REVIEW

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Longer- Versus Shorter-Duration Dual-Antiplatelet Therapy After Drug-Eluting Stent Placement

A Systematic Review and Meta-analysis

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Background: The appropriate duration of dual-antiplatelet therapy (DAPT) after drug-eluting stent (DES) placement remains controversial.

Purpose: To summarize data on clinical outcomes with longer- versus shorter-duration DAPT after DES placement in adults with coronary artery disease.

Data Sources: Ovid MEDLINE and EMBASE, 1996 to 27 March 2015, and manual screening of references.

Study Selection: Randomized, controlled trials comparing longer- versus shorter-duration DAPT after DES placement.

Data Extraction: Two reviewers screened potentially eligible articles; extracted data on populations, interventions, and outcomes; assessed risk of bias; and used the Grading of Recommendations Assessment, Development and Evaluation guidelines to rate overall confidence in effect estimates.

Data Synthesis: Among 1010 articles identified, 9 trials including 29 531 patients were eligible; data were complete for 28 808 patients. Moderate-quality evidence showed that longer-duration DAPT decreased risk for myocardial infarction (risk ratio [RR], 0.73 [95% CI, 0.58 to 0.92]) and increased mortality (RR, 1.19 [CI, 1.04 to 1.36]). High-quality evidence showed that DAPT increased risk for major bleeding (RR, 1.63 [CI, 1.34 to 1.99]).

Limitation: Confidence in estimates were decreased owing to imprecision for most outcomes (particularly myocardial infarction), risk of bias from limited blinding in 7 of 9 studies, indirectness due to variability in use of first- and second-generation stents, and off-protocol use of DAPT in some studies.

Conclusion: Extended DAPT is associated with approximately 8 fewer myocardial infarctions per 1000 treated patients per year but 6 more major bleeding events than shorter-duration DAPT. Because absolute effects are very small and closely balanced, decisions regarding the duration of DAPT therapy must take into account patients' values and preference.

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Because drug-eluting stents (DESs) decrease the risk for in-stent restenosis and repeated revascularization, clinicians frequently choose these over bare-metal stents for percutaneous revascularization in patients with coronary artery disease (1–3). Randomized trials demonstrated that dual-antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor (clopidogrel, ticagrelor, or prasugrel) effectively prevents stent thrombosis, leading to recommendations for 6 to 12 months of DAPT after placement of a DES (4–6). The appropriate duration of therapy remains, however, controversial.

Observational studies have suggested that in patients who have undergone DES placement, discontinuing DAPT—usually stopping use of the P2Y12 inhibitor—can, even after 1 year, result in acute stent thrombosis (7–9). Because stent thrombosis is frequently associated with myocardial infarction and sometimes with death, many clinicians have responded to these reports by prescribing DAPT indefinitely, despite the consequent increased risk for bleeding. In one large observational study, 43% of patients who received a DES also received DAPT for more than 1 year (mean duration of DAPT, 18.3 months) (10). More recently, randomized trials have offered apparently conflicting evidence regarding the merit of longer- versus shorter-duration DAPT (11–17).

We performed a systematic review of all randomized, controlled trials (RCTs) comparing longer- versus shorter-duration DAPT in patients receiving DES. Because composite end points varied among trials and these composites can produce misleading results (18, 19), we focused on the individual end points of all-cause death, myocardial infarction (MI), and major bleeding. Other end points included cardiovascular death, any stroke, and recurrent revascularization.

METHODS

We developed and followed a standard protocol for the review.

Eligibility Criteria

We included all RCTs that compared longer- versus shorter-duration DAPT (aspirin plus a P2Y12 inhibitor) after placement of a DES. Either of 2 designs was eligible: 1) patients randomly assigned to a longer or shorter duration of DAPT at time of initial DES placement, or 2) patients randomly assigned to receive single-antiplatelet therapy or to continue receiving DAPT for a longer duration after a specified course of DAPT following DES placement.

Included articles met 3 criteria. First, the reported study had a shorter-duration treatment group in which

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patients received DAPT, including aspirin and clopidogrel, prasugrel, or ticagrelor, for at least 3 months. Second, the study had a longer-duration treatment group in which patients received DAPT, including aspirin and clopidogrel, prasugrel, or ticagrelor for at least 6 months longer than in the shorter-duration treatment group. Finally, at least one of the following outcomes was reported: all-cause death, cardiovascular death, MI, major bleeding, recurrent revascularization, or any stroke. Each study's definitions of these outcomes is provided in the **Appendix** (available at www.annals.org). When more than one report of a study's results was available, we used the report that provided the most comprehensive data.

Data Sources and Search Strategy

We searched the Ovid MEDLINE and EMBASE databases from 1996 to 27 March 2015 and conducted a manual search of references. Keywords were "stents *or* ticlopidine *or* platelet aggregation inhibitors *or* antiplatelet therapy *or* dipyridamole *or* aspirin *or* anticoagulants *or* prasugrel *or* ticagrelor *or* clopidogrel." By using *and*, these results were combined with those from the keyword "drug-eluting stents." Results were then limited to RCTs and duplicates were removed. For every eligible study we identified, and for such studies as review articles that included citations to potentially eligible studies, one reviewer identified potentially eligible articles from the reference list.

Study Selection

Two investigators independently screened each title and abstract. If either reviewer identified a citation as potentially relevant, we obtained the full-text article and reviewers independently made a detailed review to determine eligibility. Reviewers resolved disagreements through discussion.

Data Extraction

Two investigators independently abstracted the following information from each eligible study: funding, eligibility criteria, participant demographic and clinical data, planned duration of DAPT in each group, number of patients withdrawn or lost to follow-up, indication for DES placement, type of DES, and outcome event rates.

Quality Assessment

Two reviewers assessed risk of bias by using a modified version of the Cochrane risk for bias tool (http://distillercer.com/resources/), addressing the following 7 domains: adequacy of sequence generation, allocation sequence concealment, blinding of participants and caregivers, blinding for outcome assessment, incomplete outcome data, selective outcome reporting, and the presence of other potential sources of bias not accounted for in the other 6 domains (20). The reviewers then used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to rate certainty of evidence for each outcome as high, moderate, low, or very low (21). Detailed GRADE guidance was used to assess overall risk of bias (22), imprecision (23), inconsistency (24), indirectness (25), and publication bias (26) and summarized results in an evidence profile.

For decisions regarding eligibility, risk of bias assessment, and data abstraction, reviewers resolved disagreement through discussion.

Data Synthesis and Statistical Analysis

We report descriptive statistics as proportions for categorical variables, and mean (SD) for continuous variables. Our primary analyses addressed outcomes of all-cause mortality, MI, and major bleeding. **Appendix Table 1** (available at www.annals.org) shows the bleeding classification used in each study. In the 2 studies reporting fatal bleeding events, we subtracted these events from total bleeding events because they were already counted in the total deaths (14, 17). We also addressed outcomes of cardiovascular mortality, repeated revascularization, and any stroke.

Main outcomes were all-cause mortality, MI, and major bleeding. Secondary outcomes were cardiovascular mortality, repeated revascularization, and any stroke events. Study-specific definitions for major bleeding are provided in **Appendix Table 1**. Our primary analyses were based on eligible patients who had reported outcomes for each study. We then conducted a series of sensitivity analyses to evaluate the potential effect that patients with missing outcome data may have had on the comparative effects estimates.

For the outcomes of MI, death, and major bleeding, we conducted a plausible worst-case sensitivity analysis in which all patients with missing data from one group of the study (the group with the lower event rate) were assumed to have 5 times the event rate as those with complete data, and those excluded from the other group were assumed to have the same event rate as patients with complete data (27, 28). The rationale for the choice of 5 times the event rate in patients lost to follow-up is that in studies examining the rate of events in patients who are easily followed versus those who are more difficult to follow, 5 times the event rate was the largest gradient observed.

As an example of this process, Collet and colleagues (11) reported 43 patients lost to follow-up in the longer-duration treatment group and 56 patients in the shorter-duration treatment group. In the analysis of MI, events in the longer duration group in those followed were 9, or 1.5%. Five times 1.5% is 7.5%, and we therefore assumed that in the 43 patients lost to follow-up, 3 events occurred, leading to a new numerator and denominator of 12/635 rather than 9/592.

Another sensitivity analysis added a study of questionable eligibility (29) to studies included in the primary analysis.

Given that, as described previously, the studies had 2 primary design types, we also performed analyses for the outcome of MI and major bleeding separately for studies in which patients were randomly assigned after completing at least 6 months of DAPT for DES placement and for those in which patients were randomly assigned within 1 month of DES placement. We excluded the ITALIC (Is There A Life for DES after Discon-

tinuation of Clopidogrel) study from this subset analysis because patients were randomly assigned at the time of stent insertion, but events during the first 6 months of follow-up were disregarded (30). Differences between 2 or more subgroups were calculated by using the chi-square test as described by Borenstein and colleagues (31).

We calculated pooled risk ratios (RRs) and associated 95% CIs by using random-effects models applying the Hartung–Knapp–Sidik–Jonkman method (32). We used this method because it outperforms the conventional DerSimonian–Laird method for our data situations in which the number of studies is relatively small (<20) and some outcomes have moderate heterogeneity. Absolute effects and 95% CIs were calculated by multiplying pooled RRs and 95% CIs by what we deemed to be the most credible source for baseline risk estimates: the control rate of outcomes in the largest RCT (17).

Statistical heterogeneity was assessed by using the I^2 statistic (0% to 40%, might not be important; 30% to 60%, moderate heterogeneity may be present; 50% to 90%, substantial heterogeneity may be present; and 75% to 100%, considerable heterogeneity may be present) and the *P* value obtained from the Cochran chi-square test. Analyses were performed by using RevMan, version 5.2 (Nordic Cochrane Center, The Cochrane Collaboration) and SAS software, version 9.4, (SAS Institute).

Role of the Funding Source

This study was not funded.

