Duration of Dual Antiplatelet Therapy:
A Systematic Review for the 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

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Abstract

**Background:** The optimal duration of dual antiplatelet therapy (DAPT) after implantation of newer-generation drug-eluting stents (DES) remains uncertain. Similarly, questions remain about the role of DAPT in long-term therapy of stable post–myocardial infarction (MI) patients.

**Aim:** Our objective was to compare the incidence of death, major hemorrhage, MI, stent thrombosis, and major adverse cardiac events in patients randomized to prolonged or short-course DAPT after implantation of newer-generation DES and in secondary prevention after MI.

**Methods:** We used traditional frequentist statistical and Bayesian approaches to address the following questions: Q1) What is the minimum duration of DAPT required after DES implantation? Q2) What is the clinical benefit of prolonging DAPT up to 18 to 48 months? Q3) What is the clinical effect of DAPT in stable patients who are >1 year past an MI?

**Results:** We reviewed evidence from 11 randomized controlled trials (RCTs) that enrolled 33,051 patients who received predominantly newer-generation DES to answer: A1) Use of DAPT for 12 months, as compared with use for 3 to 6 months, resulted in no significant differences in incidence of death (odds ratio [OR]: 1.17; 95% confidence interval [CI]: 0.85 to 1.63), major hemorrhage (OR: 1.65; 95% CI: 0.97 to 2.82), MI (OR: 0.87; 95% CI: 0.65 to 1.18), or stent thrombosis (OR: 0.87; 95% CI: 0.49 to 1.55). Bayesian models confirmed the primary analysis. A2) Use of DAPT for 18 to 48 months, compared with use for 6 to 12 months, was associated with no difference in incidence of all-cause death (OR: 1.14; 95% CI: 0.92 to 1.42) but was associated with increased major hemorrhage (OR: 1.58; 95% CI: 1.20 to 2.09), decreased MI (OR: 0.67; 95% CI: 0.47 to 0.95), and decreased stent thrombosis (OR: 0.42; 95% CI: 0.24 to 0.74). A risk-benefit analysis found 3 fewer stent thromboses (95% CI: 2 to 5) and 6 fewer MIs (95% CI: 2 to 11) but 5 more major bleeds (95% CI: 3 to 9) per 1,000 patients treated with prolonged DAPT per year. Post hoc analyses provided weak evidence of increased mortality rate with prolonged DAPT. We reviewed evidence from 1 RCT of 21,162 patients and a post hoc analysis of 1 RCT of 15,603 patients to answer: A3): Use of DAPT >1 year after MI reduced the composite risk of cardiovascular death, MI, or stroke (hazard ratio: 0.84; 95% CI: 0.74 to 0.95) but increased major bleeding (hazard ratio: 2.32; 95% CI: 1.68 to 3.21). A meta-analysis and a post hoc analysis of an RCT in patients with stable cardiovascular disease produced similar findings.

**Conclusions:** The primary analysis provides moderately strong evidence that prolonged DAPT after implantation of newer-generation DES entails a tradeoff between reductions in stent thrombosis and MI and increases in major hemorrhage. Secondary analyses provide weak evidence of increased mortality with prolonged DAPT after DES implantation. In patients whose coronary thrombotic risk was defined by a prior MI rather than by DES implantation, the primary analysis provided moderately strong evidence of
redruced cardiovascular events at the expense of increased bleeding. *Circulation*. 2016;133;ⅤⅤⅤⅤ–ⅤⅤⅤⅤ. DOI: 10.1161/CIR.0000000000000405.

**Introduction**

The goal of dual antiplatelet therapy (DAPT) is to prevent local thrombotic complications related to stent implantation and to reduce systemic atherothrombotic events. In 2011, the American College of Cardiology (ACC)/American Heart Association (AHA) guideline for percutaneous coronary intervention (PCI) recommended a minimum DAPT duration of at least 12 months after drug-eluting stents (DES) implantation, irrespective of clinical presentation (1):

“The duration of P2Y$_{12}$ inhibitor therapy after stent implantation should generally be as follows:

a. “In patients receiving a stent ([bare metal stent] or DES) during PCI for [acute coronary syndrome], P2Y$_{12}$ inhibitor therapy should be given for at least 12 months. Options include clopidogrel 75 mg daily (2), prasugrel 10 mg daily (3), and ticagrelor 90 mg twice daily (4). *(Class I, Level of Evidence: B)*

b. “In patients receiving DES for a non–[acute coronary syndrome] indication, clopidogrel 75 mg daily should be given for at least 12 months if patients are not at high risk of bleeding (5). *(Class I, Level of Evidence: B)*

The recommendation of at least 12 months of DAPT after DES implantation for acute coronary syndrome (ACS) (1) was supported by a subgroup analysis of a randomized trial (2) and several observational studies (6,7). In those early studies, bare metal stents (BMS) were used for the majority of PCIs, and the remaining stents were exclusively first-generation sirolimus-eluting stents and paclitaxel-eluting stents (PES).

Since the completion of the early studies and the creation of the 2011 PCI guideline, stent technology has improved, and evidence from new randomized controlled trials (RCTs) of DAPT duration has emerged. Newer DES, which are associated with a lower risk of early and late stent thrombosis than were first-generation DES (8-10) or BMS (11), have been increasingly studied in the contemporary RCTs of DAPT duration (12-24). In addition, a large RCT evaluating prolonged DAPT as part of the medical management of patients who had a myocardial infarction (MI) >1 year prior has been published (25).

The growing evidence base for DAPT duration motivated the ACC/AHA Task Force on Clinical Practice Guidelines to convene a writing committee to evaluate the usefulness of long-term DAPT to prevent thrombotic complications in patients who undergo stent implantation and in post-MI patients. To inform guideline development, a structured approach to evidence synthesis was proposed by the Institute
of Medicine (26) and endorsed by the ACC and AHA (27); it included the formation of an Evidence Review Committee to identify questions of clinical importance, framing them in what is called the PICOTS format (Population, Intervention, Comparator, Outcomes, Timing, and Setting). The writing committee formulated 3 PICOTS questions to guide the Evidence Review Committee in its evaluation of the evidence for DAPT duration:

Q1. In patients treated with newer (non-first) generation DES for stable ischemic heart disease or ACS, compared with 12 months of DAPT, is 3 to 6 months of DAPT as effective in 1) preventing stent thrombosis, 2) preventing major adverse cardiac events (MACE), and/or 3) reducing bleeding complications?

Q2. In patients treated with newer (non-first) generation DES, compared with 12 months of DAPT, does >12 (18 to 48) months of DAPT result in 1) differences in mortality rate, 2) decreased MACE, 3) decreased stent thrombosis, and/or 4) increased bleeding?

Q3. In post-MI (non–ST-elevation myocardial infarction [NSTEMI] or ST-elevation myocardial infarction [STEMI]) patients who are clinically stable and >12 months past their event, does continued DAPT, compared with aspirin monotherapy, result in differences in 1) mortality rate, 2) decreased nonfatal MI, 3) decreased MACE, and/or 4) increased bleeding?

The present report is a systematic review of the evidence to answer the 3 PICOTS questions. Beyond the standard frequentist techniques used for statistical inference, the present analysis incorporated stratified meta-analyses and Bayesian methods to establish inferences based on probability functions (28) and to put trial results into clinical perspective by presenting both relative and absolute differences in outcomes between treatment groups.

**Methods**

**Duration of DAPT After DES Implantation**

Aggregate data from 11 RCTs of patients undergoing implantation of predominantly newer-generation DES and randomized to either prolonged or short-course DAPT (12-14,16-24) comprise the evidence base for the analysis of DAPT duration after DES implantation (Table 1). Each trial underwent assessment by 2 independent reviewers (S.M.B. and D.N.W.) for relevance, fidelity, and freedom from bias (26,27). Data from each trial were abstracted in duplicate and matched with published summaries (15) by 2 reviewers (J.A.B. and U.B.), using datasets whenever possible that excluded patients receiving BMS. Of note, several RCTs contained summary statistics for patients treated with BMS or DES, but 2
RCTs presented separate summaries for patients receiving DES only (14,15,23,29), and these were used in the present analysis.

The primary outcomes of the analysis were all-cause death, major hemorrhage, MI, stent thrombosis, and the primary endpoint (e.g., MACE), as defined according in each protocol. Newer-generation DES were defined as everolimus-eluting stents (EES), zotarolimus-eluting stents, and biolimus-eluting stents with biodegradeable polymers (8).

Meta-Analysis

To illustrate the relative effectiveness of prolonged versus short-course DAPT, we used conventional statistical methods to create forest plots. We applied a random-effects model to acknowledge the variation in study design, treatment duration, and length of follow-up among the RCTs.

