Dual Antiplatelet Therapy Continuation Beyond 1 Year After Drug-Eluting Stents
A Meta-Analysis of Randomized Trials

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Background—The benefits and harms of dual antiplatelet therapy (DAPT) continuation beyond 1 year after drug-eluting stent implantation as compared with 1-year DAPT remain controversial.

Methods and Results—We searched for randomized trials that compared longer than 1-year DAPT versus 1-year DAPT after drug-eluting stenting. A meta-analysis was performed by using standard frequentist and random-effects Bayesian approaches. Four trials comprising 17,650 participants were included. Compared with 1-year DAPT, extended DAPT did not affect all-cause mortality (odds ratio [OR], 1.11; 95% confidence interval [CI], 0.79–1.5; \( P = 0.53 \)) or cardiovascular mortality (OR, 1.03; 95% CI, 0.72–1.46; \( P = 0.88 \)). Extended DAPT was associated with a reduction in the risk of myocardial infarction (OR, 0.56; 95% CI, 0.43–0.73; \( P = 0.001 \)), nonsignificant reductions of stent thrombosis (OR, 0.46; 95% CI, 0.16–1.27; \( P = 0.13 \)), similar risk of stroke (OR, 0.91; 95% CI, 0.65–1.26; \( P = 0.56 \)), and an increased risk of major bleeding (OR, 1.49; 95% CI, 1.06–2.11; \( P = 0.02 \)). By using Bayesian meta-analysis, we found moderate evidence of a reduction of myocardial infarction (OR, 0.62; 95% credible intervals, 0.39–1.05) and weak evidence of an increase in major bleeding (OR, 1.66; 95% credible intervals, 0.89–3.09) associated with extended DAPT.

Conclusions—In this meta-analysis, extended DAPT beyond 1 year prevented myocardial infarctions and increased major bleedings, but the strength of evidence for these effects was not strong. DAPT continuation beyond 1 year showed no effects on mortality. (Circ Cardiovasc Interv. 2017;10:e004139. DOI: 10.1161/CIRCINTERVENTIONS.116.004139.)

Key Words: aspirin ■ drug-eluting stents ■ hemorrhage ■ percutaneous coronary intervention ■ uncertainty

Concerns about the long-term safety of first-generation coronary drug-eluting stents and the increased risk of stent thrombosis on premature discontinuation of dual antiplatelet therapy (DAPT) with aspirin and a P2Y\textsubscript{13} inhibitor led to the recommendation for 1-year duration of DAPT in patients treated with drug-eluting stents.\textsuperscript{1,4}

Recently, several studies have investigated whether a prolonged duration of DAPT beyond 1 year could improve cardiovascular outcomes by reducing ischemic events beyond 1 year.\textsuperscript{5–7} In the DAPT study,\textsuperscript{5} DAPT continuation beyond 1 year, compared with 1-year DAPT, reduced major adverse cardiovascular events and stent thrombosis but was associated with an increased risk of major bleeding and all-cause mortality. Meta-analyses of randomized trials have investigated the effect of different DAPT durations on overall and cardiovascular mortality leading to conflicting results.\textsuperscript{8–10} However, these meta-analyses included studies assessing the comparison of an abbreviated regimen of DAPT shorter than 1 year with 1-year DAPT or longer DAPT. In some cases, they could include a wider patient population with cardiovascular disorders that did not undergo percutaneous coronary implantation.\textsuperscript{10}

Furthermore, these analyses did not include more recent randomized trials.\textsuperscript{11} Indeed, the OPTIDUAL trial (Optimal Dual Antiplatelet Therapy) reported lack of significant differences in ischemic complications and major bleeding between extended DAPT beyond 1 year and 1-year DAPT.\textsuperscript{11}

Therefore, uncertainty exists about the benefits and risks of prolonging DAPT beyond 1 year in patients undergoing drug-eluting stents.

The aim of this study was to provide a quantitative assessment of evidence from randomized trials appraising the benefit and risk profile of DAPT continuation beyond 1 year as compared with 1-year DAPT among patients treated with drug-eluting stents.

Methods

Data Sources and Search Strategy
A meta-analysis of randomized trials was performed according to the PRISMA 2009 guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).\textsuperscript{12} Two reviewers (G.F. and

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WHAT IS KNOWN

• Meta-analyses of randomized trials comparing 18 to 48 months of dual antiplatelet therapy (DAPT) with 6 to 12 months of DAPT in heterogeneous patient population undergoing drug-eluting stent implantation have reported significant reductions in myocardial infarction and stent thrombosis and increases in major bleeding associated with prolonged DAPT.