RESULTS

Trial Identification

Our search yielded 1010 abstracts, of which 18 were eligible for full-text review. Of these, 9 were excluded, leaving 9 randomized studies enrolling 29 531 patients (11–14, 16, 17, 30, 33, 34). Appendix Figure 1 (available at www.annals.org) provides details of the search strategy.

In the RESET Trial (REal Safety and Efficacy of 3-month DAPT following Endeavor zotarolimus-eluting stent implantation), patients were randomly assigned to a specific novel second-generation stent and 3 months of DAPT compared with other stents and 1 year of DAPT (29). Because the intervention included 2 confounded components (antiplatelet therapy and stent type), we excluded this study from our primary analysis but conducted secondary analyses including this study for MI, major bleeding, and death.

Trial and Patient Characteristics

Appendix Table 1 presents characteristics of the 9 eligible studies. The difference in duration of therapy between the shorter and longer groups varied from 6 to 24 months; clopidogrel was the most commonly used thienopyridine; and adherence to use of the study drug was typically high. Typical participating patients were men with hypertension in their mid-60s (Appendix Tables 2 and 3, available at www.annals.org).

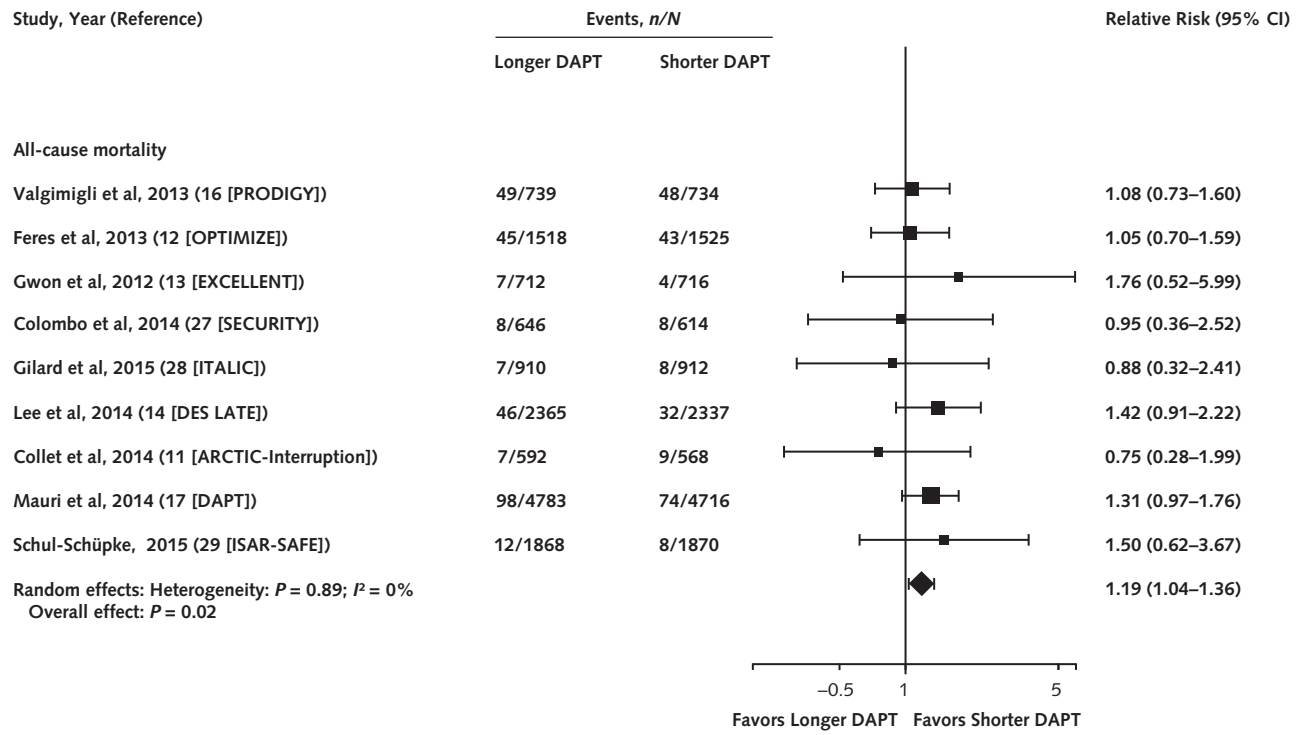
In 4 studies, patients were randomly assigned at the time of DES stent placement. Patients in these trials received a total of 3 to 6 months of DAPT (shorter-duration group) versus 12 to 24 months (longer-

Table. GRADE Assessment of Confidence in Estimates of Effect

Outcome	Participants (Studies), *n (n)*	Risk of Bias	Consistency	Directness	Precision	Publication Bias	Quality	Risk Ratio (95% CI)	Absolute Effect of Longer DAPT per 1000 Patients Treated per Year (95% CI)*
Total mortality	28 088 (9)	No serious limitations†§	No serious limitations	No serious limitations	Serious limitations‡	Not detected	Moderate	1.19 (1.04–1.36)	2 more events (0 more to 4 more events)
MI	28 088 (9)	No serious limitations†§	Serious limitations‖	No serious limitations¶	No serious limitations	Not detected	Moderate	0.73 (0.58–0.92)	8 fewer events (12 to 2 fewer events)
Major bleeding	26 475 (8)	No serious limitations†	No serious limitations	No serious limitations	No serious limitations	Not detected	High	1.63 (1.34–1.99)	6 more events 3 more to 10 more events)
Any stroke	28 088 (9)	No serious limitations†	No serious limitations	No serious limitations	Serious limitations**	Not detected	Moderate	0.99 (0.71–1.37)	0 more events (2 fewer to 2 more events)

DAPT = dual-antiplatelet therapy; GRADE = Grading of Recommendations Assessment, Development and Evaluation; MI = myocardial infarction.
* Baseline risk for each outcome in the control group, derived from event rates among patients with complete data in the shorter-duration group of the DAPT Study (17) (normalized to 1 y). Event rates per 1000 persons per year were 10 for mortality, 28 for MI, 10 for major bleeding, and 6 for stroke.
† Seven of 9 studies were open-label, resulting in lack of blinding for patients and personnel. Given the limited likelihood of the placebo effect and co-intervention as a result of unblinding, and given the blinded outcome adjudication, the risk of bias from failure to blind is limited.
‡ The 95% CI suggests potential for no benefit to harm.
§ The observed effect was no longer significant after the plausible worst-case analysis suggested potential for bias from missing data. The study was not rated down because the potential for bias was deemed to be small.
‖ Moderate heterogeneity for MI: I^2 = 36%.
¶ Studies used both first- and second-generation stents. In addition, in 2 studies, off-label use of P2Y12 inhibitor was greater than 10% in the shorter-duration group; this may have stemmed from the open-label design. The potential for applicability concerns is limited because these 2 studies accounted for a minority of patients.
** 95% CI for absolute effects suggests potential for benefit and harm.

Figure 1. Pooled risk for death with longer- versus shorter-duration DAPT after placement of a drug-eluting stent.



ARCTIC-Interruption = Assessment by a double Randomization of a Conventional antiplatelet strategy versus a monitoring-guided strategy for drug-eluting stent implantation and, of Treatment Interruption versus Continuation 1 year after stenting Interruption Study; DAPT = dual-antiplatelet therapy; DES LATE = Optimal Duration of Clopidogrel Therapy With Drug Eluting Stents to Reduce Late Coronary Arterial Thrombotic Event Study; EXCELLENT = Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting; ISAR-SAFE = Intracoronary Stenting and Antithrombotic Regimen: Safety And EFficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting; ITALIC = Is There A Life for DES after Discontinuation of Clopidogrel; OPTIMIZE = Optimized Duration of Clopidogrel Therapy Following Treatment With the Zotarolimus-Eluting Stent in Real-World Clinical Practice Study; PRODIGY = Prolonging Dual Antiplatelet Treatment After Grading Stent- Induced Intimal Hyperplasia Study; SECURITY = Second Generation Drug-Eluting Stent Implantation Followed by Six- Versus Twelve-Month Dual Antiplatelet Therapy.

duration group). In a fifth study, randomization occurred at time of DES placement, but events occurring during the first 6 months (when both groups received DAPT) were excluded. In these 5 trials, 67% to 100% of patients received second-generation (everolimus or zotarolimus) stents with decreased thrombogenicity (35–37) (Appendix Table 2). In the 4 studies in which random assignment was done 6 months or more after DAPT placement, patients received a total of 6 to 18 months of DAPT (shorter-duration group) versus 12 to 42 months (longer-duration group). In these trials, patients were less likely to receive second-generation stents (30% to 72%) (Appendix Table 3).

Assessment of Risk of Bias

Seven of the studies were open label and thus not blinded to patients, clinicians, or data or data collectors; however, all of the studies did have blinded outcome adjudication (Appendix Figure 2, available at www.annals.org). Lack of blinding may have been associated with differential use of other medication that influences outcomes, including statins and management of hypertension (no study reported on postrandomization use of these drugs). This was not deemed to be a significant source of bias.