Bayesian Approaches

To emulate the random-effects model, we used hierarchical Bayesian meta-analysis. In the absence of strong feelings about the superiority of prolonged DAPT over shorter courses of therapy, we used noninformative priors defined by a neutral treatment effect of 0.00 and a negligible precision of 0.0001 to ensure that the posterior inference would be dominated by the likelihood of the data (28,30). To put the mortality rate results of the DAPT study (23) into the context of other studies, we used a Bayesian conjugate-normal model (28,31). To estimate the posterior probability of events from normal distributions, we used standard methods to generate cumulative probability functions (28,32).

Long-Term Use of DAPT After MI

Data from 1 RCT (25) and 1 post hoc analysis (33) comprise the evidence base for the analysis of long-term DAPT after MI. Because the evidence base included both exclusively post-MI patients (25) and patients with prior stroke or peripheral arterial disease (33), studies were not pooled for an aggregate analysis. Accordingly, we present descriptive results for these studies.

Software

All analyses were intention-to-treat. Standard meta-analysis was performed with the open-source statistical program [R] 3.0.2 and library package ”meta” 3.8-0 (34). Bayesian computations were run with the open-source program OpenBUGS 3.2.3 (Open Bayesian Inference Using Gibbs Sampling) (35), using Markov chain Monte Carlo modeling (28,32), and linked to [R] with BRugs (36). Study weights from the random-effects meta-analysis model were used to calculate numbers needed to treat and absolute treatment differences (37).
Results

Duration of DAPT After Implantation of Newer-Generation DES

The evidence for assessing DAPT duration after stent implantation has been obtained from 11 RCTs (Table 1) enrolling a total of 33,051 patients who underwent implantation of predominantly newer-generation DES. All 11 RCTs were judged to be of moderate to high quality, with at least moderate relevance, fidelity, and freedom from bias (Table 2).

The DES LATE (Optimal Duration of Clopidogrel Therapy With DES to Reduce Late Coronary Arterial Thrombotic Events) trial (13) was performed by combining extensions of the ZEST-LATE (Evaluation of the Long-Term Safety after Zotarolimus-Eluting Stent, Sirolimus-Eluting Stent, or Paclitaxel-Eluting Stent Implantation for Coronary Lesions—Late Coronary Arterial Thrombotic Events) and REAL-LATE (Correlation of Clopidogrel Therapy Discontinuation in Real-World Patients Treated with Drug-Eluting Stent Implantation and Late Coronary Arterial Thrombotic Events) trials of 2,701 patients (12) with a second cohort of 2,344 patients, all of whom had been event free after having been treated with 12 to 18 months of DAPT after DES implantation. In DES LATE, the majority of patients received sirolimus-eluting stents, but one fourth received PES, and 20% received zotarolimus-eluting stents. The original trials were planned to have an expected event rate of 5% at 2 years but had actual rates of 2.5% (12). In the extension trial (13), the primary endpoint of cardiac death, MI, or stroke occurred in 61 patients treated with 24 months of DAPT and in 57 patients treated with 12 months of DAPT (2.6% versus 2.4%; hazard ratio [HR]: 1.06; 95% confidence interval [CI]: 0.74 to 1.51; p=0.75).

The PRODIGY (Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia) main trial (14) incorporated a 2 × 4 factorial design to randomize 2,013 patients to either 24 or 6 months of DAPT after randomization to a thin-strut BMS, a PES, a zotarolimus-eluting stent, or an EES. Randomization to the investigational antiplatelet strategy was performed 30 days after implantation. At 24 months of follow-up, the investigators found no difference in the primary endpoint of death, MI, stroke, or definite stent thrombosis (14). There was an excess of bleeding in patients assigned to 24 months of DAPT. The outcomes for 1,501 patients treated with DES were reported in a separate meta-analysis (15) and used for the present analysis.

In the EXCELLENT (Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting) trial (16), rates of target-vessel failure at 12 months of follow-up were 4.3% in the group treated with 12-month DAPT and 4.8% in the group treated with 6-month DAPT. Bleeding rates were numerically twice as high in the 12-month as in the 6-month treatment group. In this trial (16), patients with diabetes mellitus, a prespecified subgroup, had fewer target-vessel failures after 12-month DAPT.
than after 6-month DAPT, but a benefit of prolonged DAPT in patients with diabetes mellitus was not seen in other RCTs of DAPT duration (38).

In RESET (REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation) (17), 1,059 patients treated with a zotarolimus-eluting stent and DAPT for 3 months were compared with 1,058 patients treated with an alternative DES and DAPT for 12 months (15% received an EES). Randomization was stratified by the presence of diabetes, ACS, and short or long lesion length. The expected incidence of the primary endpoint of cardiovascular death, MI, stent thrombosis, target-vessel revascularization, or bleeding was 10.5%, but the composite endpoint occurred at 12 months in 40 (4.7%) patients assigned to 3 months of DAPT, compared with 41 (4.7%) patients assigned to 12 months of DAPT.

The ARCTIC INTERRUPTION (Dual-Antiplatelet Treatment Beyond 1 Year After Drug-Eluting Stent Implantation) trial (19), which was designed to show the superiority of 18 months of DAPT over 12 months of DAPT, was an extension of the ARCTIC study of bedside platelet function monitoring to adjust antiplatelet therapy (39). In the extension trial (19), the primary endpoint occurred in 24 (4%) patients in the group treated with 18 months of DAPT and in 27 (4%) patients in the group treated with 12 months of DAPT.

Several trials used a noninferiority design to study DAPT duration, and all met their predefined hypotheses. In the OPTIMIZE (Three Versus 12 Months of Dual Antiplatelet Therapy After Zotarolimus-Eluting Stents) trial (18), investigators observed that net adverse cardiac and cerebrovascular events occurred in 90 patients receiving 12 months of DAPT and 93 patients receiving 3 months of DAPT (5.8% versus 6.0%; risk difference: 0.17; 95% CI: 1.52 to 1.86), a finding that met the trial noninferiority hypothesis (p=0.002). The SECURITY (Second-Generation Drug-Eluting Stent Implantation Followed by 6-Versus 12-Month Dual Antiplatelet Therapy) trial (20), which was stopped after enrollment of 1,399 of 2,740 planned patients, used a noninferiority design to test the equivalence of 12 and 6 months of DAPT after newer-generation DES implantation. With rates of the primary endpoint of cardiac death, MI, stroke, definite or probable stent thrombosis, and BARC (Bleeding Academic Research Consortium) type 3 or 5 bleeding of 3.7% in patients treated with 12 months of DAPT and 4.5% in patients treated with 6 months of DAPT (risk difference: 0.8%; 95% CI: 2.4% to 1.7%), the trial appeared to meet its noninferiority hypothesis. The ITALIC (6-Versus 24-Month Dual Antiplatelet Therapy After Implantation of Drug-Eluting Stent in Patients Nonresistant to Aspirin) study (21) compared 24 months of DAPT with 6 months of DAPT and was stopped early after 2,031 of 2,475 planned patients were enrolled. With small differences in the primary endpoint between the 2 groups (risk difference: 0.11%; 95% CI: 1.04% to 1.26%), the trial also appeared to meet its noninferiority hypothesis. The ISAR-SAFE (Intracoronary
Stenting and Antithrombotic Regimen: Safety and Efficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting) trial (22) compared 12 months of DAPT with 6 months of DAPT. Despite being stopped early after enrolling 4,005 of 6,000 planned patients and having lower event rates than planned in 4,000 evaluable patients (observed 1.5% versus expected 10.0%), the trial appeared to meet its noninferiority hypothesis.

The DAPT trial (23) was the largest RCT and randomly assigned 9,961 patients to test the superiority of 30 months of DAPT over 12 months of DAPT after implantation of predominantly newer-generation DES. Prolonged DAPT reduced the rate of stent thrombosis (0.4% versus 1.4%; HR: 0.29; 95% CI: 0.17 to 0.48; p<0.001), MACE, or major adverse cardiac cerebrovascular events (MACCE; 4.3% versus 5.9%; HR: 0.71; 95% CI: 0.59 to 0.85; p<0.001) and MI (2.1% versus 4.1%; HR: 0.47; p<0.001) but was associated with borderline increased mortality rate (2.0% versus 1.5%; HR: 1.36; 95% CI: 1.00 to 1.85; p=0.05) and increased moderate or severe bleeding (2.5% versus 1.6%; p=0.001).

The OPTIDUAL (Optimal Dual Antiplatelet Therapy Trial) (24) tested the hypothesis that 48 months of DAPT was superior to 12 months of DAPT after DES implantation. The trial was stopped prematurely after enrolling 1,385 of 1,966 planned patients and did not reach its prospectively defined primary endpoint of reducing death, MI, stroke, or major hemorrhage (5.8% versus 7.5%; HR: 0.75; 95% CI: 0.50 to 1.28).