WHAT THE STUDY ADDS

• The present study explored the effects of prolonging DAPT duration beyond 1 year compared with stopping DAPT at 1 year after drug-eluting stent implantation in a homogeneous population of patients who did not have major cardiovascular and cerebrovascular events or major bleeding during the first year after stent implantation.
• The study found that DAPT continuation beyond 1 year reduces the risk of myocardial infarction at the expense of an increase in the risk of major bleeding.
• Yet no substantial effects of extended DAPT on total or cardiovascular mortality, stent thrombosis, or stroke were noted.
• These findings highlight the importance of implementing effective strategies to help identify patients in whom DAPT continuation beyond 1 year could provide a greater expected benefit versus greater expected harm.

P.P. independently identified the relevant articles by an electronic search of MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov databases (from inception to March 2016). The following search terms and key words were used: dual antiplatelet therapy, drug-eluting stent, and drug-eluting stents. No language, publication date, or publication status restrictions were imposed. Conference proceedings (from 2010 through March 2016) of the American Heart Association, the American College of Cardiology, the Transcatheter Cardiovascular Therapeutics, and the European Society of Cardiology were also searched through electronic or hand search. All suitable unpublished completed registered studies were considered for inclusion. We checked reference lists of identified articles, recent editorials, and related reviews.

Study Selection

Two reviewers (G.F. and B.R.) independently assessed trial eligibility based on titles, abstracts, full-text reports, and further information from investigators as needed.

Discrepancies in study selection were resolved by consensus.

Eligible trials had to satisfy the following prespecified criteria: (1) randomized design that compared a treatment arm consisting of longer than 1-year DAPT duration versus 1-year DAPT after drug-eluting stenting and (2) the primary outcome measure and at least 3 secondary outcomes were reported. Studies were excluded if control arm consisted of a shorter than 1-year DAPT duration.

Data Extraction and Quality Assessment

Two reviewers (G.F. and P.P.) independently extracted data (baseline characteristics, definition of outcomes, numbers of events) using a standardized data abstraction form. Two reviewers (G.F. and P.P.) independently and systematically assessed the studies’ methodological quality using the Risk of Bias Assessment Tool from the Cochrane Handbook for randomized trial, thus following the approach that identifies selection, performance, attrition, detection, reporting bias, and other sources of bias for each study and classifies each of these as low, unclear, and high by analyzing the following 7 domains: random sequence generation, allocation concealment, blinding of participants and of outcome assessment, incomplete outcome data, selective outcome reporting, and other issues. A risk of bias summary reporting each risk of bias item for each included study was reported. Disagreements were resolved via the consensus of the 2 reviewers.

Data Synthesis and Data Analysis

Outcome Measures

The primary end point was all-cause death. Secondary end points were cardiovascular death, myocardial infarction, definite stent thrombosis, stroke, major adverse cardiovascular or cerebrovascular events (MACCE), and major bleeding. End points were attributed according to definition used in each study. Stent thrombosis was defined according to the Academic Research Consortium criteria. The key safety end point was the incidence of major bleedings, which were classified across trials according to different bleeding scales.

Statistical Analysis

The odds ratios (ORs) with 95% confidence intervals (95% CI) for the end points were directly calculated by extracting the number of events, the number of total patients, and the number of no events in the treatment and control group from each trial. Trial-specific ORs were combined with the Mantel–Haenszel fixed-effects model or with the DerSimonian and Laird random-effects model. If heterogeneity was statistically significant or I² >25%, the presence of heterogeneity among studies was evaluated with the Cochran Q ² test with P≤0.10 considered to be statistically significant, estimating the between-studies variance $\tau^2$, and using $I^2$ test to evaluate the inconsistency. The $I^2$ statistic is derived from the Q statistic ([Q−df/Q]*100), and $I^2$ describes the percentage of total variation across studies that is caused by heterogeneity: values of 25%, 50%, and 75% correspond to low, moderate, and high $I^2$, respectively.

The number of patients needed to treat for an additional beneficial outcome and the number needed to treat for an additional harmful outcome were calculated from weighted estimates of pooled ORs from the random-effects meta-analytic model using the macro metannt, as 1/(projected control group event rate−projected treatment group event rate). The corresponding 95% CI was calculated by using 95% CI of the effect size applied to the control group event rate.

We also calculated trial-specific absolute risk differences with 95% CI for each end point, which were combined using fixed-effects or random-effects model, as appropriate, and reported the number of events avoided/cause per 1000 patients treated with 95% CI.