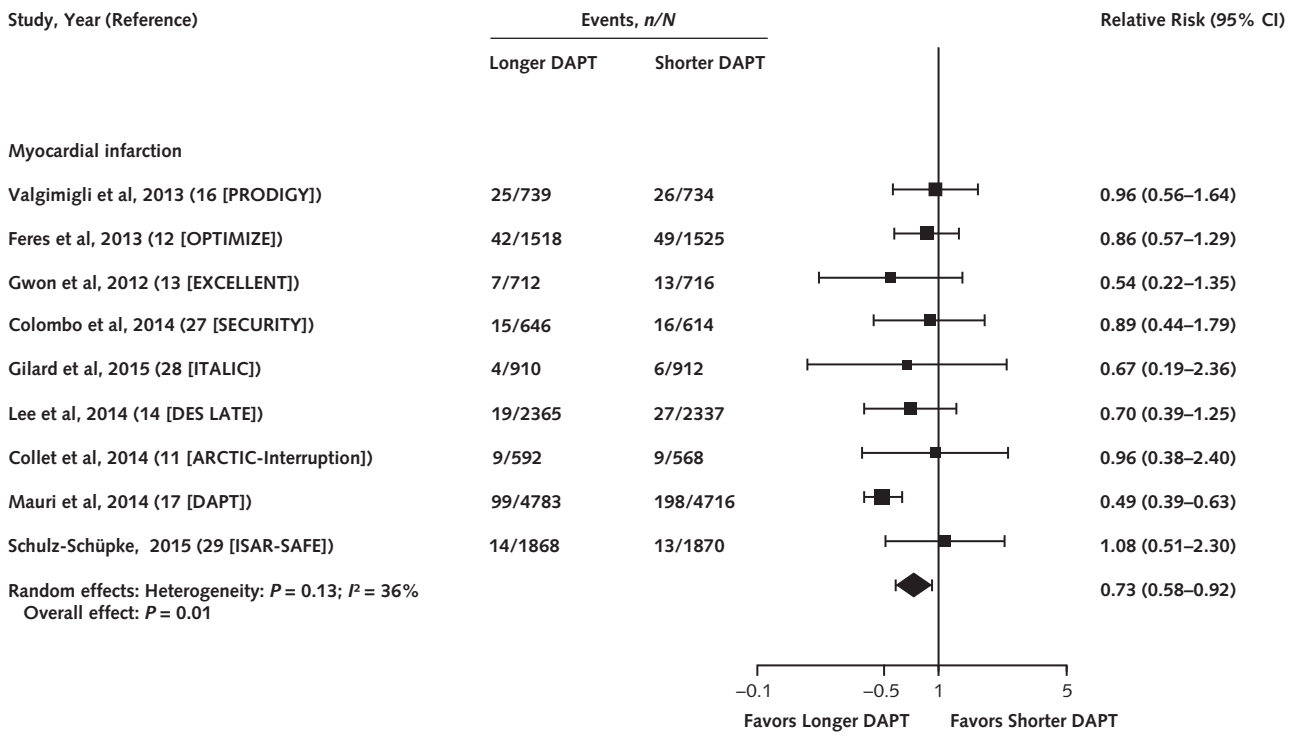
In one study, use of P2Y12 inhibitors persisted after the shorter treatment period in 17% of patients (11); in another, adherence to the treatment strategy in the shorter-duration group was 71% (13). In one study, patients were randomly assigned at time of stent insertion, but events in the first 6 months of DAPT were not reported (30). Rates of loss to follow-up or withdrawal of consent was similar in the shorter- and longer-duration groups (5% vs. 5%; range across studies, 0.1% to 9.9%).

Outcomes Assessment

Total and Cardiovascular Mortality

There were 279 deaths among 14 133 patients who were randomly assigned to receive longer-duration DAPT and 231 deaths among 13 992 patients assigned to shorter-duration therapy (RR, 1.19 [95% CI, 1.04 to 1.36]; heterogeneity: $P = 0.89$, $I^2 = 0\%$) (Figure 1). Using the observed rate of death in the shorter-duration group of the largest of the included studies (74 events in 4716 patients over 18 months = 10 events per 1000 patients per year) as a baseline, longer-duration DAPT may be associated with 2 more deaths per 1000 persons treated per year (CI, 0 more to 4 more deaths). Sensitivity analysis including the RESET

Figure 2. Pooled risk for myocardial infarction with longer- versus shorter-duration DAPT after placement of a drug-eluting stent.



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study did not appreciably alter our findings (RR, 1.20 [CI, 1.05 to 1.37]; heterogeneity: $P = 0.92$, $I^2 = 0\%$). Our plausible worst-case analysis attenuated the difference in total mortality between the longer-duration DAPT group and the shorter-duration group (RR, 1.03 [CI, 0.90 to 1.18]; heterogeneity: $P = 0.88$, $I^2 = 0\%$). Certainty in the evidence was moderate owing to imprecision and risk of bias due to loss to follow-up (results became insignificant with the plausible worst-case assumption) (Table).

Pooled data from 7 studies reporting cardiovascular death suggest no significant difference in rates of cardiovascular mortality between the longer- and shorter-duration groups (146 events vs. 137 events; RR, 1.06 [CI, 0.86 to 1.30]; heterogeneity: $P = 0.82$, $I^2 = 0\%$) (Appendix Figure 3, available at www.annals.org).

Myocardial Infarction

Of 14 133 patients assigned to longer-duration DAPT, 234 experienced MI, as did 357 of 13 992 patients assigned to shorter-duration therapy (RR, 0.73 [CI, 0.58 to 0.92]; heterogeneity: $P = 0.13$, $I^2 = 36\%$) (Figure 2). When the observed rate of MI in the shorter-duration DAPT group of the largest of the included studies was used as the baseline value (198 events in 4716 patients over 18 months = 28 events per 1000 patients per year), longer-duration DAPT may be associated with 8 fewer MIs per 1000 persons treated per year (CI, 12 fewer to 2 fewer persons) (Table). Sensitivity analysis including the RESET study did not appreciably alter our findings (RR, 0.75 [CI, 0.59 to 0.95; heterogeneity: $P = 0.12$, $I^2 = 36\%$). In our plausible worst-case analysis, the difference in MI between the longer-duration DAPT group and the shorter-duration DAPT group was attenuated and no longer significant (RR, 0.90 [CI, 0.64 to 1.27; heterogeneity: $P = 0.04$, $I^2 = 51\%$).

In the subgroup analysis focusing on study design, the RR for MI among patients assigned to longer- versus shorter-duration DAPT was 0.85 (CI, 0.64 to 1.13; heterogeneity: $P = 0.17$, $I^2 = 0\%$) in the 4 studies that enrolled patients at the time of DES placement. In the 4 studies that enrolled patients at least 1 year after DES placement (and DAPT therapy), the RR was 0.68 (CI, 0.38 to 1.22; heterogeneity: $P = 0.13$, $I^2 = 49\%$). The chi-square test for subgroup differences was not significant ($P = 0.34$) (Figure 3).

Our overall rating of confidence in estimates was moderate owing to heterogeneity (uncertainty regarding the subgroup effect), imprecision, indirectness due to use of different stents, and risk of bias due to loss to follow-up (results became insignificant with the plausible worst-case assumption).

Major Bleeding

Eight of the 9 studies reported bleeding events. There were 185 major bleeding events among 13 321

patients assigned to longer-duration DAPT versus 110 such events among 13 191 patients assigned to shorter-duration DAPT (RR, 1.63 [CI, 1.34 to 1.99; heterogeneity: P = 0.84, I^2 = 0%) (Figure 4). When the observed rate of major bleeding in the shorter DAPT group of the largest of the included studies was used as the baseline value (69 events in 4649 patients over 18 months = 10 events per 1000 patients per year), longer-duration DAPT may be associated with 6 more major bleeding events per 1000 persons treated per year (CI, 3 more to 10 more events). Sensitivity analysis including the RESET study did not appreciably alter our findings (RR, 1.65 [CI, 1.36 to 2.00]; heterogeneity: P = 0.86, I^2 = 0%). In our plausible worst-case analysis, the difference in major bleeding between the longer-duration DAPT group and the shorter-duration group was decreased slightly (RR, 1.31 [CI, 1.05 to 1.63]; heterogeneity: P = 0.66, I^2 = 0%).

In the subgroup analysis focusing on study design, the RR for major bleeding among patients assigned to longer- versus shorter-duration DAPT was 1.60 (CI, 0.99 to 2.58; heterogeneity: P = 0.88, I^2 = 0%) in the 3 studies that enrolled patients at the time of DES placement. In the 4 studies that enrolled patients at least 1 year after DES placement (and DAPT therapy), the RR was 1.62 (CI, 1.13 to 2.32; heterogeneity: P = 0.52, I^2 = 0%) (Appendix Figure 4, available at www.annals.org) The chi-square test for subgroup differences was not significant (P = 0.98) (Figure 3). Our overall rating of confidence in estimates was high (Table).

Any Stroke

Among 14 133 patients assigned to longer-duration DAPT, 98 had stroke (any type), as did 96 among 13 992 patients assigned to shorter-duration DAPT (RR, 0.99 [CI, 0.71 to 1.37]; heterogeneity: P = 0.47, I^2 = 0%) (Appendix Figure 5, available at www.annals.org). Confidence in estimates was moderate (Table).

Repeated Revascularization

Three studies reported recurrent revascularization (including stent and nonstent revascularizations). There were 132 recurrent revascularizations among 3669 patients assigned to longer-duration DAPT and 117 recurrent revascularizations among 3621 patients assigned to shorter-duration DAPT (RR, 1.12 [CI, 0.78 to 1.60]; heterogeneity: P = 0.63, I^2 = 0%) (Appendix Figure 6, available at www.annals.org). Confidence in estimates was moderate owing to imprecision.

Figure 3. Pooled risk for myocardial infarction with longer- versus shorter-duration DAPT after placement of a drug-eluting stent: subset analysis stratified by timing of randomization.

