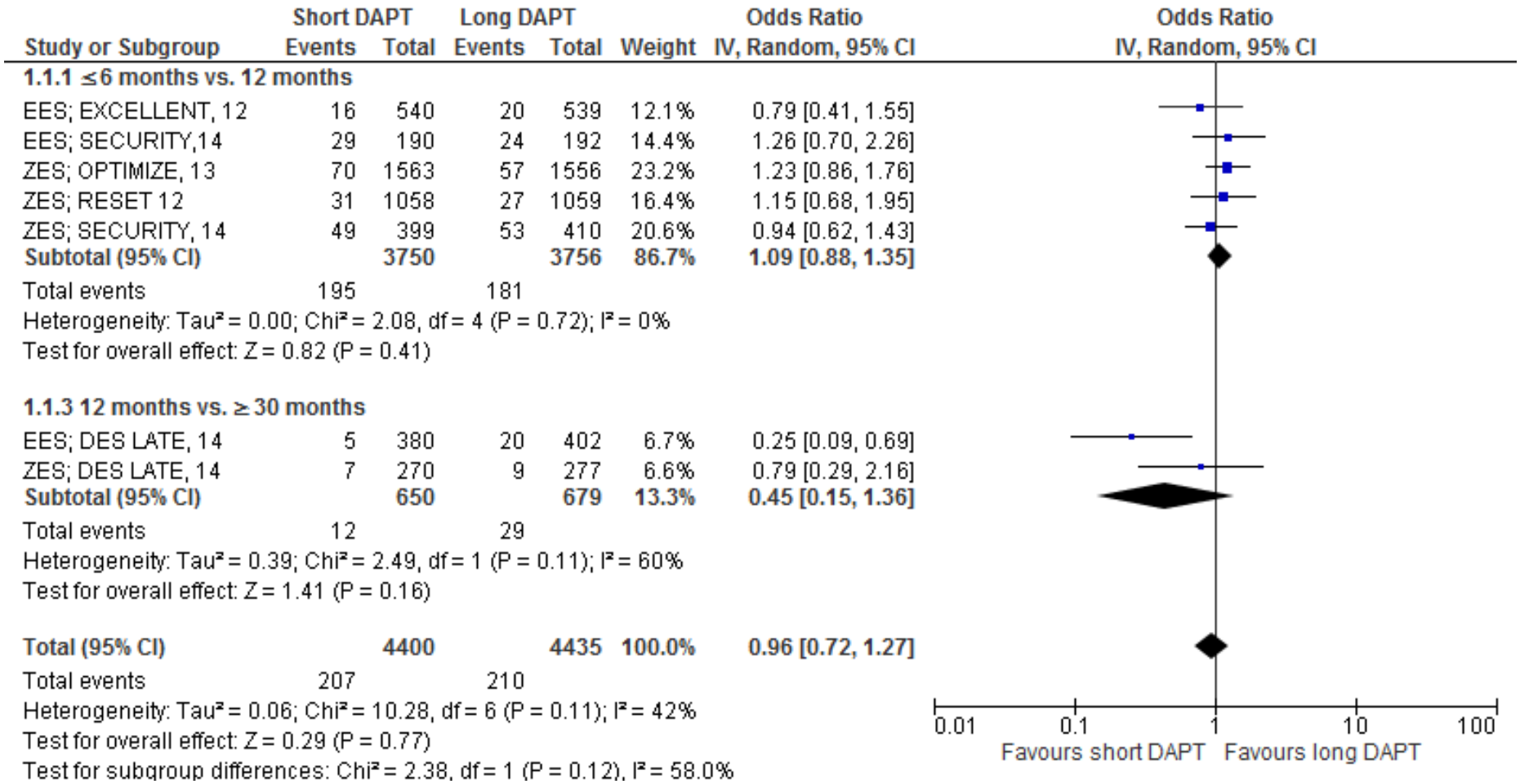

Figure 6: Target vessel revascularization according to the duration of DAPT.