Quantitative Synthesis

The 11 DES trials can be sorted into 2 groups to answer the 2 PICOTS questions: Q1) Is 12 months of DAPT more safe and effective than 3 to 6 months of DAPT? Q2) Does 18 to 48 months compared with 12 months of DAPT result in differences in deaths, major bleeding, stent thrombosis, and MACE?

12 Months of DAPT Versus 3 to 6 Months of DAPT

To answer the first PICOTS question, we quantitatively synthesized the aggregate evidence from the 5 RCTs comparing 12 months of DAPT with 3 to 6 months of therapy in 12,078 patients undergoing implantation of predominantly newer-generation DES (16-18,20-22). The experience in this group of RCTs (Figure 1) showed that DAPT of 12 months’ duration, as compared with therapy of 3 to 6 months’ duration, was associated with no differences in death (odds ratio [OR]: 1.17; 95% CI: 0.85 to 1.63), major hemorrhage (OR: 1.65; 95% CI: 0.97 to 2.82), MI (OR: 0.87; 95% CI: 0.65 to 1.18), stent thrombosis (OR: 0.87; 95% CI: 0.49 to 1.55), and the primary endpoint for each study (OR: 0.96; 95% CI: 0.80 to 1.16).

Similar results were obtained with Bayesian hierarchical meta-analyses, which showed no credible differences in death (posterior median OR: 1.22; 95% Bayesian credible interval [BCI]: 0.90 to
1.70), major hemorrhage (OR: 1.67; 95% BCI: 0.89 to 2.90), MI (OR: 0.90; 95% BCI: 0.60 to 1.30), stent thrombosis (OR: 0.91; 95% BCI: 0.43 to 1.66), and the primary study endpoints (OR: 0.96; 95% BCI: 0.76 to 1.20).

18 to 48 Months of DAPT Versus 6 to 12 Months of DAPT

To answer the second PICOTS question, we completed a quantitative synthesis of the 6 RCTs that compared 18 to 48 months of DAPT with 6 to 12 months of DAPT in 20,973 patients (12-14,19,21,23,24). The experience in this group of RCTs showed that (Figure 2) prolonged DAPT was associated with no difference in all-cause death (OR: 1.14; 95% CI: 0.92 to 1.42) but increased major hemorrhage (OR: 1.58; 95% CI: 1.20 to 2.09). Prolonged DAPT, as compared with 6 to 12 months of therapy, reduced the risk of MI (OR: 0.67; 95% CI: 0.47 to 0.95) and stent thrombosis (OR: 0.42; 95% CI: 0.24 to 0.74) and produced a borderline reduction in the prospectively defined primary endpoints (OR: 0.85; 95% CI: 0.72 to 1.00).

Similar results were obtained with Bayesian hierarchical meta-analyses, which generated similar point estimates for death (posterior median OR: 1.12; 95% BCI: 0.81 to 1.45), major hemorrhage (OR: 1.58; 95% BCI: 1.14 to 2.45), MI (OR: 0.68; 95% BCI: 0.45 to 1.09), stent thrombosis (OR: 0.42; 95% BCI: 0.19 to 0.87), and the primary study endpoints (OR: 0.86; 95% BCI: 0.70 to 1.07).

Absolute Event Rates in Trials Comparing 18 to 48 Months of DAPT With 6 to 12 Months of DAPT

A total of 415 patients died during the follow-up period in the 6 RCTs comparing 18 to 48 months of DAPT with 6 to 12 months of DAPT (12-14,19,21,23,24). The weighted annual mortality rate of 1.62% (95% CI: 1.31% to 2.00%) after prolonged DAPT was no different than the rate of 1.42% after a shorter course of DAPT, with the lower bound of the 95% CI for prolonged DAPT crossing the point estimate for short-course DAPT. In the group treated with prolonged DAPT, 16 patients (95% CI: 13 to 20) of every 1,000 died during each year of extended therapy, as compared with 14 during comparable follow-up after shorter courses of DAPT. This corresponded to a nonsignificant number needed to treat to number needed to harm of 512, with wide confidence intervals extending from -172 to 892.

A total of 307 patients had major bleeding during the follow-up period in the 6 RCTs comparing 18 to 48 months of DAPT with 6 to 12 months of DAPT (12-14,19,21,23,24). The weighted annual rate of major hemorrhage of 1.26% (95% CI: 0.96% to 1.66%) after prolonged DAPT exceeded the rate of 0.80% after a shorter course of DAPT. In other words, 13 (95% CI: 10 to 17) of 1,000 patients had major bleeding during each year of extended therapy, as compared with 8 receiving shorter courses of DAPT. In this case, the number needed to harm for major bleeding was 219 (95% CI: 117 to 632).
A total of 422 patients experienced MI during follow-up in the 5 RCTs reporting the outcome (12-14,19,21,23). The weighted annual MI rate of 1.19% (95% CI: 0.83% to 1.67%) after prolonged DAPT was lower than the rate of 1.76% after a shorter course of DAPT. This corresponded to 12 (95% CI: 8 to 17) of 1,000 patients experiencing MI during each year of prolonged DAPT, as compared with 18 after shorter courses of DAPT during the same follow-up. The number needed to treat to benefit 1 patient (NNTB) with prolonged DAPT to prevent an MI was 175 (95% CI: 109 to 1,156).

Only 126 patients had stent thrombosis in the 5 RCTs reporting the outcome (12-14,19,21,23). The weighted annual rate of stent thrombosis of 0.27% (95% CI: 0.15% to 0.47%) after prolonged DAPT was significantly lower than the rate of 0.64% after a shorter course of DAPT. In other words, 3 (95% CI: 2 to 5) of 1,000 patients receiving prolonged DAPT had stent thrombosis per year, as compared with 6 receiving shorter courses of DAPT, corresponding to a NNTB with prolonged DAPT of 271 (95% CI: 206 to 604).

A risk-benefit analysis found that extending DAPT to 18 to 48 months, as compared with stopping DAPT after 6 to 12 months, resulted in 3 fewer stent thromboses (95% CI: 2 to 5) and 6 fewer MIs (95% CI: 2 to 11) but 5 more major bleeds (95% CI: 3 to 9) and a statistically nonsignificant 2 more deaths (95% CI: -1 to 4) per 1,000 patients per year.

**Bayesian Analysis of Mortality Rate**

The present analysis placed the mortality rate results of the DAPT trial (23) into the context of the other 10 RCTs (12-14,16-22,24). A traditional statistical approach (Figure 3) to mortality rate in all 11 RCTs found nonsignificantly higher mortality rates after 18 to 48 months of DAPT than after 3 to 12 months of DAPT (OR: 1.16; 95% CI: 0.98 to 1.37), which were driven predominantly by the borderline finding (p=0.05) of increased mortality rate with prolonged therapy in the DAPT trial (23). A Bayesian approach (Figure 4) found that the borderline mortality rate increase (OR: 1.31; 95% CI: 0.97 to 1.77) in the DAPT trial (23) was preceded by a mortality rate signal (OR: 1.10; 95% CI: 0.90 to 1.34) in the 10 smaller RCTs (12-14,16-22,24), thus identifying that prolonged DAPT was associated with a credible increase in mortality rate (OR: 1.16; 95% BCI: 0.98 to 1.37). This is because the definition of BCI, which differs from the definition of traditional confidence intervals,* allowed direct statistical inferences to be made. The Bayesian analysis identified a 4.3% probability that the null hypothesis was correct (i.e., no mortality

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*A traditional frequentist 95% CI is not a conditional coverage probability but rather a label of convenience to describe the hypothetical performance of a large number of similar RCTs. Such a theoretical exercise would generate a large number of CIs, of which 95% will contain the true OR but the actual probability that a particular CI contains the true OR cannot be stated. On the other hand, the Bayesian approach generates a 95% BCI that has a 95% probability of containing the true OR, a characteristic that is commonly but erroneously attributed to the traditional frequentist CI (28,31).*
rate difference) and a <0.2% probability that prolonged DAPT reduced mortality rate by a threshold of 10%. On the other hand, the Bayesian approach identified a 95.7% probability that the alternative hypothesis was correct (i.e., prolonged DAPT increased mortality rate) and probabilities of 72.7%, 33.9%, 8.8%, and 1.3% that prolonged DAPT increased mortality rate by thresholds of 10%, 20%, 30%, and 40%, respectively (Figure 5).