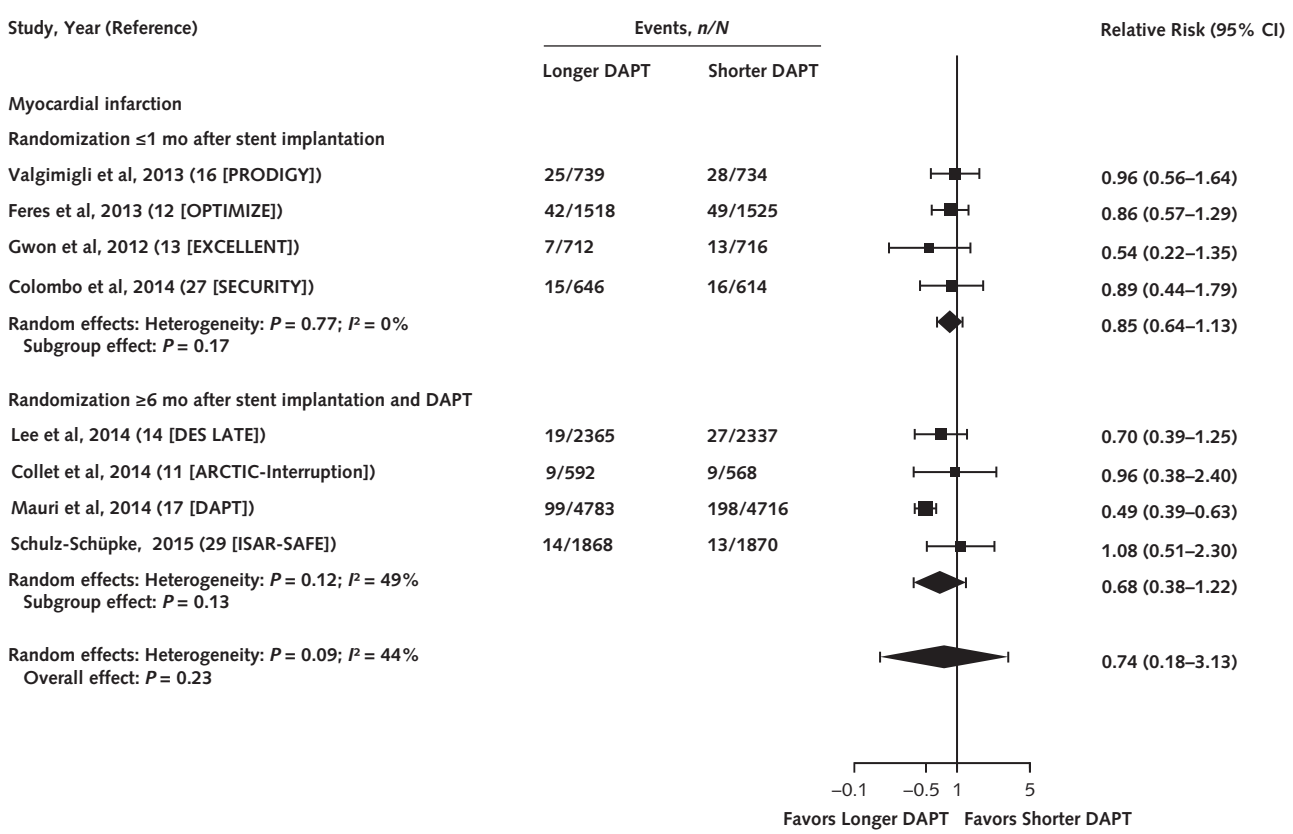

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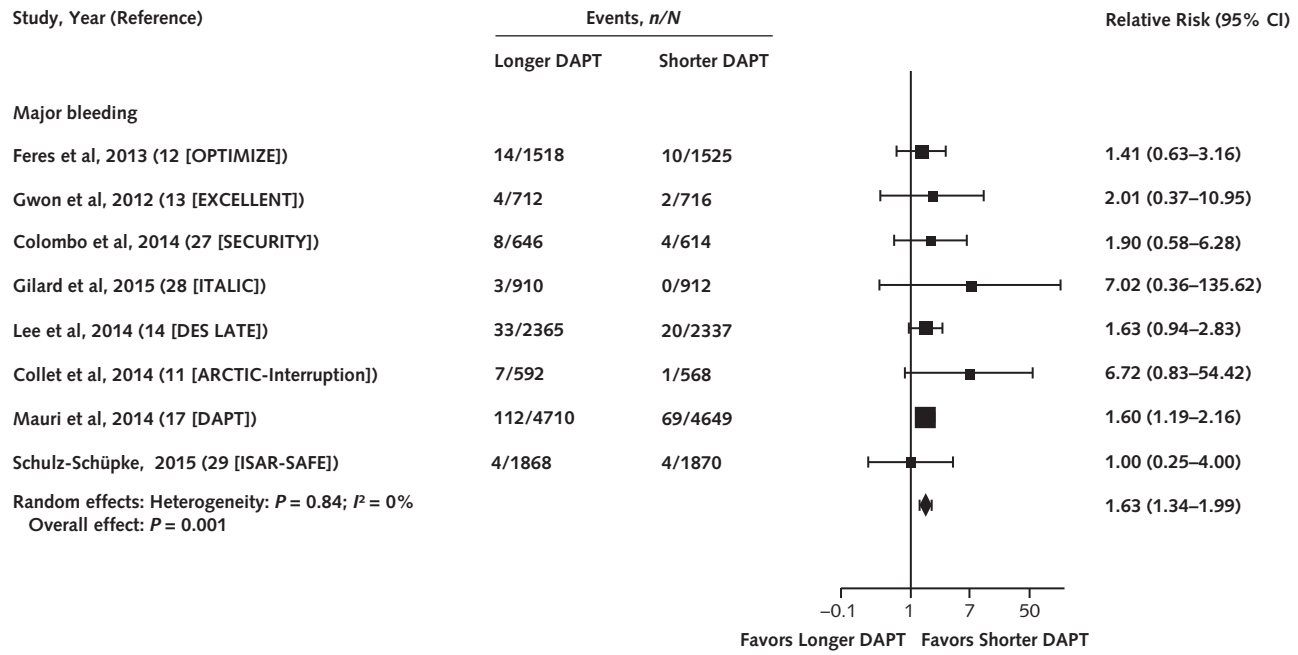
Figure 4. Pooled risk for major bleeding with longer- versus shorter-duration DAPT after placement of a drug-eluting stent.



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DISCUSSION

On the basis of pooled data from 9 RCTs that included over 28 000 patients receiving a DES and either longer or shorter duration of DAPT, we found moderate-quality evidence that longer-duration DAPT decreases the risk of for MI and high-quality evidence of an increase in the risk for major bleeding. The absolute magnitude of effects in both outcomes is, however, small: Best estimates suggest that prolonging DAPT will reduce the number of MIs by 8 per 1000 persons treated and increase the risk for major bleeding by about 6 events per 1000 persons, each over 1 year.

Several factors decrease our certainty in the estimate for MI, resulting in the moderate quality rating of the evidence (Table). First, the CI is relatively wide, including a reduction in MI from 2 per 1000 persons per year (which many would consider trivial) to 12 per 1000 persons per year (which many would consider important).

Second, studies used a variety of stent types, and the effect may be larger in first-generation stents with a larger risk for subsequent MI than in second-generation stents with a smaller risk. The GRADE system would classify this as an issue of indirectness (overall estimates are indirect for both first- and second-generation stents) (25). Another source of indirectness is the off-protocol use of DAPT in the shorter-duration groups, which would decrease any effect of longer DAPT use.

Studies also differed in timing of randomization relative to DES placement and in duration of follow-up. Furthermore, the definitions of short and long duration of therapy differed across studies. Finally, lack of blinding of patients and investigators in 7 of 9 studies introduces a small possibility of bias as a result of co-intervention. Although each of these limitations is of insufficient concern to lead by themselves to lowering our certainty in the evidence, taken together, they warrant rating down from high to moderate certainty.

In this review, we found moderate-quality evidence of an increase in overall mortality (RR, 1.19 [CI, 1.04 to 1.36]) with prolonged DAPT, with no clear effect on cardiovascular mortality. The absolute effect was very small (2 events per 1000 persons per year). Confidence in this finding is decreased by imprecision (the CI borders on no difference) and risk of bias due to loss to follow-up (results became insignificant with the plausible worst-case assumption). Our findings are similar to those of another recent meta-analysis that found a 22% increased risk for all-cause mortality associated with prolonged DAPT (primarily due to an increase in non-cardiovascular mortality) (38).

Strengths of our analysis compared with other reviews are that we assessed the quality of evidence by using the GRADE approach (Table) and offer estimates of the absolute effects of prolonged DAPT that are crucial for informed clinical decision making. Other strengths include a comprehensive literature search; restriction of studies to RCTs; duplicate assessment of eligibility, risk of bias, and data abstraction; use of the Hartung–Knapp–Sidik–Jonkman method for analysis of pooled risk ratios and 95% CIs; and a plausible worst-case sensitivity analysis exploring the potential effect of loss to follow-up.

Our review has limitations. For most outcomes, and particularly for MI and death, our certainty in the estimates decreased as a result of imprecision. In addition,

we found potential bias due to limited blinding in 7 of 9 studies; suboptimal study design (randomization in the first month after DES placement rather than after the initial period of DES use) in 3 studies; and indirectness due to variability in use of first- and second-generation stents and off-protocol use of DAPT in the shorter-duration group of studies.

In conclusion, pooled data from over 28 000 patients receiving DES suggest that extended DAPT is associated with approximately 8 fewer MIs per 1000 patients per year (moderate confidence) but 6 more major bleeding events (high confidence). Results also suggest a possible small increase in all-cause mortality (2 events per 1000 persons per year; moderate confidence). These data demonstrate a trade-off between a small reduction in MI on the one hand and a small increase in bleeding and a possibly even smaller increase in mortality on the other. Accordingly, decisions regarding DAPT must involve value and preference judgments about the relative aversion to MI and major bleeding. Patients who are reluctant to use drugs to achieve small or very small net benefits, those who do not want to risk bleeding events, or those who are risk-averse in general are likely to decline use of extended DAPT.

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Appendix: Outcome Definitions, by Study

PRODIGY

Myocardial Infarction

The diagnosis of acute MI was based on the universal definition of MI. The term "myocardial infarction" should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Under these conditions, any one of the following criteria meets the diagnosis of MI:

1. Detection of an increase or decrease in the levels of cardiac biomarkers (preferably troponin) with at least 1 value above the 99th percentile of the upper reference limit (URL), together with evidence of myocardial ischemia with at least one of the following: symptoms of ischemia; electrocardiography (ECG) changes indicative of new ischemia (new ST-T changes or new left bundle branch block [LBBB]); development of pathologic Q waves on ECG; or imaging evidence of new loss of viable myocardium or new regional wall-motion abnormality.

2. Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.

3. For percutaneous coronary interventions (PCIs) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of periprocedural myocardial necrosis. By convention, increases in biomarker level greater than 3 times the 99th percentile URL have been designated as defining PCI-related MI. A subtype related to a documented stent thrombosis is recognized.