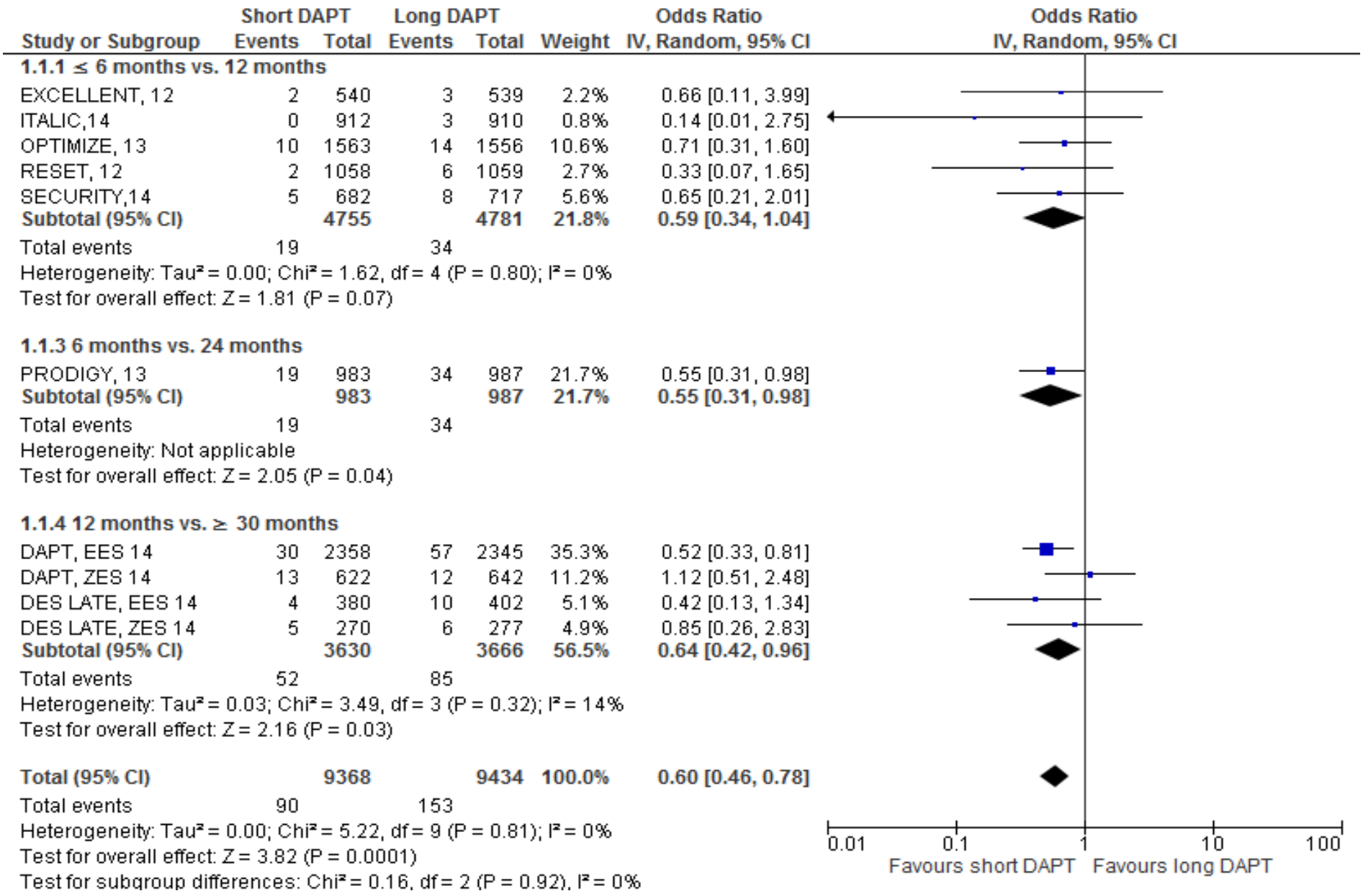

Figure 7: Major bleeding according to the duration of DAPT.