The presence of publication bias was investigated by visual estimation with the use of contour-enhanced funnel plots. The interpretation and meaning of contour-enhanced funnel plots have been reported elsewhere. Briefly, contour-enhanced funnel plots allow to determine whether the presence of any observed asymmetry could be related to publication bias or to factors other than publication bias, on the basis of which areas within the graph studies that seem to be missing (to eliminate the asymmetry) would be plotted. The Peters’ test or similar tests were not used given the final number of studies included in the meta-analysis was <5.

As sensitivity analysis, we used a Bayesian method developed for random-effects meta-analysis on the log OR scale, reporting OR with 95% credible intervals. We implemented this model in a fully probabilistic Bayesian approach, which will provide posterior probability distributions given the model and the data but requires that prior distributions are defined for all parameters in the statistical model. For the control groups of each study, we set vague priors on the log of the odds of the event risk using normal distributions centered at zero with variance of 1000. We conducted the analyses using weakly informative prior distributions with a half-normal distribution with a mean of 0.5 and a 95% interval from 0.02 to 1.4 for $\tau$. We also calculated the minimum Bayes factor using the formula reported by Goodman, where the Z score was derived using the Bayesian estimates of the population effect d and its SE, and reported the strength of evidence...
of treatment effect based on the minimum Bayes factor as weak, moderate, to strong, and strong to very strong.

All analyses were conducted according to the intention-to-treat principle.

The statistical level of significance for the summary treatment effect estimate was 2-tailed \( P<0.05 \). STATA 11.2 statistical software (StataCorp LP, College Station, TX), Review Manager (RevMan; computer program, version 5.1; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011), and Winbugs version 1.4.3. were used for statistical analyses.

Results

Search Results

Of the 2079 citations screened, a total of 7 randomized controlled trials were selected\(^5\)–\(^7\),\(^11\),\(^23\)–\(^25\) (PRISMA flow diagram, Figure 1). Two studies comparing shorter than 1-year DAPT with 24-month DAPT duration were excluded.\(^23\),\(^24\) The study by Garrat et al\(^{25}\) was excluded because this study included a cohort of patients undergoing Taxus Liberté Paclitaxel-Eluting Coronary Stent implantation, which was already included in the DAPT study.\(^7\)

Therefore, a total of 4 trials comprising 17650 patients who underwent drug-eluting stent implantation, comparing longer than 1-year DAPT with 1-year DAPT, were finally selected and included in the present analysis.\(^5\)–\(^7\),\(^11\)

Study Characteristics

The main trial characteristics, patient characteristics, and angiography features of the included studies are reported in Table 1.

The mean age was comparable across studies ranging from 62 to 64 years, and the prevalence of diabetes mellitus ranged from 28% to 36%.

Figure 1. Flow diagram of the literature search for studies included in meta-analysis according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. DAPT indicates dual antiplatelet therapy; and RCT, randomized controlled trial.
A low prevalence of ST-segment-elevation myocardial infarction at presentation was found across studies. In all trials, DAPT consisted of aspirin and clopidogrel, with prasugrel use as alternative to clopidogrel in a small proportion of patients in few studies. Loss at follow-up was variable across studies ranging from 4.9% to 8.2% in the ARCTIC-interruption trial (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 One Year After Stenting). Three out of 4

### Table 1. Main Clinical, Angiographic, and Procedural Characteristics of the Included Studies

<table>
<thead>
<tr>
<th>Study characteristics</th>
<th>ARCTIC-Interruption</th>
<th>DES-LATE</th>
<th>DAPT</th>
<th>OPTIDUAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of therapy, mo</td>
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<td>Short</td>
<td>Long</td>
<td>Short</td>
</tr>
<tr>
<td>No. of patients</td>
<td>635</td>
<td>624</td>
<td>2531</td>
<td>2514</td>
</tr>
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<td>No. of sites</td>
<td>38</td>
<td>24</td>
<td>...</td>
<td>...</td>
</tr>
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<td>Primary end point</td>
<td>All-cause death, MI, stroke, or TIA</td>
<td>Cardiac death, MI, stroke</td>
<td>Coprimary: ST or composite of all-cause death, MI, stroke</td>
<td>All-cause death, MI, stroke, major bleeding</td>
</tr>
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<td>Urgent revascularization, ST</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Study design</td>
<td>Superiority</td>
<td>Superiority</td>
<td>Superiority/noninferiority</td>
<td>Superiority</td>
</tr>
<tr>
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<td>Open label</td>
<td>Open label</td>
<td>Double blind</td>
<td>Open label</td>
</tr>
<tr>
<td>Follow-up, mo, mean</td>
<td>17</td>
<td>24</td>
<td>18</td>
<td>36</td>
</tr>
<tr>
<td>Loss at follow-up, %</td>
<td>6.3</td>
<td>8.2</td>
<td>5.4</td>
<td>4.6</td>
</tr>
</tbody>
</table>

