Best duration of dual antiplatelet therapy after drug-eluting stent implantation: an updated network meta-analysis of randomized controlled trials

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ABSTRACT

Background: Drug-eluting stent (DES) implantation is the main interventional treatment for coronary artery disease, and dual antiplatelet therapy (DAPT) remains the gold standard strategy to prevent ischemic events. However, the optimal duration of DAPT after DES implantation remains controversial. Therefore, we aimed to evaluate the best duration of DAPT following DES implantation.

Method: We searched PubMed, Embase, Cochrane Library, and clinicaltrials.gov for all randomized clinical trials (RCTs) that compared different durations of DAPT after DES implantation. Major adverse cardiac events (MACE) and major bleeding were the primary and secondary outcomes, respectively.

Results: We included 16 RCTs (n = 42,993). The mean age of included patients was 63.1 ± 10.1. The primary outcome was statistically significant for lower MACE in patients who received DAPT for 24–48 months (mo) following DES when compared with those who received 3–6 mo of DAPT (odds ratio [OR] 0.75; 95% credible interval [CI] 0.58–0.97). There was nonstatistically significant difference in MACE when comparing those who received 12 mo of DAPT to those taking either 3–6 mo of DAPT (OR 0.86; 95% CI 0.69–1.08) or 24–48 mo of DAPT (OR 0.87; 95% CI 0.72–1.05). In contrast, major bleeding was significantly lower in those who received 3–6 mo of DAPT (OR 0.32; 95% CI 0.17–0.54) and 12 mo of DAPT (OR 0.43; 95% CI 0.27–0.63) than in those who received 24–48 mo of DAPT.

Conclusion: In patients who undergo DES implantation, a longer duration of DAPT is associated with lower MACE, despite the increased risk of major bleeding events. Therefore, individualizing the duration of DAPT after DES according to the patient’s risk of bleeding and recurrent ischemia is recommended.

1. Introduction

The efficacy of percutaneous coronary intervention (PCI) has improved significantly with the use of drug-eluting stents (DESs). However, the concern regarding their safety, specifically stent thrombosis, is rising. Although the rate of stent thrombosis is generally low, its occurrence is potentially fatal [1–3]. Current PCI guidelines recommend dual antiplatelet therapy (DAPT) with aspirin and thienopyridine as the cornerstone of treatment after DES implantation [4,5]. The first 6–12 months (mo) post–coronary stent implantation hold the highest risk of thrombotic complications [1,6,7]. Therefore, DAPT is recommended during this ‘ischemic phase’. The use of DAPT during the ‘maintenance phase’, however, is associated with an increased bleeding risk [5]. Strategies to reduce bleeding risk, such as reducing the DAPT duration, have emerged, especially with the establishment of a new, safer generation of DESs [8,9]. In contrast, patients with a stenosed stent, diabetes, or low bleeding risk may experience the benefit of prolonged (more than a year) DAPT without a similar bleeding risk [8–11].

Multiple randomized clinical trials (RCTs) have evaluated the safety and efficacy of different DAPT durations with conflicting results [12–15]. Previous meta-analyses and systematic review have also shown mixed results [16–19]. Therefore, we conducted our network meta-analysis to evaluate the safety and efficacy of various DAPT durations in patients undergoing DES implantation.

2. Methodology

2.1. Literature search and data source

An electronic literature search was performed independently by two authors (A.A. and Y.Z.) according
to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) Statement 2015. We comprehensively searched PubMed, Embase, Cochrane Library, and clinicaltrials.gov from inception to 8 March 2018. Any disagreement was resolved by a discussion between the two authors and in consultation with a third author (M.B.). Neither language nor demographic restrictions were applied. Furthermore, references of the relevant studies and meta-analyses were reviewed for possible eligibility. The search terms were: ‘drug eluting stent*’, ‘DES’, ‘stent’, ‘dual antiplatelet’, ‘DAPT’, ‘aspirin’, ‘clopidogrel’, ‘Plavix’, ‘P2Y12’, ‘thienopyridines’, ‘ticagrelor’, ‘prasugrel.’

Studies were first screened by their titles and abstracts for eligibility. Then, full texts of the eligible studies were reviewed before exclusion. The search process is detailed in Figure 1. The electronic search was archived through Mendeley and is available on request. Our study was a systematic review and meta-analysis and thus did not require institutional review board (IRB) approval.