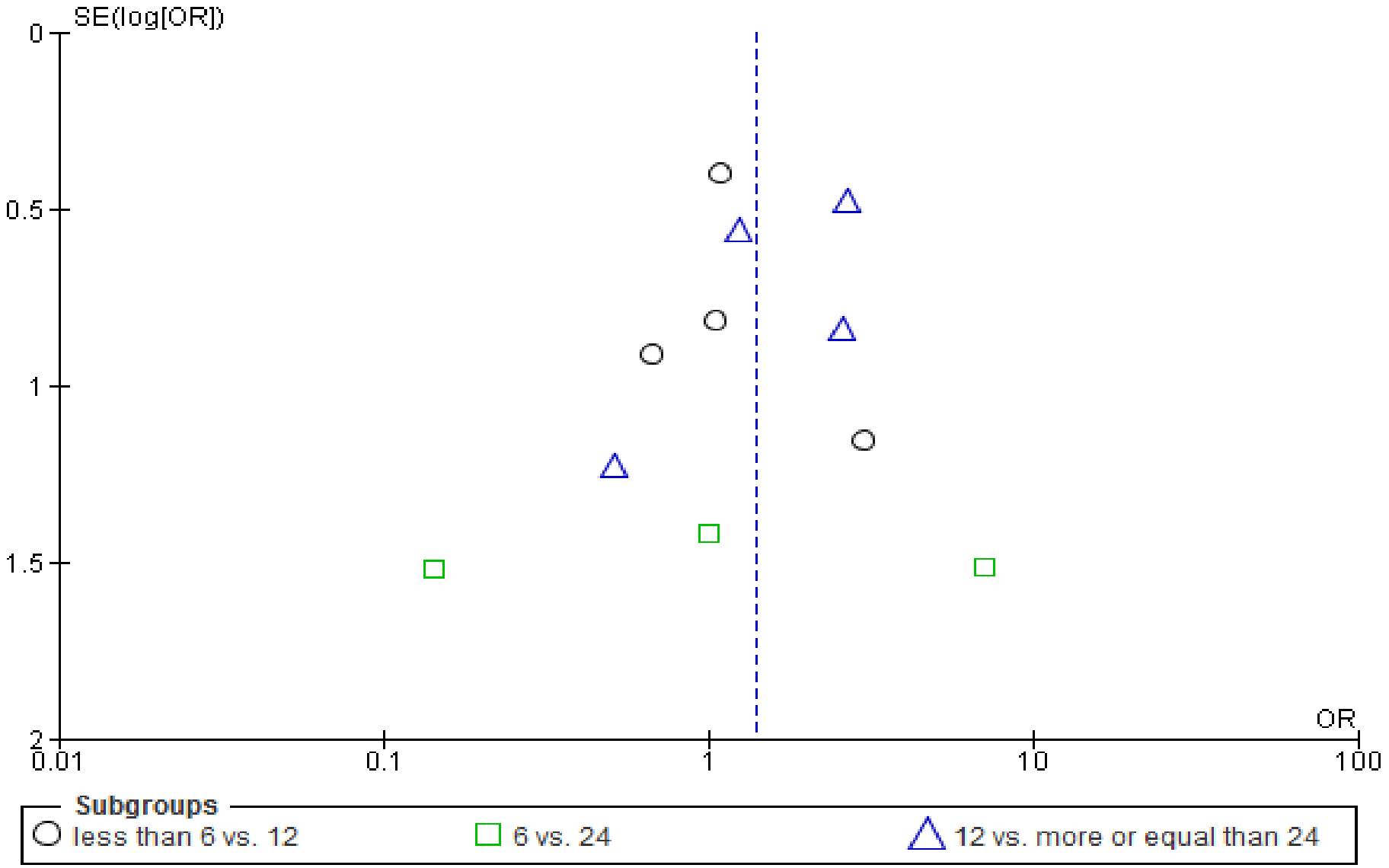

Figure 8: Funnel plot analysis of the included studies.