### Patient characteristics

| | ARCTIC-Interruption | DES-LATE | DAPT | OPTIDUAL |
| Age, mean (SD) | 64 (57–73) | 64 (57–73) | 62.5 (10.0) | 62.3 (10.1) |
| Men, n (%) | 508 (80.0) | 503 (81) | 1749 (69.1) | 1749 (69.6) |
| Diabetes mellitus,† n (%) | 198 (31) | 222 (36) | 709 (28.0) | 709 (28.2) |
| Stable CAD, n (%) | 479 (75.4) | 457 (73.2) | 1011 (39.9) | 956 (38.0) |
| Unstable, n (%) | NA NA 930 (36.7) | 971 (36-6) | 838 (16.7) | 825 (16.7) |
| NSTEMI, n (%) | 156 (24.6) | 167 (26.7) | 268 (10.6) | 266 (10.6) |
| Treatment | Clopidogrel | Prasugrel | Ticagrelor |
| Clopidogrel | 569 (90) | 562 (90) | 1159 (98.7) | 3222 (65.2) | 686 (98.7) |
| Prasugrel | 54 (9) | 53 (9) | 0 (0) | 0 (0) |
| Ticagrelor | 0 (0) | 0 (0) | 0 (0) | 0 (0) |

CAD indicates coronary artery disease; MI, myocardial infarction; NA, not available; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

*Multivessel PCI.
†Type II diabetes mellitus.
studies had an open-label design,5,6,11 whereas the DAPT study was double blinded.7 Studies differed in regard of the primary end point (Table 1). Three out of 4 studies had a superiority trial design,5,6,11 and the DAPT study7 had 2 coprimary end points of superiority and 1 noninferiority safety end point. Furthermore, DAPT duration varied from 18 to 48 months in the treatment arm across studies.

Bias Assessment
Figure 2 summarizes the quality assessment of the included studies.

Overall, there was a high prevalence of low bias in most domains across the studies, except for performance bias caused by lack of blinding of participants and personnel for treatment assignment. Further, high risk of reporting bias was noted for 1 study5 because of the lack of data on cardiac mortality. Because of the smaller number of studies, the Peter test was not used to assess publication bias. Contour-enhanced funnel plots for all end points are reported in Figures I through VII in the Data Supplement. Evidence for some asymmetry was found for the end point of myocardial infarction, definite stent thrombosis, MACCE, and major bleeding (Figures II, III, VI, and VII in the Data Supplement), which was the result of the combination of publication bias based on statistical significance and the role of other confounding factors.

Heterogeneity
Moderate heterogeneity was found for all-cause death, stent thrombosis, and MACCE, and mild heterogeneity was found for myocardial infarction and cardiac death (Table I in the Data Supplement). No heterogeneity was detected for major bleeding and stroke. We used a random-effects method for all end points for which mild-to-moderate heterogeneity was detected and a fixed-effects model for the remaining end points.

Outcomes

Extended DAPT Versus 1-Year DAPT
Compared with 1-year DAPT, extended DAPT did not affect all-cause mortality (1.88% versus 1.58%; OR, 1.11, 95% CI, 0.79–1.57; P=0.53; Figure 3; Table 2).

Extended DAPT was associated with a significantly lower risk of myocardial infarction (1.55% versus 2.85%; OR, 0.56; 95% CI, 0.43–0.73; P<0.001; Figure 4), but it did not significantly reduce the risk of stent thrombosis (0.28% versus 0.82%;
OR, 0.46; 95% CI, 0.16–1.27; \( P = 0.13 \); Figure 5) or stroke (0.78% versus 0.85%; OR, 0.91; 95% CI, 0.65–1.26; \( P = 0.56 \); Figure 6), nor did it affect cardiovascular death (1.0% versus 0.98%; OR, 1.03; 95% CI, 0.72–1.46; \( P = 0.88 \); Figure 7), or MACCE (3.8% versus 4.8%; OR, 0.81; 95% CI, 0.63–1.06; \( P = 0.12 \); Figure VIII in the Data Supplement; Table 2).