Evidence Synthesis: Effect of Trial Type

Trials carried to completion provide stronger evidence than do RCTs that were stopped prematurely, particularly when trials were stopped because enrollment was poor (40,41). When the present analysis was stratified by trial completion (Figure 6), we observed increased mortality rates with prolonged DAPT in the 7 RCTs that met their planned enrollments (OR: 1.22; 95% CI: 1.02 to 1.47) but not in the 4 RCTs that were stopped prematurely (OR: 0.88; 95% CI: 0.58 to 1.34). Because the CIs were widely overlapping, this post hoc analysis provided weak evidence of increased mortality rate with prolonged DAPT.

Long-Term Use of DAPT After MI

The CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial was an RCT that compared DAPT (clopidogrel plus aspirin) with aspirin alone in patients at risk for a cardiovascular event (42). The trial enrolled 15,603 patients who were 45 years of age or older and had multiple atherothrombotic risk factors or a history of coronary disease, cerebrovascular disease, or symptomatic peripheral arterial disease. At a median follow-up of 28 months, the rate of the composite primary endpoint of death, MI, or stroke was 6.8% in the clopidogrel group and 7.3% in the placebo group (relative risk [RR]: 0.93; 95% CI: 0.83 to 1.05; p=0.22). The rate of severe bleeding was 1.7% in the clopidogrel group and 1.3% in the placebo group (RR: 1.25; 95% CI: 0.97 to 1.61; p=0.09). Although there were no significant differences for the primary analysis, in a prespecified subgroup of 12,153 patients with a prior history of cardiovascular disease, clopidogrel therapy was associated with a reduction in the primary endpoint (6.9% versus 7.9%; RR: 0.88; 95% CI: 0.77 to 0.998; p=0.046).

The findings in the enriched subgroup analysis led to a post hoc analysis of patients with a documented history of MI, stroke, or symptomatic peripheral artery disease (33). In this cohort of 9,478 patients, the rate of the composite outcome of cardiovascular death, MI, or stroke was 7.3% in patients treated with clopidogrel and 8.8% in patients treated with placebo (HR: 0.83; 95% CI: 0.72 to 0.96; p=0.01). A total of 3,846 patients (40.6%) in the high-risk cohort had prior MI, with a median time from
the qualifying MI to randomization of 2.0 years. Among patients with prior MI, the rate of the composite outcome was 6.6% in the clopidogrel-plus-aspirin arm and 8.3% in the placebo-plus-aspirin arm (HR: 0.77; 95% CI: 0.61 to 0.98; p=0.03)

The PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared with Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54) trial evaluated the effect of ticagrelor in addition to low-dose aspirin on the risk of cardiovascular events in stable patients with a prior history of MI and an additional cardiovascular risk factor (25). The median time from qualifying MI event to randomization in this study was 1.7 years (interquartile range, 1.2 to 2.3 years), and 83% of enrolled patients had prior PCI. The primary composite endpoint was cardiovascular death, MI, or stroke, with a primary safety endpoint of TIMI (Thrombolysis In Myocardial Infarction) major bleeding. The study randomized patients in a 1:1:1 manner to 2 different doses of ticagrelor (90 mg and 60 mg). Because the 90-mg dose of ticagrelor was associated with no greater efficacy than the 60-mg dose, the comparisons that follow are for ticagrelor 60 mg twice daily, a dose that was recently approved by the U.S. Food and Drug Administration for secondary prevention after prior MI.

At 3 years’ follow-up, the composite primary endpoint occurred in 7.77% of patients treated with 60 mg ticagrelor twice daily and in 9.04% treated with placebo (HR: 0.84; 95% CI: 0.74 to 0.95; p=0.004). The rate of TIMI major bleeding at 3 years was 2.30% in the ticagrelor group and 1.06% in the placebo group (HR: 2.32; 95% CI: 1.68 to 3.21; p<0.001).

The CHARISMA substudy (33) and the PEGASUS trial (25) evaluated initiation of DAPT beyond 1 year among patients with prior MI, regardless of whether PCI had been undertaken at the time of the MI. Among trials of DAPT prolongation in the setting of PCI, the DAPT trial (23) alone evaluated the impact of extended-duration DAPT in the subgroup of patients presenting with MI as the clinical indication for PCI (43). Of the 11,648 patients randomized in the DAPT trial, 30.7% presented with an MI. Continued DAPT beyond 1 year reduced the rate of MACCE by a larger amount in patients presenting with MI (3.9% versus 6.8%, p<0.001) than in patients without MI at presentation (4.4% versus 5.3%; p for interaction=0.03).

A recent meta-analysis compared prolonged DAPT in patients treated with PCI for ACS or MI as the presenting indication (44). This post hoc meta-analysis found that extended DAPT decreased the risk of MACE (6.4% versus 7.5%; RR: 0.78; 95% CI: 0.67 to 0.90; p=0.001) without an effect on all-cause death (RR: 0.92; 95% CI: 0.83 to 1.03; p=0.13). A complementary analysis (Figure 7), however, suggested weak evidence of increased mortality rate with prolonged DAPT in the cohort of patients without a prior history of ACS.
NNTB or Number Needed to Harm After MI

The use of DAPT as part of long-term therapy in post-MI patients requires consideration of both reduced cardiovascular risk and increased bleeding risk. In the PEGASUS trial (25), treating 1,000 post-MI patients with 90 mg of ticagrelor twice daily resulted in 4 fewer ischemic events (95% CI: 1 to 8) and 4 more bleeding events (95% CI: 2 to 5) per year. Treating 1,000 patients with the recently approved dose of 60 mg of ticagrelor twice daily resulted in 4 fewer ischemic events (95% CI: 1 to 8) and 3 more bleeding events (95% CI: 2 to 4) per year. The magnitude of effort required to obtain such outcomes can be illustrated in a population plot (Figure 8), which also shows that ischemic events were seldom observed in the overall population and only partly prevented by active treatment.

Discussion

The present systematic review evaluated the evidence from RCTs defining the optimal duration of DAPT in patients after DES implantation and in patients with a prior history of MI. To answer the question about the minimum duration of DAPT therapy after implantation of predominantly newer-generation DES to prevent local stent-related thrombotic complications, we analyzed 5 RCTs comparing 12 months of DAPT with 3 to 6 months of DAPT and found no significant differences in death, major hemorrhage, MI, stent thrombosis, and the primary study endpoints. To answer the question about the optimal prolongation of therapy to prevent increasingly systemic atherothrombotic complications, we analyzed 6 RCTs comparing 18 to 48 months of DAPT with 6 to 12 months of DAPT and found reductions in MI and stent thrombosis, no difference in MACE, an increase in major hemorrhage, and no change in death in the primary analyses. In secondary analyses of trials stratified by enrollment, we found weak evidence of increased mortality rate with prolonged DAPT in RCTs that successfully achieved their predefined enrollment targets.

To answer the question about using extending therapy in patients more than 1 to 3 years after MI, we found a significant reduction in MACE but an increase in major hemorrhage. A risk-benefit analysis helped to put the treatment effect of extended DAPT in this population into perspective.

All analyses in the present report followed the approach recommended by the Institute of Medicine (26) and focused on the population of patients undergoing implantation of predominantly newer-generation DES and the population of patients undergoing secondary prevention after prior MI, in contradistinction to other meta-analyses (45) and position statements (46) that combined old and new RCTs of DAPT duration in heterogeneous patient populations with a broad range of diagnoses, including atrial fibrillation, peripheral arterial disease, stroke, and BMS implantation.
Duration of DAPT After DES Implantation

A Brief History of DAPT After PCI

Before clopidogrel was approved by the U.S. Food and Drug Administration in 1997, many physicians prescribed ticlopidine for 2 weeks after BMS implantation. After clopidogrel was approved, physicians initially prescribed the drug for 4 weeks after BMS implantation because a study at the time reported less toxicity but similar rates of stent thrombosis at 28 days (1.4% versus 1.5%) after a 4-week course of clopidogrel compared with a 2-week course of ticlopidine (47). A subsequent RCT confirmed the superiority of a 4-week course of clopidogrel over a 4-week course of ticlopidine (48). The duration of treatment was increased to 3 months after approval of a sirolimus-eluting stent in 2003 and then to 6 months after the approval of a PES in 2004. Soon thereafter, many physicians increased the duration of clopidogrel therapy to 12 months (5), on the basis of findings in PCI-CURE (a substudy of the Clopidogrel in Unstable angina to prevent Recurrent Events trial) (2), CREDO (Clopidogrel for the Reduction of Events During Observation) (49), and observational studies that documented a persistent risk of stent thrombosis beyond 6 months, when DAPT was stopped after implantation of older types of stents (50). In the PCI-CURE (2) and CREDO (49) trials, however, all stents were BMS. In later trials, such as PLATO (Platelet Inhibition and Patient Outcomes) (4) and TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction 38) (3), DES were used in 19% and 40% of cases, respectively, but all these stents were first-generation sirolimus-eluting stents and PES.