4. For coronary artery bypass grafting (CABG) in patients with normal baseline troponin values, elevations of cardiac biomarker levels above the 99th percentile URL are indicative of periprocedural myocardial necrosis. By convention, increases of biomarkers greater than 5 times the 99th percentile URL plus either new pathologic Q waves or new LBBB, or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium have been designated as defining CABG-related MI.

5. Pathologic findings of acute MI.

Major Bleeding

This was defined per the Thrombolysis in Myocardial Infarction (TIMI) criteria.

Stroke

This was considered to have occurred if a new neurologic deficit was confirmed by a neurologist and on imaging. In contrast, the occurrence of a transient ischemic attack required hospitalization and clinical confirmation by a neurologist.

Death

All deaths were considered to be of cardiovascular causes unless an unequivocal noncardiovascular cause could be established.

EXCELLENT

Myocardial Infarction

During the first 48 hours after PCI, MI was defined as an increase in cardiac enzyme levels (creatine kinase–MB [CK-MB] fraction or troponin T/troponin I) 3 times above the upper limit of normal (ULN) in stable patients. In patients with elevated baseline levels of cardiac enzymes, MI was defined as a subsequent increase of greater than 2-fold from baseline values. After the first 48 hours, MI was defined as the presence of clinical signs of MI, combined with a CK-MB fraction or troponin T/troponin I increase higher than the ULN.

Major Bleeding

This was defined per the TIMI criteria.

Stroke

This was considered to have occurred if a new neurologic deficit was confirmed by a neurologist and detected on imaging.

Death

All deaths were considered cardiac unless a definite noncardiac cause could be established.

OPTIMIZE

Myocardial Infarction

Myocardial infarction was classified as Q wave (new pathologic Q waves in 2 or more continuous ECG leads) or non-Q wave, and:

1. Periprocedural: within 48 hours after PCI with baseline biomarkers less than the ULN, increase in CK-MB or troponin level 3 times the ULN. (For CABG-related MI: baseline biomarker levels less than the ULN, increase in CK-MB or troponin levels 5 times the ULN, and new Q wave/LBBB or new native or graft vessel occlusion or loss of viable myocardium).
2. Spontaneous: CK-MB or troponin level greater than the ULN.
3. Reinfarction: stable or decreasing biomarker values on 2 samples and a greater than 20% increase 3 to 6 hours postintervention compared with baseline samples.

Major Bleeding

The OPTIMIZE (modified REPLACE-2 definition)/GUSTO criteria were used:

1. Intracranial, intraocular, or retroperitoneal hemorrhage.
2. Clinically overt blood loss resulting in a decrease in hemoglobin of more than 30 g/L (3 g/dL).
3. Any decrease in hemoglobin of more than 40 g/L (4 g/dL); transfusion of 1 or more units of packed red blood cells or whole blood.
4. Bleeding that causes hemodynamic compromise and requires intervention.

Cerebrovascular Accident

This event was classified as hemorrhagic or ischemic and was defined as an acute neurologic event with a duration of 24 hours or more, with confirmation by either computed tomography or magnetic resonance imaging or pathologic confirmation.

Death

Deaths were classified as cardiac or noncardiac. Any unknown cause of death or death that could not be clearly attributed to a noncardiac cause was considered cardiac.

SECURITY (Second Generation Drug-Eluting Stent Implantation Followed by Six- Versus Twelve-Month Dual Antiplatelet Therapy)

Myocardial Infarction

Spontaneous MI was defined by the following criteria: elevation of cardiac enzyme levels (troponin T/troponin I or CK-MB) above the ULN associated with at least 1 ischemic symptom; development of Q waves on ECG; and electrocardiogram changes indicative of ischemia or coronary artery intervention.

Major Bleeding

This was defined as Bleeding Academic Research Consortium criteria type 3 or 5 bleeding.

Stroke

This was defined as any new neurologic deficit lasting more than 24 hours and associated with neuroimaging evidence (computed tomography or magnetic resonance imaging).

Death

Cardiac death included any death without a noncardiac cause.

ITALIC

Myocardial Infarction

Myocardial infarction was classified as Q-wave or non–Q-wave MI. Q-wave MI was defined by recurrence of symptoms and/or development of new pathologic Q waves in 2 or more contiguous leads, with elevated CK, CK-MB, or troponin levels. Non–Q-wave MI was defined by a greater than 2-fold elevation in the CK level, with an elevated CK-MB or troponin level without new pathologic Q waves.

Major Bleeding

This was defined according to the TIMI classification as intracranial hemorrhage, a 50-g/L (5-g/dL) decrease in hemoglobin concentration, or 15% absolute decrease in hematocrit.

Stroke

This was defined as an acute new neurologic deficit ending in death or lasting longer than 24 hours, diagnosed as stroke by a physician. Stroke was classified as hemorrhagic (on computed tomography, cardiac magnetic resonance imaging, or autopsy) or nonhemorrhagic.

Death

Cardiovascular and total deaths were recorded, but no definitions of cardiovascular versus noncardiovascular death were provided.

DES-LATE

Myocardial Infarction

The diagnosis of acute MI was based on the universal definition of MI (provided in the section above on the PRODIGY study).

Major Bleeding

This was defined per the TIMI criteria.

Stroke

This was considered to have occurred if a new neurologic deficit was detected and confirmed by a neurologist and imaging studies.

Death

All deaths were considered to have resulted from cardiac causes unless an unequivocal noncardiac cause could be established.

ARCTIC-Interruption

Myocardial Infarction

Periprocedural MI, was defined as follows:

1. In patients with elevated biomarker levels before PCI, a positive diagnosis of reinfarction is made when all of the following criteria are present: documentation that the troponin level (or CK level in the absence of CK-MB) is decreasing; troponin (or CK-MB) measured 6 hours after PCI is greater than 3 times upper limit of normal; and the peak troponin (or CK-MB) level measured within 24 hours after the event is elevated by at least 50% above the previous level.

2. In patients in whom biomarker levels are normal or have returned to normal before PCI, periprocedural MI is defined when the troponin (or CK- MB) level measured 6 hours after PCI is greater than 3 times upper limit of normal. Measurements of biomarkers are requested before and 6 hours after PCI and at discharge.

Major Bleeding

The STEEPLE definition was used:

1. Fatal bleeding.

2. Retroperitoneal, intracranial, or intraocular bleeding.

3. Bleeding that requires intervention (surgical or endoscopic) or decompression of an enclosed place to stop or control the event.

4. Clinically overt bleeding, requiring transfusion of 1 or more units of packed red cells or whole blood.

5. Clinically overt bleeding, causing a decrease in the hemoglobin level of 30 g/L (3 g/dL) or greater (or if hemoglobin level is not available, a decrease in hematocrit of 10% or more).

Stroke

This event was not described.

Death

All deaths were considered cardiovascular unless an unequivocal noncardiovascular cause can be established. Hemorrhagic deaths were also considered cardiovascular.

DAPT

Myocardial Infarction

Periprocedural MI. Troponin or CK-MB level greater than 3 times the URL within 48 hours of the procedure.

Periprocedural CABG MI. Troponin or CK-MB level greater than 5 times the URL within 72 hours of the procedure, or baseline value less than the URL and any of the following:

1. New pathologic Q waves or LBBB.
2. New native or graft vessel occlusion.
3. Imaging evidence of loss of viable myocardium.

Spontaneous MI. Troponin or CK-MB level greater than the URL, with a baseline value less than the URL and any of the following:

1. Symptoms of ischemia.
2. ECG changes indicative of new ischemia (new ST-T changes or new LBBB).
3. Development of pathologic Q waves.
4. Imaging evidence of a new loss of viable myocardium or a new regional wall-motion abnormality.

Silent MI. No biomarker data available and new pathologic Q waves or LBBB.

Sudden death. Death before biomarkers were obtained or before levels were expected to be elevated, and symptoms suggestive of ischemia and any of the following:

1. New ST elevation or LBBB.
2. Documented thrombus by angiography or autopsy.
3. Reinfarction, spontaneous, and periprocedural MI: Stable or decreasing values on 2 samples obtained more than 6 hours apart and a 20% increase 3 to 6 hours after the second sample was obtained.

Major Bleeding

Major bleeding was defined by using the GUSTO classification; severe and moderate bleeding were combined.

Severe or life-threatening. Either intracranial hemorrhage or bleeding that causes hemodynamic compromise and requires intervention.

Moderate. Bleeding that requires blood transfusion but does not result in hemodynamic compromise.

Stroke

Cerebrovascular accident was defined as the occurrence of cerebral infarction (ischemic stroke) or intracerebral hemorrhage and subarachnoid hemorrhage (hemorrhagic stroke). Stroke was defined as sudden onset of vertigo; numbness; dysphasia; weakness; visual field defects; dysarthria; or other focal neurologic deficits due to vascular lesions of the brain, such as hemorrhage, embolism, thrombosis, or rupturing aneurysm that:

1. Persists more than 24 hours or results in death in less than 24 hours *or*

2. Persists less than 24 hours if pharmacologic therapy (a thrombolytic drug) or nonpharmacologic therapy (a neurointerventional procedure, such as intracranial angioplasty) is used *or*

3. Persists less than 24 hours, but has neuroradiologic (magnetic resonance imaging or computed tomography) diagnostic changes suggestive of acute tissue injury.

Death

All deaths were considered cardiac unless an unequivocal noncardiac cause could be established. Specifically, any unexpected death, even in persons with coexisting, potentially fatal noncardiac disease (such as cancer or infection), should be classified as cardiac.

ISAR-SAFE

Myocardial Infarction

The definition was adapted from the TIMI study group. The biomarker levels required for the diagnosis of MI were dependent on the relationship to cardiac procedures:

1. If the suspected event is within 48 hours of PCI, the CK-MB value must be more than 3 times the ULN on a single measurement. No symptoms are required.

2. If the suspected event is within 48 hours of CABG, the CK-MB value must be more than 10 times the ULN on a single measurement. No symptoms are required.