Compared with 1-year DAPT, extended DAPT significantly increased the risk of major bleeding (0.96% versus 0.65%; OR, 1.49; 95% CI, 1.06–2.11; \( P = 0.02 \); Figure 8; Table 2).

**Absolute Effects of Extended DAPT Versus 1-Year DAPT**

Extended DAPT, as compared with 1-year DAPT, resulted in 12 fewer myocardial infarctions (95% CI, 7–16) per 1000 treated patients, which corresponds to a number of patients needed to treat for an additional beneficial outcome of 82 (95% CI, 62–135), and in a statistically nonsignificant 4 fewer stent thromboses (95% CI, −2 to 7), 0.8 strokes (95% CI, −2.2 to 2.9), and 8 MACCE (95% CI, −2.6 to 17; Table 3).

However, extended DAPT resulted in 3 more major bleeds (95% CI, 0.4–7) per 1000 treated patients, which corresponds to a number needed to treat for an additional harmful outcome of 311 (141–2500), and to statistically nonsignificant 2 more deaths (95% CI, −3.2 to 9; Table 3).

**Bayesian Meta-Analysis**

Bayesian meta-analysis found that extended DAPT could be associated with 38% risk reduction in myocardial infarction, although the 95% credible interval entailed as much as 5% risk increase (OR, 0.62; 95% credible intervals, 0.39–1.05) and the strength of evidence for a beneficial effect of extended DAPT was moderate (Table 4).

The evidence for an increase in major bleeding associated with extended DAPT was weak (OR, 1.66, 95% credible intervals, 0.89–3.09). Bayesian estimates of OR for the remaining end points were in agreement with results of standard meta-analytic approach (Tables 3 and 4).

**Discussion**

This meta-analysis including 17 650 patients who were treated with drug-eluting stents in 4 studies investigates a well-defined clinical question about the benefits and harms of prolonging DAPT beyond 1 year versus stopping DAPT at 1 year after stent implantation. Our findings refer to a selected homogeneous population of patients from randomized controlled trials, who did not have major cardiovascular and cerebrovascular events or major bleeding during the first year after drug-eluting stent implantation.

We found evidence that extended DAPT could reduce the risk of myocardial infarction and increase the risk of major bleeding at follow-up with no substantial effects on total or cardiovascular mortality, stent thrombosis, stroke, and MACCE.

However, using a Bayesian meta-analytic approach, the strength of evidence for risk reduction in myocardial infarction...
associated with extended DAPT was found to be moderate, and evidence for the increase in major bleeding associated with extended DAPT was weak, with 95% credible intervals of ORs including the null value of 1. Furthermore, analyses of absolute treatment effects showed a clinically modest beneficial effect of extended DAPT on myocardial infarction prevention consisting of 12 fewer events avoided per 1000 treated patients, corresponding to a point estimate of number of patients needed to treat for an additional beneficial outcome of 82.

Discrepancies between Bayesian and traditional frequentist approaches in estimating treatment effects are not rare in clinical trials. Several Bayesian reanalyses of clinical trials have shown that the observed differences may not be true, mainly because the weight of evidence against the null hypothesis is not nearly as strong as the magnitude of the $P$ value suggests.

Besides this methodological issue, other factors may play a role in explaining the lack of a strong benefit of an extended DAPT regimen beyond 1 year on total thrombotic complications after drug-eluting stent implantation. The small absolute pooled cumulative event rate at follow-up of myocardial infarction at 2.8% and of stent thrombosis at 0.8% in the control arm may reduce the power of this, albeit large, analysis in detecting significant treatment effects. This situation may reflect the fact that all studies included in this metaanalysis selected only patients who remained free of major cardiovascular and cerebrovascular events or major bleeding since drug-eluting stent implantation to the time of randomization, which occurred at a mean follow-up of 12 months. This selection bias yielded to the enrollment of a lower risk patient population. By study design, these studies could explore only very late stent–related thrombotic events or cardiovascular events related to coronary disease progression late at follow-up. In this regard, our findings should be analyzed in the context of the type of drug-eluting stent used and patient population enrolled in the included studies. In most trials, there was a prevalent use of second-generation drug-eluting stents, mainly cobalt-chromium everolimus-eluting stents, whereas first-generation drug-eluting stents, that is, sirolimus- or paclitaxel-eluting stents, were more frequently used in one trial only. Second-generation drug-eluting stents have been shown to have lower risk of stent thrombosis and thus an improved safety profile, as compared with first-generation drug-eluting stents and even compared with bare metal stents. Further, a small prevalence of patients admitted with ST-segment–elevation myocardial infarction, a higher proportion of patients with stable coronary artery disease, and the frequent exclusion of patients with cardiogenic shock reduced the risk of stent thrombosis. Heterogeneity in DAPT duration in the treatment arm from 18 to 48 months across studies may further reduce the accrual of events over time.