Since publication in 2011 of the most recent guideline that included recommendations for DAPT (1), stent type has emerged as an important risk factor for stent thrombosis. Several lines of evidence suggest that the newer-generation DES, which were used in 65% of patients in the 11 RCTs in the present analysis (12-14,16-24), are associated with a risk of stent thrombosis approximately one half that of the first-generation DES (9,10).

Current Perspectives on DAPT After Implantation of Newer-Generation DES

An editorial (51) accompanying the PRODIGY study (14) noted, “The interventional practitioner is commonly faced with a number of very simple questions, the answers of which should be obvious but in truth are completely unknown. Perhaps the most common such question concerns the appropriate duration of dual antiplatelet therapy.” The editorial concluded, “Courses of clopidogrel exceeding 12 months do not contribute favorably to patient outcomes and may in fact be detrimental (51).” Comments on EXCELLENT (16) surmised that “DAPT may not be necessary beyond the initial 6 months, at least in low-risk patients (52).” Commenting on RESET (17), the editorialist wrote, “With newer-generation
DES, 6 months DAPT might be sufficient, and 3 months not completely off the wall in low-risk groups (53).” Comments on SECURITY (20) concluded, “Shorter DAPT duration seems very reasonable to consider and is increasingly used in the art of taking care of these patients (54).” Comments about the DAPT trial (23) concluded, “The safest and most effective duration of dual antiplatelet therapy therefore remains uncertain and must be individualized (55).” Subsequent commentary concluded, “The net clinical benefit of 30 months over 12 months DAPT overall seems marginal (56).”

A critique of PEGASUS (25) concluded, “Bonaca et al. found that, as compared with placebo, ticagrelor was associated with an absolute benefit of 1.19 percentage points (with the 90-mg dose) and 1.27 percentage points (with the 60-mg dose) in the primary endpoint, as well as with absolute increases of 1.54 and 1.24 percentage points, respectively, for clinically significant bleeding and 1.71 and 1.37 percentage points for transfusion. On the basis of the 60-mg ticagrelor dose, treating 10,000 patients for 1 year would prevent approximately 42 primary endpoint events and produce approximately 31 TIMI major bleeding events—close to an even proposition (57).” The critique noted that the PEGASUS results “remind us of the fragile balance between efficacy and adverse events.”

**Primacy of Mortality Rate**

The DAPT trial (23) met its primary endpoints and thus stood apart from the remaining 10 RCTs, which either refuted a superiority hypothesis or met a noninferiority hypothesis. The DAPT trial, however, reported that prolonged therapy was associated with a borderline increase in mortality rate. Although the mortality outcome in the trial has been attributed to noncardiovascular causes (23), the play of chance, or the unstable behavior of p values in megatials (58,59), the finding of a 31% increase in mortality rate in the DAPT trial was directionally consistent with the point estimate of a 10% increase in mortality rate with prolonged DAPT seen in the 10 smaller RCTs. In a Bayesian context, the mortality rate increase in the DAPT report (23) was predictable and not likely to be a chance finding.

Additional evidence for increased mortality rate with prolonged DAPT emerged when RCTs were stratified by trial completion in the present analysis, which found that prolonged DAPT was associated with a significant 21% increase in mortality rate in the 7 completed RCTs. Separating trials results by completion seemed justified, because incomplete RCTs with slow enrollment were susceptible to lower than expected event rates, overoptimistic hypotheses, and reduced statistical power (41,60).

In the hierarchy of evidence (61), RCTs stopped early are weaker than RCTs carried to completion. Some experts believe that investigators should limit conclusions from prematurely stopped trials to observational statements of harm from experimental therapies and avoid the tendency to
extrapolate or perform post hoc analyses (40,41). This may be interpreted as a caveat against including prematurely stopped trials in systematic reviews that weight all trial evidence equally.

In the present analysis of completed RCTs, the 21% increase in mortality rate with prolonged DAPT was supported by several other published reports. An investigation using a plausible worst-case sensitivity analysis found a significant 19% increase in mortality rate with prolonged DAPT (62); a systemic review using a pairwise meta-analysis found a significant 22% increase in mortality rate (15); a fixed-effect meta-analysis found a significant 30% increase in mortality rate (63); and a pooled analysis of studies evaluating very long duration of DAPT found a borderline 26% increase in mortality rate (64).

The suggestion of increased mortality rate with prolonged DAPT is critical from both a clinical and a statistical perspective. Some experts argue that differences in mortality rate may offset differences in nonfatal endpoints (65). In the context of antiplatelet therapy, bleeding events may compete with ischemic endpoints. To put this into perspective, it was proposed that, “Although treatment with DAPT beyond 1 year after DES implantation reduces MI and stent thromboses, it is associated with increased mortality because of an increased risk of noncardiovascular mortality not offset by a reduction in cardiac mortality (15).”

The idea of increased mortality rate may seem counterintuitive, given the reductions in nonfatal MI and stent thromboses with prolonged DAPT, but the finding may reflect the declining mortality risk of stent thromboses over time. Whereas acute and subacute stent thromboses are associated with mortality rates approaching 50%, late stent thromboses and very late stent thromboses are associated with mortality rates of approximately 10% (66). In a registry analysis, stent thromboses within 30 days of implantation were associated with a mortality rate of 39%, but stent thromboses occurring 30 days to 1 year after implantation and stent thromboses occurring >1 year after implantation were associated with mortality rates of 12% (p<0.001) (67). With the declining risk of late stent thrombosis in the face of a constant risk of bleeding, extension of DAPT beyond 12 months may simultaneously reduce MI and stent thrombosis without influencing mortality rate.

**Stent Type**

A subgroup analysis of the DAPT trial (23) raised additional concerns about the safety of prolonged DAPT after implantation of EES, which are the most prevalent stents implanted in current practice. The DAPT investigators (68) reported that the 4,703 patients who underwent EES implantation in the DAPT trial had higher mortality rates after 30 months of DAPT than after 12 months of therapy (2.1% versus 1.1%, p=0.02). The DAPT appendix (23) presented additional observations. In the overall study population receiving a mix of stent types, prolonged DAPT reduced the risk of stent thrombosis from
1.4% to 0.4%, corresponding to a NNTB of 100. In the 4,703 patients who underwent EES implantation, however, prolonged DAPT reduced the risk of stent thrombosis from 0.7% to 0.3%, corresponding to a NNTB of 250. In the overall DAPT population receiving a mix of different stents, prolonged DAPT reduced the risk of MACCE from 5.9% to 4.3%, corresponding to a NNTB of 38, whereas in the subgroup receiving EES, prolonged DAPT reduced MACCE from 4.5% to 4.3%, corresponding to a NNTB of 500.

### Acuity of Presentation

In a subgroup analysis of the DAPT trial, investigators (44) found that the reduction in MACCE seen with prolonged DAPT was greater for patients with MI at presentation (3.9% versus 6.8%; HR: 0.56; p<0.001) than for those without MI at presentation for PCI (4.4% versus 5.3%; HR: 0.83; p=0.08; interaction p=0.03). Given that the interaction p value was borderline for an analysis combining patients undergoing DES implantation in the main DAPT report (23) along with those undergoing BMS implantation from a separate report (29), the findings can be considered hypothesis generating. Similarly, the systematic overview of the ACS subgroups from a heterogeneous mix of RCTs, which showed a 22% reduction in ischemic events (RR: 0.78; 95% CI: 0.67 to 0.90) and a 73% increase in major bleeding (RR: 1.73; 95% CI: 1.19 to 2.50) with prolonged DAPT should also be considered hypothesis generating (44).

### Risk/Benefit Tradeoff

Clinical decision making surrounding the optimal duration of DAPT requires a simultaneous appraisal of both risks and benefits. To characterize the tradeoff of using prolonged DAPT, we simulated its net clinical benefit by measuring the ratio of NNTB to number needed to harm, which reflects the risks and benefits of using DAPT for 18 to 48 months compared with using DAPT for 6 to 12 months. In these analyses, a ratio <1 indicates net benefit, whereas a ratio >1 indicates net harm. After applying the pooled risk estimates to different rates of ischemic and bleeding events over 2 years in the pooled analysis of 6 studies (12-14,19,21,23) and the DAPT report (23), we simulated the therapeutic tradeoff across different ischemic and bleeding event rates (Figure 9). In these analyses, we found that extension of DAPT beyond 12 months to prevent MI may be optimal in patients at relatively low bleeding risk of <2% over 2 years. In contrast, DAPT durations beyond 12 months appear to yield an incremental risk for hemorrhage that is not counterbalanced by lower stent thrombosis. This suggests that the net benefit of extending DAPT is not static but dynamic, as a function of the bleeding and thrombotic propensity for each patient being treated (Figure 9).
Long-Term Use of DAPT After MI

Activation of platelets, with resultant thrombosis, occurs not only in response to implantation of DES, but also as part of the process of atherosclerosis (69). Patients with a recent atherothrombotic coronary event are at high risk of recurrent events. Several trials have demonstrated the ability of DAPT to inhibit platelet activation and reduce the risk of recurrent MI in the year after an acute MI (2,70,71). Accordingly, current guidelines recommend that DAPT should be continued for up to 12 months after MI (72).