2.2. Study selection and data extraction

We included only RCTs that compared long-term versus short-term DAPT after PCI and their effect on various clinical outcomes. The duration of DAPT was classified into three categories: 3–6 mo, 12–24 mo, and 24–36 mo. Retrospective studies were excluded to reduce biases and eliminate confounding variables. The main outcome of each included RCT and the baseline patient characteristics are shown in Tables 1 and 2.

2.3. Quality assessment

We performed a quality assessment for the included RCTs. We assessed the included RCTs for random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other biases. We classified studies as low-risk for bias only if all the described items were adequately described as low-risk. Quality assessment results are attached in the online supplemental data.

2.4. Data extraction

Two authors (A.A., M.B.) independently and separately extracted the data from the included studies into a predesigned form. Any disagreement was resolved by a discussion between the two reviewers and a third investigator (Y.Z.).

![Figure 1. Preferred reporting items for systematic reviews and meta-analyses chart of the studies selection process.](image-url)
| Name of study/Author       | Number of patients | Follow up duration | Treatment duration | Study population                  | Study period       | Primary Outcome                                                                                                                                 |
|---------------------------|--------------------|--------------------|--------------------|-----------------------------------|--------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| EXCELLENT/Goon et al. 2012| 1443               | *12 months         | 6 months vs 12 months | Exclude recent MI (within 72 h)   | 2008–2009          | Composite of cardiac death, myocardial infarction, or target vessel revascularization                                                          |
| PRODIGY/Valgimigli et al. 2012 | 1443               | *24 months         | 6 months vs 24 months | Any PCI                          | 2006–2008          | Cumulative incidence of death of any cause, nonfatal myocardial infarction, or cerebrovascular accident                                      |
| RESET/Kim et al. 2012      | 2117               | *12 months         | 3 months vs 12 months | Any PCI                          | 2009–2010          | Composite of death from cardiovascular cause, myocardial infarction, stent thrombosis, ischemia-driven target-vessel revascularization, or bleeding |
| OPTIMIZE/Feres et al. 2013 | 3119               | *12 months         | 3 months vs 12 months | STEMI excluded                    | 2010–2012          | Composite of cardiac death, MI, stroke, definite or probable stent thrombosis, or BARC criteria type 3 or 5 bleeding                          |
| SECURITY/Colombo et al. 2014 | 1399              | *21.4 months       | 6 months vs 12 months | Exclude STEMI                     | 2009–2014          | Composite of death from any cause, MI, stroke, or major bleeding                                                                            |
| ARCTIC-Interruption/Collet et al. 2014 | 1259           | **17 months        | 12 months vs 30 months | Planned PCI, no STEMI            | 2011–2012          | Composite of all-cause death, myocardial infarction, stroke or transient ischemic attack, urgent coronary revascularization, and stent thrombosis |
| DES LATE/Lee et al. 2014   | 5045               | **4 months         | 12 months vs 36 months | Any PCI                          | 2007–2011          | Composite of death resulting from cardiac causes, myocardial infarction, or stroke                                                            |
| DAPT/Mauri et al. 2014     | 9961               | *17 months         | 12 months vs 30 months | Any PCI                          | 2009–2011          | Cumulative incidence of definite or probable stent thrombosis and of major adverse cardiovascular and cerebrovascular events (defined as the composite of death, myocardial infarction, or stroke) |
| OPTIDUAL/Helft et al. 2015 | 1385               | **33.9 months      | 12 months vs 48 months | Any PCI                          | 2009–2013          | Net adverse clinical events defined as the composite of all-cause mortality, nonfatal myocardial infarction, stroke, or major bleeding       |
| ISAR-SAFE/Schu pke. 2015   | 4000               | **6.6 months       | 6 months vs 12 months | Any PCI                          | 2008–2014          | Composite of death, myocardial infarction, stent thrombosis (definite or probable), stroke, or TIMI major bleeding                          |
| ITALIC/Gilard et al. 2015  | 1822               | *12 months         | 6 months vs 24 months | Any PCI                          | 2012–2013          | Composite of death, MI, repeat emergency TVR, stroke, or major TIMI bleeding                                                                  |
| I LOVE IT-2/Han et al. 2016| 1829               | *18 months         | 6 months vs 12 months | Any PCI                          | n/a                | Cardiac death, target vessel myocardial infarction, or clinically indicated target lesion revascularization                                       |
| IVUS-XPL/Hong et al. 2016  | 1400               | *12 months         | 6 months vs 12 months | Any PCI                          | 2010–2014          | Composite of cardiac death myocardial infarction, stroke, or TIMI major bleeding                                                                |
| NIPPON/Nakamura et al. 2017| 3307               | **14.5 months      | 6 months vs 18 months | Any PCI                          | 2011–2015          | Composite of all cause death, Q-wave or non-Q-wave MI, cerebrovascular events, and major bleeding events                                        |
| OPTIMA-C/Lee et al. 2017   | 1367               | *12 months         | 6 months vs 12 months | STEMI excluded                    | 2011–2014          | Composite of cardiac death, Target vessel related MI, Ischemia-driven target lesion revascularization                                           |
| SMART-DATE/Hahn et al. 2018| 2712               | *18 months         | 6 months vs 12 months | Acute ACS PCI                    | 2012–2015          | Composite of major adverse cardiac and cerebrovascular events, defined as a composite of all-cause mortality, myocardial infarction, or stroke |