In the DAPT study, the largest among the included trials, extended DAPT decreased the risk of myocardial infarction that was not related to stent thrombosis (1.8% versus 2.9%...
hazard ratio, 0.59; \( P<0.001 \), and this accounted for 55% of the treatment benefit. The Prospect study has shown that \( \approx 50\% \) of major adverse cardiovascular events at follow-up after stent implantation are caused by coronary disease progression at nonculprit lesions, thus unrelated to stent failure.\(^{34}\) Given the small event rate of stent thrombosis in this pooled analysis, it is likely that the benefit of extended DAPT on the reduction of myocardial infarctions at follow-up could mainly depend on the prevention of nonculprit coronary events.

Our traditional frequentist meta-analysis found an increased risk of major bleeding associated with extended DAPT, although number needed to treat for an additional harmful outcome was large, and Bayesian meta-analysis found that the strength of evidence for this harm was weak.

Both methodological approaches found no evidence of increase in total or cardiovascular mortality risk associated with extended DAPT.

It is likely that the small increase in the absolute rate of major bleedings at 0.4% associated with extended DAPT, as compared with 1-year DAPT, did not translate into an increase in total mortality. Findings from previous studies reported an association between longer DAPT duration and the occurrence of major bleeding,\(^{35,36}\) and several studies have reported a relation between major bleeding and increased mortality.\(^{36,37,38}\)

In the DAPT study,\(^7\) a higher number of deaths from any cause was observed among patients prolonging DAPT beyond 1 year as compared with 1-year DAPT (2.0% versus 1.5%; \( P=0.05 \)). In that study, differences in all-cause mortality were driven by differences in noncardiovascular mortality, which were mainly attributed to an imbalance in cancer-related mortality between treatment arms, which was considered the result of the play of chance. Also, trial investigators did not report an association between bleeding occurrence and noncardiovascular deaths. Previous meta-analyses reported small increase in higher total mortality in patients undergoing longer DAPT regimens,\(^{8,9,39}\) whereas others did not.\(^10\) Such conflicting findings could arise from the inclusion of studies comparing shorter than 1 year with 1-year DAPT together with studies comparing extended DAPT beyond 1 year with 1-year DAPT and may also depend in part on the inclusion of wider patient population with cardiovascular diseases in some analyses,\(^{10}\) therefore with a different cardiovascular risk profile.

Our analysis instead does not include studies where the control arm consisted of shorter than 1-year DAPT and is focused on patients undergoing drug-eluting stent implantation only, thus providing comprehensive findings that refer to this specific clinical setting.

Nevertheless, our results should be interpreted in the context and in comparison with available literature with the aim of tailoring the selection of the most appropriate DAPT duration for different settings. In this regard, several observations have suggested that patients with previous myocardial infarction

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**Table 1**

<table>
<thead>
<tr>
<th>Study</th>
<th>Extended DAPT OR (95% CI) n/N</th>
<th>1-year DAPT n/N</th>
</tr>
</thead>
<tbody>
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<td>DES LATE, 2014</td>
<td>1.47 (0.82, 2.64) 28/2531</td>
<td>19/2514</td>
</tr>
<tr>
<td>DAPT, 2014</td>
<td>0.94 (0.62, 1.42) 45/5020</td>
<td>47/4941</td>
</tr>
<tr>
<td>OPTIDUAL, 2016</td>
<td>0.70 (0.31, 1.66) 10/695</td>
<td>14/690</td>
</tr>
<tr>
<td></td>
<td>1.03 (0.72, 1.46) 83/8246</td>
<td>80/8145</td>
</tr>
</tbody>
</table>

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**Figure 6.** Pooled analysis of studies\(^5–7,11\) comparing shorter than 12-mo dual antiplatelet therapy (DAPT) vs at least 12-mo DAPT. Forest plot reporting trial-specific and summary odds ratios (OR) with 95% confidence interval (CI) for the end point of stroke. ARCTIC indicates 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 One Year After Stenting; and OPTIDUAL, Optimal Dual Antiplatelet Therapy.