The premise for the CHARISMA (42) and the PEGASUS (25) trials is consistent with a consideration of atherothrombotic risk. The CHARISMA trial failed to demonstrate a benefit of DAPT, likely as a result of including patients with cardiovascular risk factors but no prior history of a cardiovascular event (42). The subsequent post hoc analysis of patients with a prior history of MI, stroke, or symptomatic peripheral arterial disease reflected the benefit of DAPT in a population at higher risk of atherothrombotic events (33). Similarly, PEGASUS was conducted in post-MI patients with at least one additional high-risk factor. Finally, the substudy of the DAPT trial demonstrated the greater reduction of MACCE with continuation of DAPT beyond 1 year among patients with MI as the initial presentation (43). Together, these findings highlighted the potential benefit of DAPT among patients with high atherothrombotic risk.

Limitations of the Analyses

The use of various bleeding definitions in the trials may have compromised the interpretation of the analyses. If we had access to individual-level data and compared a common definition of bleeding, such TIMI major or minor bleeding across all trials, our results might have greater relevance.

The RCTs evaluating DAPT duration in patients undergoing DES implantation generally enrolled low-risk patients, with 8 of 11 trials reporting lower than expected event rates (Table 1). Because event rates were low and rates of MI and bleeding outcomes were imprecise, confidence intervals were wide. Although some of the trials had apparently reasonable follow-up rates of 92% to 95%, these rates need to be considered with regard to the actual bleeding and mortality rates of 1% to 4% over the course of the trials.

The measurement of the “hard” endpoint of mortality rate was judged to be more precise than the measurement of the other endpoints. Death was an endpoint for which ascertainment or occurrence was unlikely to be influenced during endpoint committee adjudication by the lack of blinding as much as the other outcomes. Thus, the Evidence Review Committee has placed more emphasis on the primacy of mortality rate from a clinical—as well as a statistical—point of view than it did for the other endpoints.
Conclusions

Evidence from RCTs suggests that patients undergoing implantation of safer, newer-generation DES may be treated with a minimum DAPT duration of 3 to 6 months to prevent early and largely stent-related thrombotic events, but extension of DAPT beyond 12 months entails a tradeoff. The declining risk of late stent thrombosis with newer-generation DES and the inability to predict life-threatening bleeding limits the appeal of 18 to 48 months of DAPT over 6 to 12 months of therapy. In contrast, patients with prior MI at high risk of atherothrombosis experience fewer ischemic events with prolonged DAPT at a cost of increased bleeding events.

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References


Tables and Figures

Table 1. RCTs of DAPT Duration After Implantation of DES

<table>
<thead>
<tr>
<th>Study</th>
<th>Year*</th>
<th>Trial Completion</th>
<th>Primary Study Endpoint</th>
<th>Trial Design and Outcome</th>
<th>Expected Event Rate in Control Group (%)</th>
<th>Observed Event Rate in Control (%)</th>
<th>Proportion With Newer-Generation DES (%)</th>
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<tr>
<td>DES LATE (12 vs. 36 mo) (13)</td>
<td>2010</td>
<td>Extension of ZEST-LATE and REAL-LATE (12)</td>
<td>Cardiac death, MI, or stroke &lt;24 h</td>
<td>Superiority not shown</td>
<td>2.7</td>
<td>2.6</td>
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<td>PRODIGY (6 vs. 24 mo) (14,15)</td>
<td>2012</td>
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<td>RESET (3 vs. 12 mo) (17)</td>
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<td>Cardiac death, MI, ST, revasc, or bleeding</td>
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<td>OPTIMIZE (3 vs. 12 mo) (18)</td>
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<td>2014</td>
<td>Extension of ARCTIC (39)</td>
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<td>6.0</td>
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<td>SECURITY (6 vs. 12 mo) (20)</td>
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<td>Cardiac death, MI, ST, or stroke</td>
<td>Noninferiority confirmed</td>
<td>4.5</td>
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**Bittl JA, et al.**  
*Duration of DAPT ERC Systematic Review Report*

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Enrollment Status</th>
<th>Planned Enrollment</th>
<th>Outcomes Described</th>
<th>Noninferiority showed</th>
<th>Superiority shown</th>
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<td>4,005</td>
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<td><strong>DAPT (12 vs. 30 mo)</strong></td>
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<td><strong>OPTIDUAL (12 vs. 48 mo)</strong></td>
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</table>

*Year of initial publication.

ARCTIC indicates Assessment by a Double Randomisation 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; 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 Events; 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; MACCE, major adverse cardiac and cerebrovascular events (death, MI, or stroke); MI, myocardial infarction; OPTIDUAL, Optimal Dual Antiplatelet Therapy; OPTIMIZE, Optimized Duration of Clopidogrel Therapy Following Treatment With the Zotarolimus-Eluting Stent in Real-World Clinical Practice; NACCE, net adverse cardiac and cerebrovascular events (death, MI, stroke, or major bleeding); PRODIGY, Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia; RCT, randomized controlled trial; REAL-LATE, REAL-world patients treated with drug-eluting stent implantation and Late coronary Arterial Thrombotic Events; RESET, Real Safety and Efficacy of 3-month Dual Antiplatelet Therapy Following Endeavor Zotarolimus-Eluting Stent Implantation; revasc, revascularization; SECURITY, Second Generation Drug-Eluting Stent Implantation Followed by Six- Versus Twelve-Month Dual Antiplatelet Therapy; ST, stent thrombosis; TIMI, Thrombolysis In Myocardial Infarction; TVF, target-vessel failure; TVR, target-vessel revascularization; and ZEST-LATE, Zotarolimus-Eluting Stent, Sirolimus-Eluting Stent, or Paclitaxel-Eluting Stent Implantation for Coronary Lesions-Late coronary Arterial Thrombotic Events.
Table 2. Relevance, Fidelity and Risk of Bias* of Included Randomized Controlled Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Cochrane Collaboration Risk of Bias Tool</th>
<th>Relevance of Study Sample, Interventions, Outcome, Follow-Up Period, and Setting</th>
<th>Fidelity—Assessment of Monitoring, Protocol Adherence, and Data Validity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Random Sequence Generation</td>
<td>Allocation Concealment</td>
<td>Blinding of Participants, Personnel, and Outcome Assessment (Mortality)</td>
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<tr>
<td>DES LATE (14)</td>
<td>Intermediate relevance</td>
<td>Intermediate fidelity</td>
<td></td>
</tr>
<tr>
<td>PRODIGY (15)</td>
<td>Intermediate relevance</td>
<td>High fidelity</td>
<td></td>
</tr>
<tr>
<td>EXCELLENT (16)</td>
<td>High relevance</td>
<td>Intermediate fidelity</td>
<td></td>
</tr>
<tr>
<td>RESET (17)</td>
<td>Intermediate relevance</td>
<td>Unclear fidelity</td>
<td></td>
</tr>
<tr>
<td>OPTIMIZE (18)</td>
<td>High relevance</td>
<td>High fidelity</td>
<td></td>
</tr>
<tr>
<td>ARCTIC (19)</td>
<td>High relevance</td>
<td>Intermediate fidelity</td>
<td></td>
</tr>
<tr>
<td>SECURITY (20)</td>
<td>High relevance</td>
<td>Intermediate fidelity</td>
<td></td>
</tr>
<tr>
<td>ITALIC (21)</td>
<td>High relevance</td>
<td>Intermediate fidelity</td>
<td></td>
</tr>
<tr>
<td>ISAR-SAFE (22)</td>
<td>High relevance</td>
<td>High fidelity</td>
<td></td>
</tr>
<tr>
<td>DAPT (23)</td>
<td>High relevance</td>
<td>High fidelity</td>
<td></td>
</tr>
<tr>
<td>OPTIDUAL (24)</td>
<td>Intermediate relevance</td>
<td>Intermediate fidelity</td>
<td></td>
</tr>
<tr>
<td>CHARISMA (34,43)</td>
<td>Intermediate relevance</td>
<td>High fidelity</td>
<td></td>
</tr>
<tr>
<td>PEGASUS (25)</td>
<td>High relevance</td>
<td>High fidelity</td>
<td></td>
</tr>
</tbody>
</table>