Abbreviation. ARCTIC; Double Randomization of a Monitoring Adjusted Antiplatelet Treatment Versus a Common Antiplatelet Treatment for DES Implantation, and Interruption Versus Continuation of Double Antiplatelet Therapy; BARC: Bleeding Academic Research Consortium; DAPT: Dual Antiplatelet Therapy; DES LATE: Duration of Clopidogrel Therapy After Drug-Eluting Stent; EXCELLENT: The Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting; I LOVE IT: Evaluate Safety and Effectiveness of the Tivoli DES and the Firebird DES for Treatment of Coronary Revascularization; ISAR-SAFE: Safety And Efficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting; MI: myocardial infarction; ITALIC: Is There A Life for DES After Discontinuation of Clopidogrel? IVUS-XPL: Impact of Intravascular Ultrasound Guidance on Outcomes of XIENCE PRIME Stents in Long Lesions; NIPPON: Nobori Dual Antiplatelet Therapy as Appropriate Duration; OPTIDUAL: Optimal Duration of Dual Antiplatelet Therapy After Drug-eluting Stent Implantation; OPTIMA-C: Optimal Duration of Clopidogrel in Second-Generation Drug-Eluting Stents; OPTIMIZE: OPTIMIZE IDE for the Treatment of ACS; PCI: Percutaneous coronary intervention; PRODIGY: Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia; RESET: Real Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation; SECURITY: Second-Generation Drug-Eluting Stent Implantation Followed by 6- Versus 12-Month Dual Antiplatelet Therapy; SMART-DATE: Safety of 6-month Duration of Dual Antiplatelet Therapy After Acute Coronary Syndromes; STEMI: ST-elevation myocardial infarction; TIMI: Thrombolysis in Myocardial Infarction.

*mean  
**median
Table 2. Demographic features.