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**Figure 7.** Pooled analysis of studies\(^5–7,11\) comparing shorter than 12-mo dual antiplatelet therapy (DAPT) vs at least 12-mo DAPT. Forest plot reporting trial-specific and summary odds ratios (OR) with 95% confidence interval (CI) for the end point of cardiac death. OPTIDUAL indicates Optimal Dual Antiplatelet Therapy.
would benefit the most from the extension of DAPT beyond 1 year. Indeed, in a subgroup analysis of the CHARISMA trial (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) of patients with previous myocardial infarction, the addition of clopidogrel to aspirin significantly reduced the primary end point of cardiovascular death, myocardial infarction, or stroke during a median of 27.6 months. Similar results were observed in the subgroup of patients with myocardial infarction from the DAPT trial. In the PEGASUS-TIMI 54 study (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction), DAPT with ticagrelor and low-dose aspirin, as compared with low-dose aspirin alone, significantly reduced the primary end point of cardiovascular death, myocardial infarction, or stroke, although DAPT was associated with increased risk of TIMI major bleeding but not in fatal bleeding or intracranial hemorrhage.

Recently, other studies have developed clinical prediction scores based on ischemic and bleeding risk factors to help identify patients in whom DAPT continuation beyond 1 year could provide a greater expected benefit versus greater expected harm. These scores may differ because of differences in study design and population from which they are developed. In the DAPT study, among patients with prediction scores of \( \geq 2 \) (high score group), the absolute risk reduction in myocardial infarction or stent thrombosis associated with DAPT continuation was 8.2 times greater than the absolute risk increase in moderate or severe bleeding, whereas patients with scores <2 experienced an absolute increase in bleeding that was 2.4 times the absolute reduction in myocardial infarction or stent thrombosis, after DAPT continuation.

In the PARIS registry enrolling 4190 real-world patients undergoing percutaneous coronary intervention with drug-eluting stents, Baber et al developed separate models to predict thrombotic and bleeding events in the first 2 years after stent implantation. In that study, clinical risk factors alone, rather than procedural parameters, predicted risks for thrombotic events. This data is in contrast with previous studies reporting associations between procedural factors such as lesion complexity, stent size or stent length, the type of procedural techniques, stent endothelialization, and risk of stent thrombosis. Therefore, it seems clinically plausible to consider DAPT continuation beyond 1 year for the prevention of thrombotic complications in the setting of such complex percutaneous coronary intervention procedures.

Furthermore, the selection of the optimal DAPT duration after drug-eluting stent implantation should also take into account the different prognostic implications of thrombotic events versus bleeding events. Major bleeding events not leading to fatal or disabling consequences may be less detrimental than the majority of thrombotic events, which may be associated with worse cardiovascular outcomes.

To further unravel the trade-off between risks and harms related to DAPT continuation, some investigators have introduced the concept of the therapeutic threshold as the level of platelet inhibition, measured as the minimum inhibition of platelet aggregation, required to prevent stent thrombosis at a given time period after percutaneous coronary intervention. Given that the therapeutic threshold varies with the completeness of stent endothelialization and therefore it may change over time, being higher for a freshly placed stent that is not covered with neointima (inhibition of platelet aggregation possibly >40% to 50%) and becoming lower as the stent is endothelialized, it has been hypothesized that clopidogrel administration on alternate days, in addition to aspirin, after 1 year could represent an alternative DAPT regimen sufficient to prevent very late stent thrombosis, while decreasing the risks of bleeding.

### Table 3. Absolute Effects of Extended DAPT Versus 1-Y DAPT

<table>
<thead>
<tr>
<th>End Point</th>
<th>NNTB/NNTH</th>
<th>95% CI</th>
<th>No. of Events Avoided/ Caused per 1000 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause death</td>
<td>NNTB 566</td>
<td>114 to ( \infty ) 312</td>
<td>1.8 (−3.2 to 8.8)</td>
</tr>
<tr>
<td>MI</td>
<td>NNTB 82</td>
<td>62 to 135</td>
<td>12.2 (7.4 to 16.0)</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>NNTB 225</td>
<td>147 to ( \infty ) 454</td>
<td>4.4 (−2.2 to 6.8)</td>
</tr>
<tr>
<td>Stroke</td>
<td>NNTB 1286</td>
<td>344 to ( \infty ) 454</td>
<td>0.8 (−2.2 to 2.9)</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>NNTB 3881</td>
<td>222 to ( \infty ) 370</td>
<td>0.3 (−2.7 to 4.5)</td>
</tr>
<tr>
<td>MACCE</td>
<td>NNTB 117</td>
<td>58 to ( \infty ) 384</td>
<td>8.5 (−2.6 to 17.2)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>NNTB 311</td>
<td>141 to 2500</td>
<td>3.2 (0.4 to 7.1)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; MACCE, major adverse cardiovascular and cerebrovascular events; MI, myocardial infarction; NNTB, number needed to treat to benefit; and NNTH, number needed to treat to harm.
DAPT on total or cardiovascular mortality, stent thrombosis, stroke, and MACCE.