*Risk of bias is denoted as low risk of bias (green box), high risk of bias (red box), or unclear risk of bias (yellow box). Trials stopped early for poor enrollment (20-22,24) and the trial analyzed using post hoc definitions (33,42) are denoted as having a high risk of bias. Stent trial acronyms are defined in Table 1. CHARISMA indicates Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance; and PEGASUS–TIMI 54, Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54.
Figure 1. Forest plots of mortality rate (A), major hemorrhage (B), myocardial infarction (C), stent thrombosis (D), and primary study endpoints (E) after 12-month course versus shorter course of dual antiplatelet therapy after drug-eluting stent implantation. Study acronyms (16-8,20,22) are defined in Table 1. CI indicates confidence interval; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; and OR, odds ratio.
Figure 2. Forest plots of mortality rate (A), major hemorrhage (B), myocardial infarction (C), stent thrombosis (D), and primary study endpoints (E) after prolonged course versus 6- to 12-month course of dual antiplatelet therapy after drug-eluting stent implantation. Study acronyms (12-14,19,21,23,24) are defined in Table 1. CI indicates confidence interval; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; and OR, odds ratio.
Figure 3. Forest Plot of Mortality Rates in 11 RCTs After Stent Implantation

<table>
<thead>
<tr>
<th>Study</th>
<th>Prolonged Events</th>
<th>Prolonged Total</th>
<th>Short Events</th>
<th>Short Total</th>
<th>Odds Ratio (OR)</th>
<th>OR</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>DES–LATE (12 vs. 36 mo)</td>
<td>46</td>
<td>2531</td>
<td>32</td>
<td>2514</td>
<td>1.44</td>
<td>(0.91–2.26)</td>
<td></td>
</tr>
<tr>
<td>PRODIGY (6 vs. 24 mo)</td>
<td>49</td>
<td>750</td>
<td>45</td>
<td>751</td>
<td>1.10</td>
<td>(0.72–1.67)</td>
<td></td>
</tr>
<tr>
<td>EXCELLENT I (6 vs. 12 mo)</td>
<td>7</td>
<td>721</td>
<td>4</td>
<td>722</td>
<td>1.76</td>
<td>(0.51–6.04)</td>
<td></td>
</tr>
<tr>
<td>RESET (3 vs. 12 mo)</td>
<td>8</td>
<td>1058</td>
<td>5</td>
<td>1059</td>
<td>1.61</td>
<td>(0.52–4.93)</td>
<td></td>
</tr>
<tr>
<td>OPTIMIZE (3 vs. 12 mo)</td>
<td>45</td>
<td>1556</td>
<td>43</td>
<td>1563</td>
<td>1.05</td>
<td>(0.69–1.61)</td>
<td></td>
</tr>
<tr>
<td>ARCTIC (12 vs. 18 mo)</td>
<td>7</td>
<td>635</td>
<td>9</td>
<td>624</td>
<td>0.76</td>
<td>(0.28–2.06)</td>
<td></td>
</tr>
<tr>
<td>SECURITY (6 vs. 12 mo)</td>
<td>8</td>
<td>717</td>
<td>8</td>
<td>682</td>
<td>0.95</td>
<td>(0.35–2.55)</td>
<td></td>
</tr>
<tr>
<td>ITALIC (6 vs. 24 mo)</td>
<td>7</td>
<td>910</td>
<td>8</td>
<td>912</td>
<td>0.88</td>
<td>(0.32–2.43)</td>
<td></td>
</tr>
<tr>
<td>ISAR–SAFE (6 vs. 12 mo)</td>
<td>12</td>
<td>2003</td>
<td>8</td>
<td>1997</td>
<td>1.50</td>
<td>(0.61–3.67)</td>
<td></td>
</tr>
<tr>
<td>DAPT (12 vs. 30 mo)</td>
<td>98</td>
<td>5020</td>
<td>74</td>
<td>4941</td>
<td>1.31</td>
<td>(0.97–1.78)</td>
<td></td>
</tr>
<tr>
<td>OPTIDUAL (12 vs. 48 mo)</td>
<td>16</td>
<td>695</td>
<td>24</td>
<td>690</td>
<td>0.65</td>
<td>(0.34–1.24)</td>
<td></td>
</tr>
</tbody>
</table>

**Bayesian hierarchical meta-analysis**

<table>
<thead>
<tr>
<th>Model</th>
<th>Prolonged Events</th>
<th>Prolonged Total</th>
<th>Short Events</th>
<th>Short Total</th>
<th>Odds Ratio (OR)</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed effect model</td>
<td>303</td>
<td>16596</td>
<td>260</td>
<td>16455</td>
<td>1.16</td>
<td>(0.98–1.37)</td>
<td></td>
</tr>
<tr>
<td>Random effects model</td>
<td>1.16</td>
<td>(0.98–1.37)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: I²-squared=0%, tau-squared=0, p=0.725

Study acronyms (12-14, 16-24) are defined in Table 1. DAPT indicates dual antiplatelet therapy; OR, odds ratio; and RCT, randomized controlled trial.
Figure 4. Mortality Rate

A triplot illustrates the way that the Bayesian approach combines information from various sources. The prior (blue) shows the distribution of OR describing the mortality rate differences between prolonged and short-course DAPT seen in 10 trials (12-14,16-22,24), which suggests that prolonged DAPT could be associated with as much as a 10% reduction or a 34% increase in mortality rate (OR: 1.10; 95% BCI: 0.90 to 1.34) as compared with short courses of DAPT. The prior distribution is consistent with the likelihood (red), which represents the likely range of ORs from the DAPT trial (23) and more strongly suggests a mortality hazard with increased mortality rate (OR: 1.31; 95% BCI: 0.97 to 1.77) than a mortality benefit. The posterior distribution (black), which combines the prior (blue) with the likelihood (red), shows that the mortality rate remains credibly higher after prolonged than after short-course therapy (OR: 0.16; 95% BCI: 0.98 to 1.37). In a Bayesian triplot, all probability density functions are normalized to 1 and plotted on the familiar OR scale as well as on a θ scale (θ=\log_e[OR]). The width of each curve represents the strength of evidence for each source of information. A narrow curve represents a stronger source of evidence than a wide curve because it excludes more parameter values. The posterior distribution is not twice the height of the prior or the likelihood because precision is additive in the Bayesian context. BCI indicates Bayesian confidence interval; DAPT, dual antiplatelet therapy; and OR, odds ratio.
Figure 5. Cumulative Probability Distributions

The probability distribution function (black) of the null hypothesis of no mortality rate difference and the probability unit distribution ("probit," blue) of the alternative hypothesis are plotted as a function of the mortality rate increase with prolonged DAPT, as compared with short-course DAPT. DAPT indicates dual antiplatelet therapy; and \( \theta \), the natural logarithm of the odds ratio.
Figure 6. Forest Plots of Mortality Rates by Study Completion

### A. Studies Completing Enrollment

<table>
<thead>
<tr>
<th>Study</th>
<th>Prolonged Events</th>
<th>Total</th>
<th>Events</th>
<th>Short Events</th>
<th>Total</th>
<th>Odds Ratio (OR)</th>
<th>OR</th>
<th>95% CI</th>
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<td>8</td>
<td>1058</td>
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<tr>
<td>OPTIMIZE (3 vs. 12 mo)</td>
<td>45</td>
<td>1556</td>
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<td>1583</td>
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<td>1.05</td>
<td>0.76</td>
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<td>74</td>
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<td></td>
<td>1.31</td>
<td>1.22</td>
<td>(0.97–1.78)</td>
</tr>
<tr>
<td><strong>Bayesian hierarchical meta-analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>1.22</strong></td>
<td></td>
<td><strong>(0.97–1.53)</strong></td>
</tr>
</tbody>
</table>

*Fixed effect model*

*Random effects model*

*Heterogeneity: I²=0%, τ²=0%, p=0.8278*

### B. Studies Stopped Prematurely

<table>
<thead>
<tr>
<th>Study</th>
<th>Prolonged Events</th>
<th>Total</th>
<th>Events</th>
<th>Short Events</th>
<th>Total</th>
<th>Odds Ratio (OR)</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>SECURITY (6 vs. 12 mo)</td>
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<td>717</td>
<td>8</td>
<td>682</td>
<td></td>
<td>0.95</td>
<td>0.88</td>
<td>(0.35–2.55)</td>
</tr>
<tr>
<td>ITALIC (6 vs. 24 mo)</td>
<td>7</td>
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<td>8</td>
<td>912</td>
<td></td>
<td>0.88</td>
<td>1.50</td>
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</tr>
<tr>
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<td>12</td>
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<td>8</td>
<td>1997</td>
<td></td>
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<td>0.65</td>
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<tr>
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<td>695</td>
<td>24</td>
<td>690</td>
<td></td>
<td>0.65</td>
<td>0.88</td>
<td>(0.57–1.35)</td>
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<tr>
<td><strong>Bayesian hierarchical meta-analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>0.88</strong></td>
<td></td>
<td><strong>(0.58–1.34)</strong></td>
</tr>
</tbody>
</table>