3. If the suspected event is not within 48 hours of PCI or CABG (spontaneous MI), the diagnostic criteria are met if the person has CK-MB or cardiac troponin levels greater than the ULN and either chest pain for more than 20 minutes or ST-segment deviation greater than 1 mm in 1 or more leads on the ECG.

4. If cardiac biomarkers are elevated at the time of suspected new-onset MI, it must be demonstrated that the biomarkers were decreasing before the suspected event and that the peak postevent CK-MB value is more than 50% higher than the previous trough value.

In any clinical circumstance, the appearance of the following would be considered appropriate evidence of MI: new Q waves on the ECG distinct from the baseline ECG, pathologic evidence (such as autopsy) showing a new MI thought to have occurred during study follow-up, ST-segment elevation (>1 mm in 2 contiguous leads) accompanied by ischemic chest pain lasting for more than 20 minutes or hemodynamic decompensation.

A Q wave MI is diagnosed if new pathologic Q waves (≥0.04 s) in 2 or more contiguous ECG leads appear (according to the Minnesota Code Classification System). All other MIs not fulfilling the previously mentioned criteria are considered non–Q-wave MI.

Major Bleeding

"TIMI major bleeding" was defined as intracranial bleeding or clinically significant overt sign of hemorrhage associated with a decrease in hemoglobin of 50 g/L (5 g/dL) or greater, or an absolute decrease in hematocrit of at least 15% when hemoglobin was not available.

Stroke

Stroke was defined as an acute neurologic event of at least 24 hours' duration, with focal signs and symptoms and no evidence supporting an alternative explanation. Diagnosis of stroke requires confirmation by computed tomography or magnetic resonance imaging or pathologic confirmation.

Death

The primary end point includes death from any cause. In addition, the cause of death will be adjudicated. All deaths will be assumed to be cardiovascular unless a noncardiovascular cause can be clearly provided (eg, cancer, trauma, and infection).

Appendix Table 1. Study Characteristics

Study, Year (Reference)	Patients Enrolled, *n*	Timing of Randomization Relative-DES Implantation	Total DAPT Duration*		Definition of Major Bleeding	Type of P2Y12 Inhibitor	Use of Aspirin and P2Y12 Inhibitor at End of Follow-up	
			Shorter-Duration Group	Longer-Duration Group			Shorter-Duration Group	Longer-Duration Group
Randomization within 1 mo of DES implantation								
PRODIGY, 2012 (16)	1478	≤1 mo after	6 mo	24 mo	TIMI	Clopidogrel	Aspirin: 98.1% Clopidogrel: 0.7%	Aspirin: 98.4% Clopidogrel: 94.8%
OPTIMIZE, 2013 (12)	3119	Immediately after	3 mo	12 mo	Modified REPLACE-2 + GUSTO	Clopidogrel	Aspirin 98.9% Clopidogrel: 6.2%	Aspirin 98.9% Clopidogrel: 97.9%
EXCELLENT, 2012 (13)	1443	Immediately before	6 mo	12 mo	TIMI	Clopidogrel	Not reported†; adherence, 71.2%	Not reported†; adherence, 93.2%
SECURITY, 2014 (33)	1399	Immediately after	6 mo	12 mo	BARC 3 or 5	Clopidogrel: 98.7% Prasugrel: 0.2% Ticagrelor: 0.4%	Aspirin only: 63.6% Aspirin + clopidogrel: 33.8% Clopidogrel only: 1.8%	Aspirin only: 2% Aspirin + clopidogrel: 96.1% Clopidogrel only: 1.2%‡
ITALIC, 2015 (30)	1822	Immediately after, but patients with events in the first 6 mo were then excluded	6 mo	24 mo but outcomes reported only for period from 6-12 mo post stent	TIMI	Clopidogrel: 98.6% Prasugrel: 1.7% Ticagrelor: <0.1%	Not reported	Not reported
Randomization ≥ 6 mo after DES placement and DAPT								
DES-LATE, 2014 (14)	5045	12–18 mo after	12-18 mo	36-42 mo	TIMI	Clopidogrel	Aspirin: 97.2% Clopidogrel: 8.1%	Aspirin: 95.7% Clopidogrel: 79.4%
ARCTIC-Interruption, 2014 (11)	1259	12–15 mo after	12-15 mo after	18-21 mo	STEEPLE	Clopidogrel: 90% Prasugrel: 10%	Aspirin: 97% P2Y12 inhibitor: 17%§	Aspirin: 94% P2Y12 inhibitor: 78%§
DAPT Study, 2014 (17)	9961	12 mo after	12 mo	30 mo	GUSTO	Clopidogrel: 65% Prasugrel: 35%	Not reported‖; discontinuation of study drug; 20.3%	Not reported‖; discontinuation of study drug: 21.4%
ISAR-SAFE, 2015 (34)	4005	6 mo after	6 mo	12 mo	TIMI	Clopidogrel: 100%	Not reported‖	Not reported‖

ARCTIC-Interruption = Assessment by a double Randomization of a Conventional antiplatelet strategy versus a monitoring-guided strategy for drug-eluting stent implantation and of Treatment Interruption versus Continuation 1 year after stenting Interruption Study; BARC = Bleeding Academic Research Consortium; DAPT = dual-antiplatelet therapy; DES = drug-eluting stent; DES-LATE = Optimal Duration of Clopidogrel Therapy With Drug Eluting Stents to Reduce Late Coronary Arterial Thrombotic Event Study; EXCELLENT = Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting; ISAR-SAFE = Intracoronary Stenting and Antithrombotic Regimen: Safety And EFficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting; GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries; ITALIC = Is There A Life for DES after Discontinuation of Clopidogrel; OPTIMIZE = Optimized Duration of Clopidogrel Therapy Following Treatment With the Zotarolimus-Eluting Stent in Real-World Clinical Practice Study; PRODIGY = Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study; REPLACE-2 = Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events); SECURITY = Second Generation Drug-Eluting Stent Implantation Followed by Six- Versus Twelve-Month Dual Antiplatelet Therapy; STEEPLE = Safety and Efficacy of Enoxaparin in PCI Patients, an International Randomized Evaluation; TIMI = Thrombolysis in Myocardial Infarction.

* Includes the duration before randomization.

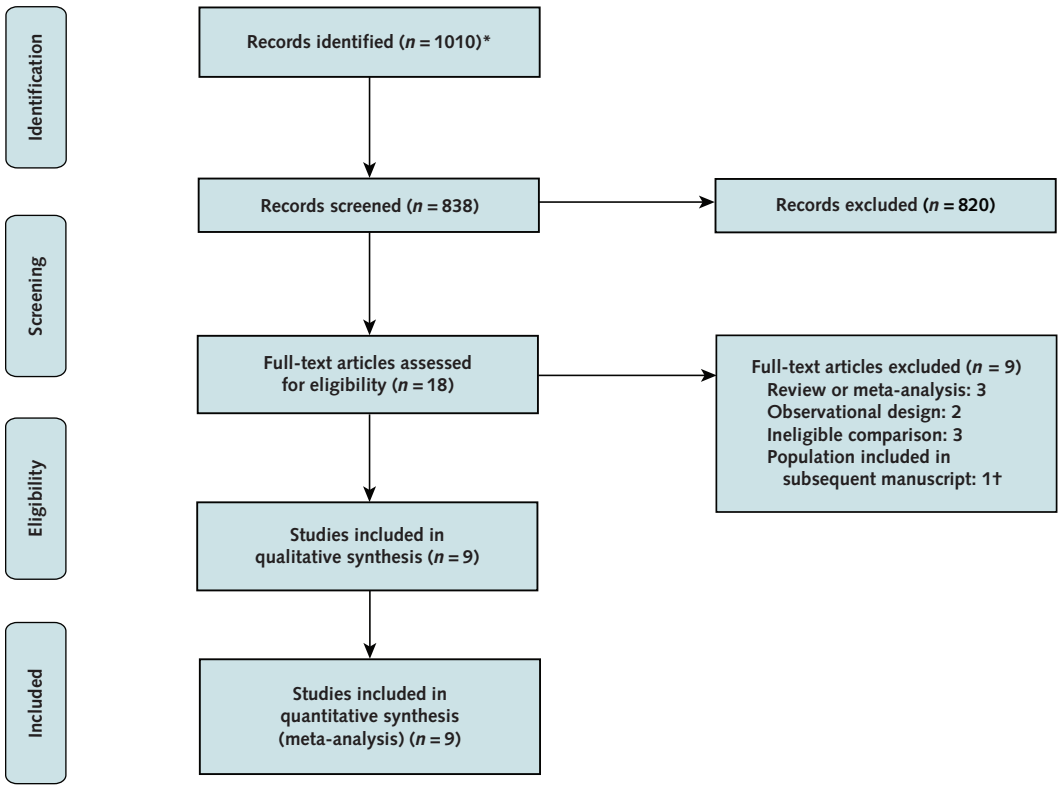
† Individual use of aspirin and clopidogrel was not reported; instead, "adherence" to planned duration of DAPT was reported instead. Decreased adherence in the shorter-duration group may be related to clopidogrel use after 6 mo. The median duration of DAPT was 190 d (interquartile range, 181–260 d) in the 6-mo DAPT group.

‡ Aspirin + prasugrel, 0.2%; aspirin + ticagrelor, 0.2%.

§ The P2Y12 inhibitor included clopidogrel, 75 mg/d; clopidogrel, 150 mg/d; or prasugrel, 10 mg.

‖ Placebo-controlled trial. The study drug was clopidogrel or prasugrel versus placebo.

Appendix Figure 1. Summary of evidence search and selection.



* Records were identified using Ovid MEDLINE and EMBASE (1996 to 27 March 2015).
† Data from a later manuscript were used.