On the basis of these findings, the extension of DAPT beyond 1 year should not be routinely applied to these patients, while evaluation of the trade-off between the benefits and risks should be assessed for decision making.

**Disclosures**

None.

**References**


Dual Antiplatelet Therapy Continuation Beyond 1 Year After Drug-Eluting Stents: A Meta-Analysis of Randomized Trials
Giuseppe Ferrante, Gianluigi Condorelli, Paolo Pagnotta and Bernhard Reimers

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Figure legends for eFigures from 1 to 8

eTable 1

eFigures 1 to 8
eFigure legends

eFigure 1. Contour-enhanced funnel plot for all-cause death. 1/standard error is plotted against logarithm odds ratio.

eFigure 2. Contour-enhanced funnel plot for myocardial infarction. 1/standard error is plotted against logarithm odds ratio.

eFigure 3. Contour-enhanced funnel plot for definite stent thrombosis. 1/standard error is plotted against logarithm odds ratio.

eFigure 4. Contour-enhanced funnel plot for stroke. 1/standard error is plotted against logarithm odds ratio.

eFigure 5. Contour-enhanced funnel plot for cardiac death. 1/standard error is plotted against logarithm odds ratio.

eFigure 6. Contour-enhanced funnel plot for MACCE. 1/standard error is plotted against logarithm odds ratio.

eFigure 7. Contour-enhanced funnel plot for major bleeding. 1/standard error is plotted against logarithm odds ratio.

eFigure 8. Pooled analysis of studies comparing longer than 12-month DAPT duration vs. 12-month DAPT. Forest plot reporting trial-specific and summary odds ratios (OR) with 95% confidence interval (CI) for the endpoint of MACCE.
**eTable 1. Heterogeneity. Pooled analysis of studies comparing extended DAPT vs. 1-year DAPT.**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Heterogeneity chi²</th>
<th>df</th>
<th>P</th>
<th>Tau²</th>
<th>I²(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause death</td>
<td>5.17</td>
<td>3</td>
<td>0.16</td>
<td>0.048</td>
<td>42</td>
</tr>
<tr>
<td>MI</td>
<td>3.47</td>
<td>3</td>
<td>0.32</td>
<td>0.013</td>
<td>13.4</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>7.03</td>
<td>0.071</td>
<td>0.07</td>
<td>0.53</td>
<td>57.3</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.93</td>
<td>3</td>
<td>0.82</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>2.42</td>
<td>2</td>
<td>0.298</td>
<td>0.018</td>
<td>17.3</td>
</tr>
<tr>
<td>MACCE</td>
<td>6.37</td>
<td>3</td>
<td>0.095</td>
<td>0.036</td>
<td>52.9</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>2.46</td>
<td>3</td>
<td>0.483</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Df = degree of freedom; I² = inconsistency; MACCE: major adverse cardiovascular and cerebrovascular events; MI = myocardial infarction; ST: stent thrombosis; Tau² = between-study variance Tau-squared; TIMI = thrombolysis in myocardial infarction.
eFigure 1
eFigure 4

![Diagram showing the relationship between effect estimate and inverse standard error with legend indicating significance levels.](image-url)
eFigure 6
eFigure 7
**eFigure 8**

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95% CI)</th>
<th>Extended DAPT n/N</th>
<th>1-year DAPT n/N</th>
</tr>
</thead>
<tbody>
<tr>
<td>DES LATE, 2014</td>
<td>1.13 (0.81, 1.57)</td>
<td>78/2531</td>
<td>69/2514</td>
</tr>
<tr>
<td>DAPT, 2014</td>
<td>0.72 (0.60, 0.86)</td>
<td>211/5020</td>
<td>285/4941</td>
</tr>
<tr>
<td>ARCTIC-Interruption, 2014</td>
<td>0.86 (0.47, 1.55)</td>
<td>21/635</td>
<td>24/624</td>
</tr>
<tr>
<td>OPTIDUAL, 2016</td>
<td>0.64 (0.40, 1.03)</td>
<td>29/695</td>
<td>44/690</td>
</tr>
<tr>
<td></td>
<td>0.62 (0.63, 1.06)</td>
<td>339/8881</td>
<td>422/8769</td>
</tr>
</tbody>
</table>

Extended DAPT better 1-year DAPT better