*Fixed effect model*

*Random effects model*

*Heterogeneity: I²=0%, τ²=0%, p=0.5319*

Findings are stratified by trial completion: (A) completed randomized controlled trials and (B) prematurely terminated trials. Study acronyms (12-14,16-24) are defined in Table 1. CI indicates confidence interval; and OR, odds ratio.
Figure 7. All-Cause Mortality Rate in All Patients (A) and in Those With (B) and Without (C) A Prior History of Acute Coronary Syndrome

A. Overall

<table>
<thead>
<tr>
<th>Study</th>
<th>Prolonged Events</th>
<th>Total</th>
<th>Events</th>
<th>Odds Ratio (OR)</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHARISMA</td>
<td>371</td>
<td>7802</td>
<td>374</td>
<td>0.99</td>
<td>(0.86–1.15)</td>
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<tr>
<td>PRODIGY</td>
<td>65</td>
<td>987</td>
<td>65</td>
<td>1.00</td>
<td>(0.70–1.42)</td>
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<tr>
<td>ARCTIC</td>
<td>9</td>
<td>624</td>
<td>7</td>
<td>1.31</td>
<td>(0.49–3.55)</td>
<td></td>
</tr>
<tr>
<td>DAPT</td>
<td>98</td>
<td>5020</td>
<td>74</td>
<td>1.31</td>
<td>(0.97–1.78)</td>
<td></td>
</tr>
<tr>
<td>DES–LATE</td>
<td>46</td>
<td>2531</td>
<td>32</td>
<td>1.44</td>
<td>(0.91–2.26)</td>
<td></td>
</tr>
<tr>
<td>PEGASUS</td>
<td>615</td>
<td>14095</td>
<td>326</td>
<td>0.94</td>
<td>(0.82–1.08)</td>
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</tr>
<tr>
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<td>1.04</td>
<td>(0.90–1.30)</td>
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<td>1204</td>
<td>31059</td>
<td>878</td>
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<td>1.03</td>
<td>(0.92–1.16)</td>
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B. History of Acute Coronary Syndromes

<table>
<thead>
<tr>
<th>Study</th>
<th>Prolonged Events</th>
<th>Total</th>
<th>Events</th>
<th>Odds Ratio (OR)</th>
<th>OR</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>CHARISMA</td>
<td>82</td>
<td>1903</td>
<td>99</td>
<td>0.84</td>
<td>(0.62–1.13)</td>
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<tr>
<td>PRODIGY</td>
<td>52</td>
<td>732</td>
<td>56</td>
<td>0.92</td>
<td>(0.62–1.37)</td>
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<tr>
<td>ARCTIC</td>
<td>1</td>
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<td>(0.05–5.93)</td>
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<td>DAPT</td>
<td>24</td>
<td>1805</td>
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<td>(0.50–1.51)</td>
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<tr>
<td>DES–LATE</td>
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<td>1512</td>
<td>43</td>
<td>0.88</td>
<td>(0.56–1.37)</td>
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<tr>
<td>PEGASUS</td>
<td>615</td>
<td>14095</td>
<td>326</td>
<td>0.94</td>
<td>(0.82–1.08)</td>
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<tr>
<td>Bayesian hierarchical meta-analysis</td>
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<td>(0.75–1.07)</td>
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<tr>
<td>Fixed effect model</td>
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<td>(0.82–1.03)</td>
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<tr>
<td>Random effects model</td>
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<td>(0.82–1.03)</td>
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C. No History of Acute Coronary Syndrome

<table>
<thead>
<tr>
<th>Study</th>
<th>Prolonged Events</th>
<th>Total</th>
<th>Events</th>
<th>Odds Ratio (OR)</th>
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<td>275</td>
<td>1.05</td>
<td>(0.88–1.24)</td>
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<td>PRODIGY</td>
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<tr>
<td>ARCTIC</td>
<td>8</td>
<td>468</td>
<td>5</td>
<td>1.61</td>
<td>(0.52–4.96)</td>
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</tr>
<tr>
<td>DAPT</td>
<td>74</td>
<td>3215</td>
<td>47</td>
<td>1.57</td>
<td>(1.08–2.26)</td>
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<tr>
<td>DES–LATE</td>
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<td>1019</td>
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<td>(1.05–311.7)</td>
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<tr>
<td>PEGASUS</td>
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<td>0</td>
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<tr>
<td>Bayesian hierarchical meta-analysis</td>
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<td>(0.93–2.36)</td>
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<td>Fixed effect model</td>
<td>1.17</td>
<td>(1.01–1.35)</td>
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<tr>
<td>Random effects model</td>
<td>1.35</td>
<td>(0.94–1.93)</td>
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Stent trial acronyms (13,14,19,23) are defined in Table 1. Medical-treatment trial acronyms (25,42) are defined in Table 2. CI indicates confidence interval; and OR, odds ratio.
Figure 8. Population Plot Showing the Size of the Treatment Effect of Extended Ticagrelor Therapy After MI

Data from the PEGASUS–TIMI 54 trial (25) are presented in a Cates plot (37) and show that for every 1,000 patients treated with ticagrelor 60 mg twice daily, there were 4 fewer ischemic events but 3 more TIMI (Thrombolysis in Myocardial Infarction) major hemorrhages. Prolonged therapy with ticagrelor prevented a fraction of ischemic complications but contributed to a larger proportion of major hemorrhages. MI indicates myocardial infarction.
The risk of myocardial infarction (A) and stent thrombosis (B) is presented as a function of bleeding risk for patients enrolled in 5 randomized controlled studies (12-14,19,21,23,24) comparing 18 to 48 months of DAPT with 6 to 12 months of DAPT after implantation of newer-generation drug-eluting stents. NNTB indicates number needed to treat to benefit 1 patient; and NNTH, number needed to treat to harm 1 patient.
## Appendix 1. Evidence Review Committee Member Relationships With Industry and Other Entities (Relevant)—Duration of Dual Antiplatelet Therapy: A Systematic Review for the 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease (February 2015)

<table>
<thead>
<tr>
<th>Committee Member</th>
<th>Employment</th>
<th>Consultant</th>
<th>Speakers Bureau</th>
<th>Ownership/Partnership/Principal</th>
<th>Personal Research</th>
<th>Institutional, Organizational, or Other Financial Benefit</th>
<th>Expert Witness</th>
</tr>
</thead>
<tbody>
<tr>
<td>John A. Bittl <em>(ERC Chair)</em></td>
<td>Munroe Regional Medical Center—Interventional Cardiologist</td>
<td>None</td>
<td>None</td>
<td>None</td>
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<tr>
<td>Usman Baber</td>
<td>Mount Sinai Medical Center—Assistant Professor of Medicine, Cardiology</td>
<td>None</td>
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<tr>
<td>Steven M. Bradley</td>
<td>VA Eastern Colorado Heath Care System—Cardiologist; University of Colorado—Assistant Professor of Medicine, Cardiology</td>
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<tr>
<td>Duminda Wijeysundera</td>
<td>Li Ka Shing Knowledge Institute of St. Michael’s Hospital—Scientist; Toronto General Hospital—Staff, Department of Anesthesia and Pain Management; University of Toronto—Assistant Professor, Department of Anesthesia and Institute of Health Policy Management and Evaluation; Institute for Clinical Evaluative Sciences—Adjunct Scientist</td>
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*For transparency, the ERC members’ comprehensive disclosure information is available as an online supplement.*

ACC indicates American College of Cardiology; AHA, American Heart Association; and VA, Veterans Affairs.
Duration of Dual Antiplatelet Therapy: A Systematic Review for the 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

John A. Bittl, Usman Baber, Steven M. Bradley and Duminda N. Wijeysundera

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### Evidence Review Committee Member Relationships With Industry and Other Entities (Comprehensive)—Duration of Dual Antiplatelet Therapy: A Systematic Review for the 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease (February 2015)

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<tr>
<td>Steven M. Bradley</td>
<td>VA Eastern Colorado Heath Care System—Cardiologist; University of Colorado—Assistant Professor of Medicine, Cardiology</td>
<td>• Heart Journal</td>
<td>• CMS</td>
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<td>• Collaborative Care to Alleviate Symptoms and Adjust to Illness Study (DSMB)†</td>
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*Significant relationship.
†No financial benefit.

ACC indicates American College of Cardiology; AHA, American Heart Association; CMS, Centers for Medicare and Medicaid Services; and DSMB, data safety monitoring board.