Appendix Table 2. Characteristics of Patients in Trials That Performed Randomization Within 1 Month of DES Implantation*

Patient Characteristic	Study				
	PRODIGY	OPTIMIZE	EXCELLENT	SECURITY	ITALIC
Demographic					
Patients, *n*†	1970	3119	1443	1399	1822
Mean age (SD), *y*	67.8 (11)	61.6 (10.5)	62.7 (10)	65.2 (10.1)	61.6 (11.0)
Male, %	76.7	63.3	64.5	77.5	80.0
Clinical, %					
Diabetes	24.2	35.4	38.1	30.7	37.0‡
Hypertension	71.8	87.2	73.3	72.8	65.0
Prior MI	26.8	34.7	5.1	20.7	15.1
Prior cerebrovascular incident	3.9	2.5	6.6	NR	2.8
Prior PCI	18.2	20.0	8.9	17.7	23.3
Prior CABG	10.9	7.7	1.2	5.5	5.8
Indication for stent, %					
STEMI	32.9	0.0	3.1	0	0.2
Non–ST-elevation ACS or unstable angina	41.5	31.9	48.4	31.6	23.3
Angina, silent ischemia, or other	25.7	68.1	48.4	50.7	61.5
Type of DES, %					
First-generation					
Total	33.2	0	25.2	0	0
Paclitaxel	33.2	0	0	0	0
Sirolimus	0	0	25.2	0	0
Second-generation					
Total	66.8	100	74.8	100	100
Everolimus	33.3	0	74.8	21.2	100
Zotarolimus	33.5	100	0	43.4	0
Other	–	–	–	35.4§	–

ACS = acute coronary syndrome; CABG = coronary artery bypass graft; DES = drug-eluting stent; EXCELLENT = Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting; ITALIC = Is There A Life for DES after Discontinuation of Clopidogrel; MI = myocardial infarction; NR = not reported; OPTIMIZE = Optimized Duration of Clopidogrel Therapy Following Treatment With the Zotarolimus-Eluting Stent in Real-World Clinical Practice Study; PCI = percutaneous coronary intervention; PRODIGY = Prolonging Dual Antiplatelet Treatment After Grading Stent- Induced Intimal Hyperplasia Study; SECURITY = Second Generation Drug-Eluting Stent Implantation Followed by Six- Versus Twelve-Month Dual Antiplatelet Therapy; STEMI = ST-segment elevation myocardial infarction.

* Duration of dual-antiplatelet therapy was 3 to 6 mo in the shorter-duration group and 12 to 24 mo in the longer-duration group.

† The number of patients may differ from the number who were randomly assigned because of individual study reporting of participant characteristics.

‡ Type 2 diabetes.

§ Other types of second-generation stents.

Appendix Table 3. Characteristics of Patients in Trials That Performed Randomization at 6 or More Months After DES Implantation*

Patient Characteristic	Study			
	DES LATE	ARCTIC-Interrupted	DAPT Study	ISAR-SAFE
Demographic				
Patients, *n*†	5045	1259	9961	4000
Mean age (SD), *y*	62.4 (10)	64 (NR)	61.7 (10.2)	67.2
Male, %	69.3	80.3	74.8	80.6
Clinical, %				
Diabetes	28.1	33.4	30.6	24.5
Hypertension	57.5	60.7	74.9	90.7
Prior MI	3.9	30.4	21.6	25.2
Prior cerebrovascular incident	4.0	5.2	3.3	NR
Prior PCI	11.7	41.5	30.7	NR
Prior CABG	NR	6.5	11.6	7.6
Indication for stent, %				
STEMI	12.4	0.0	10.5	8.1
Non ST-elevation ACS or unstable angina	48.3	25.7	32.2	32
Angina, silent ischemia, or other	39.0	74.3	57.3	59.9
Type of DES,%				
First-generation				
Total	64.3	41.9	38.0	10.6
Paclitaxel	20.4	NR	26.8	2.3
Sirolimus	43.9	NR	11.2	8.3
Second-generation or higher				
Total	35.7	62.5	59.9	72.4
Everolimus	11.1	NR	47.2	48.8
Zotarolimus	19.0	NR	12.7	15.2
Biolimus	5.6	0	0	8.4
Other			NR‡	16.2§

ACS = acute coronary syndrome; ARCTIC-Interruption = Assessment by a double Randomization of a Conventional antiplatelet strategy versus a monitoring-guided strategy for drug-eluting stent implantation and, of Treatment Interruption versus Continuation 1 year after stenting Interruption Study; CABG = coronary artery bypass graft; DAPT = dual-antiplatelet therapy; DES = drug-eluting stent; DES LATE = Optimal Duration of Clopidogrel Therapy With Drug Eluting Stents to Reduce Late Coronary Arterial Thrombotic Event Study; ISAR-SAFE = Intracoronary Stenting and Antithrombotic Regimen: Safety And EFficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting; NR = not reported; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

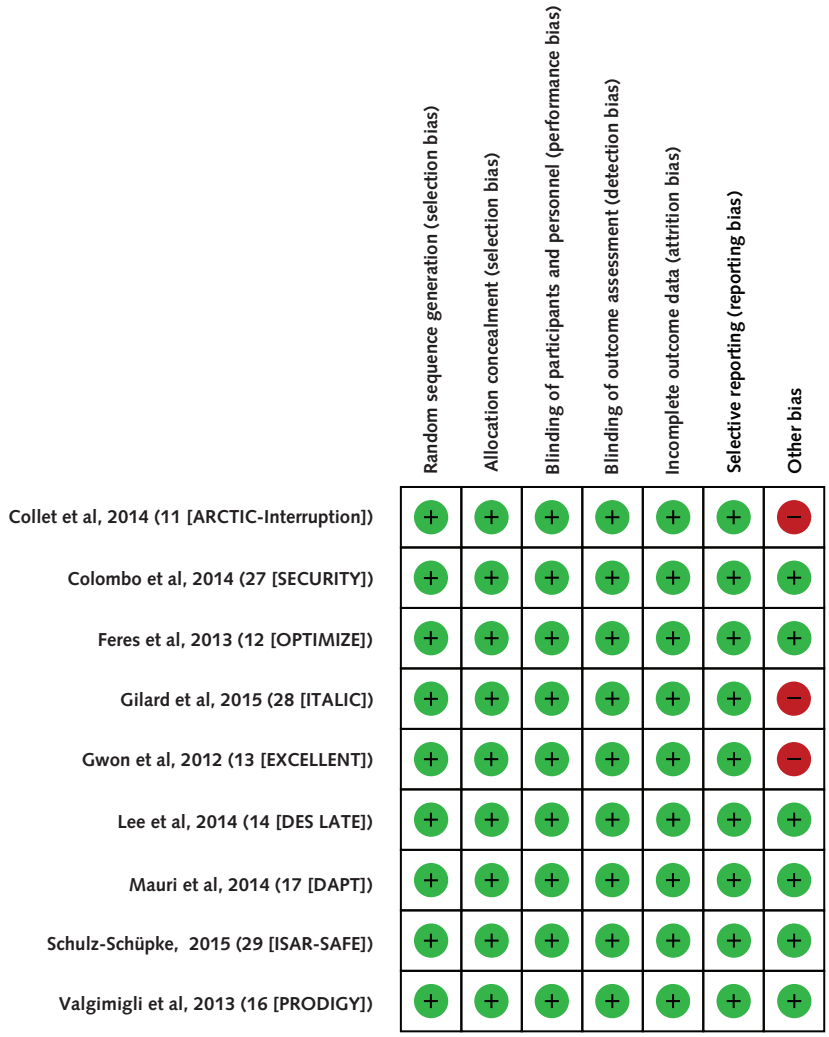
* Duration of DAPT was 6 to 18 mo in the shorter-duration group and 12 to 42 mo in the longer-duration group.

† The number of patients may differ from number who were randomly assigned because of individual study reporting of participant characteristics.

‡ 2.1% received more than 1 type of stent.

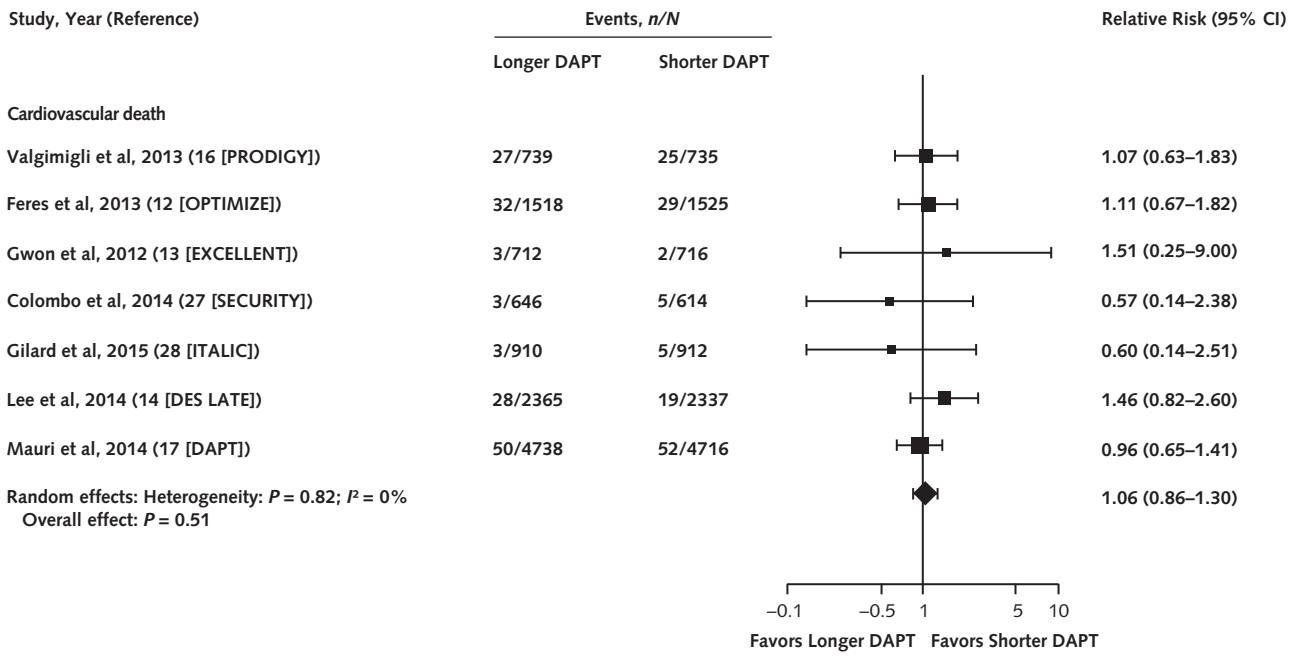
§ Second-generation sirolimus.

Appendix Figure 2. Assessment of risk of bias.



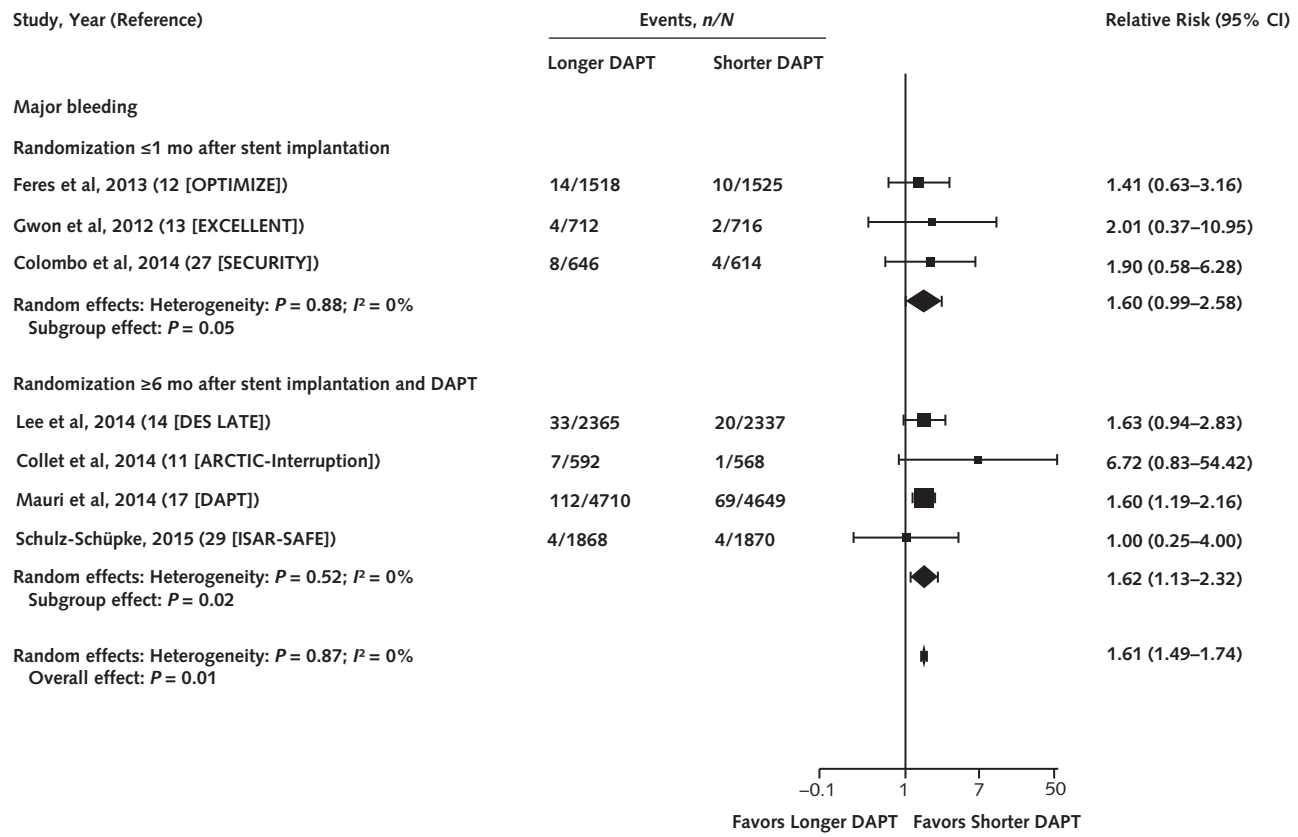
See the legend for **Figure 1** for abbreviation expansions. A green circle with a plus sign means no risk of bias; a red circle with a minus sign means potential risk of bias.

Appendix Figure 3. Pooled risk for cardiovascular death with longer- versus shorter-duration DAPT after placement of a drug-eluting stent.



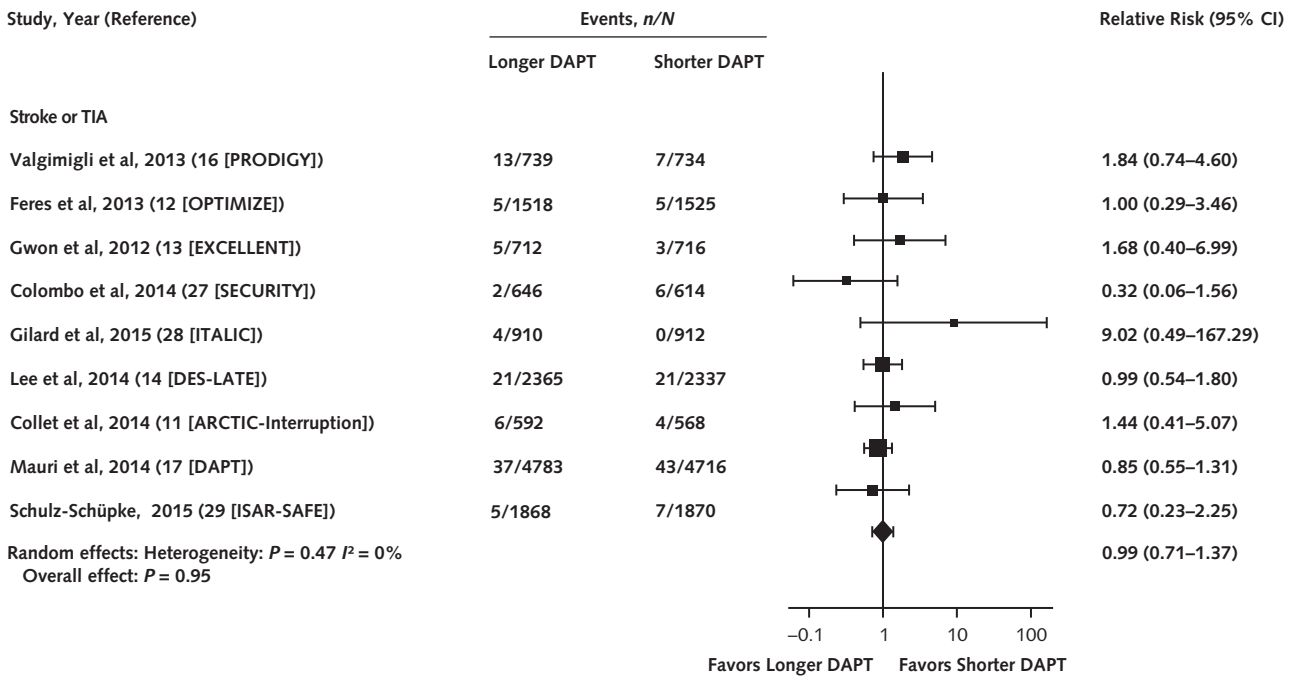
See the legend for Figure 1 for abbreviation expansions.

Appendix Figure 4. Pooled risk for major bleeding with longer- versus shorter-duration DAPT after placement of a drug-eluting stent: subset analysis stratified by timing of randomization.



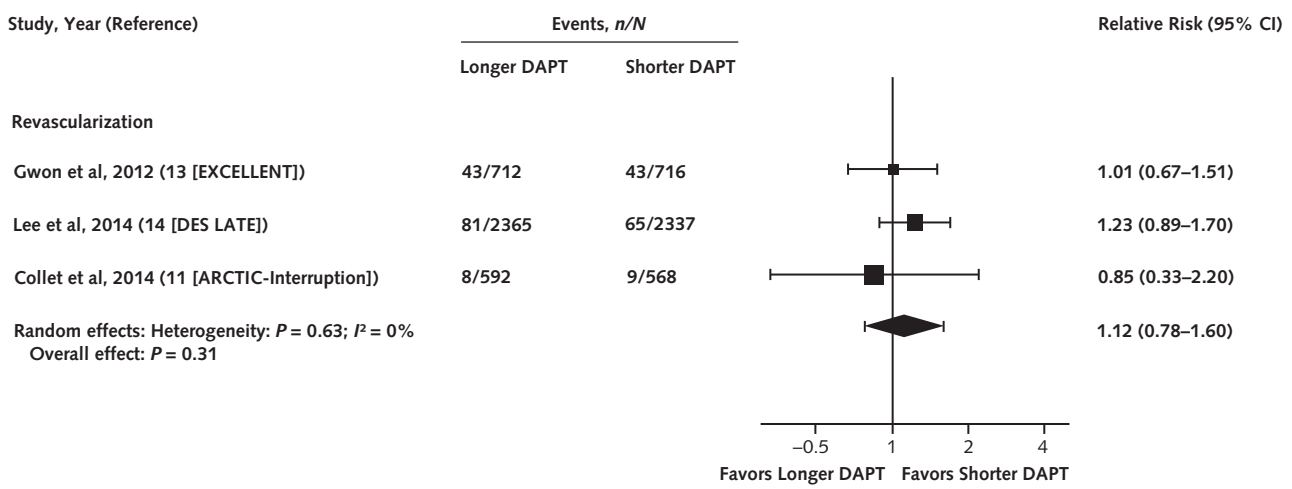
See the legend for Figure 1 for abbreviation expansions.

Appendix Figure 5. Pooled risk for any stroke with longer- versus shorter-duration DAPT after placement of a drug-eluting stent.



See the legend for Figure 1 for abbreviation expansions.

Appendix Figure 6. Pooled risk for revascularization with longer- versus shorter-duration DAPT after placement of drug-eluting stent.



See the legend for Figure 1 for abbreviation expansions.