| Duration | Age(year) | Male (n) | DM | HTN | Dyslipidemia | Current smoker | Previous MI | Previous PCI | Previous CABG | CVA | PVD | Stable angina | Unstable Angina/NSTEMI | STEMI |
|----------|-----------|----------|----|-----|-------------|----------------|-------------|--------------|--------------|-------------|----|-----|----------------|------------------------|-------|
| EXCELLENT| Long      | 64.2 ± 10.4 | 461 | 278 | 532        | 550            | 186         | 27           | 62           | 7           | 48     | -    | 346             | 349                    | 26    |
|          | Short     | 63.0 ± 9.6  | 470 | 272 | 525        | 543            | 198         | 47           | 67           | 11          | 47    | -    | 353             | 350                    | 19    |
| PRODIGY  | -         | -         | -  | -   | -           | -              | -           | -            | -            | -           | -     | -    | -               | -                       | -     |
| RESET    | Long      | 62.4 ± 9.8  | 665 | 305 | 650        | 634            | 241         | 17           | 32           | 6           | -     | -    | 490             | 422                    | 146   |
|          | Short     | 62.4 ± 9.4  | 682 | 316 | 660        | 611            | 267         | 19           | 37           | 2           | -     | -    | 471             | 432                    | 156   |
| OPTIMIZE | Long      | 61.9 ± 10.6 | 982 | 549 | 1371       | 952            | 269         | 542          | 279          | 128         | 38    | 46   | 143             | 84                      | -     |
|          | Short     | 61.3 ± 10.4 | 992 | 554 | 1350       | 953            | 290         | 541          | 327          | 111         | 38    | 43   | 134             | 84                      | -     |
| SECURITY | Long      | 65.3 ± 10.1 | 551 | 355 | 231        | 147            | 186         | 104          | 274          | 139         | 38    | -    | 368             | 229                    | -     |
|          | Short     | 64.9 ± 10.2 | 529 | 216 | 508        | 446            | 139         | 135          | 132          | 38          | -     | -    | 341             | 213                    | -     |
| ARCTIC-Interruption | Long | 64 ± 7 | 503 | 222 | 388 | 426 | 152 | 186 | 249 | 35 | 38 | - | - | - | - |
|          | Short     | 64 ± 8     | 504 | 198 | 376 | 428 | 147 | 197 | 273 | 47 | 28 | - | - | - | - |
| DES LATE | Long      | 62.5 ± 10.0 | 1749 | 709 | 1479 | 695 | 103 | 313 | - | 15 | - | 1011 | 930/268 | 314 |
|          | Short     | 62.3 ± 10.1 | 1749 | 709 | 1423 | 722 | 92 | 94 | - | - | - | 956 | 971/266 | 314 |
| DAPT trial | Long   | 61.8 ± 10.2 | 3778 | 1556 | 3796 | - | 1222 | 1092 | 1518 | 568 | 155 | 284 | 1882 | 838/776 | 534 |
|          | Short     | 61.6 ± 10.1 | 3657 | 1481 | 3649 | - | 1210 | 1026 | 1529 | 581 | 169 | 284 | 1870 | 825/767 | 511 |
| OPTIDUAL trial | Long | 64.1 ± 10.8 | 568 | 213 | 396 | - | 425 | 119 | 180 | 37 | 29 | 34 | 240 | 66/99 | 74 |
|          | Short     | 64.2 ± 11.5 | 547 | 222 | 417 | - | 399 | 122 | 186 | 35 | 25 | 45 | 207 | 63/117 | 82 |
| ISAR-SAFE | Long      | 67.2 ± 6.5  | 1612 | 484 | 1830 | 1748 | 306 | 491 | - | 149 | - | - | 956 | 438/203 | 166 |
|          | Short     | 67.2 ± 7.9  | 1611 | 495 | 1797 | 1747 | 292 | 516 | - | 152 | - | - | 969 | 429/207 | 158 |
| ITALIC   | Long      | 61.5 ± 11.1 | 721 | 344 | 589 | 611 | 480 | 134 | 205 | 45 | 26 | - | - | - | - |
|          | Short     | 61.7 ± 10.9 | 737 | 331 | 595 | 612 | 464 | 142 | 220 | 61 | 25 | - | - | - | - |
| I-LOVE-IT 2 | Long   | 60.0 ± 10.0 | 632 | 203 | 596 | 215 | 352 | 145 | 60 | 4 | 87 | 10 | 139 | 520/98 | 126 |
|          | Short     | 60.4 ± 10.2 | 611 | 211 | 554 | 230 | 333 | 156 | 77 | 4 | 84 | 13 | 130 | 527/103 | 122 |
| IVUS-XPL | Long      | 64.9 ± 9.4  | 295 | 457 | 455 | 456 | 165 | 29 | 73 | 14 | - | - | - | - | - |
|          | Short     | 63.9 ± 9.6  | 470 | 249 | 443 | 473 | 171 | 34 | 72 | 22 | - | - | - | - | - |
| NIPPON   | Long      | 67.2 ± 9.9  | 1312 | 635 | 1209 | 1132 | 967 | 159 | 432 | 29 | 48 | 44 | 734 | 330/26 | 196 |
|          | Short     | 67.4 ± 9.6  | 1304 | 619 | 1177 | 1130 | 990 | 201 | 413 | 22 | 41 | 62 | 805 | 296/33 | 198 |
| OPTIMA-C | Long      | 64.4 ± 10.3 | 464 | 203 | 437 | 195 | 282 | 25 | 71 | - | - | - | - | - | - |
|          | Short     | 64.8 ± 10.8 | 478 | 199 | 426 | 204 | 184 | 14 | 59 | - | - | - | - | - | - |
| SMART-DATE | Long   | 62.3 ± 11.5 | 1028 | 379 | 654 | 336 | 536 | 35 | 33 | 26 | 207 | 416/242 | 514 |
|          | Short     | 62.0 ± 11.5 | 1016 | 365 | 669 | 322 | 506 | 30 | 46 | 38 | 256 | 423/246 | 509 |

Abbreviation. ARCTIC; Double Randomization of a Monitoring Adjusted Antiplatelet Treatment Versus a Common Antiplatelet Treatment for DES Implantation, and Interruption Versus Continuation of Double Antiplatelet Therapy; CAPG: coronary artery bypass graft; CVA: Cerebrovascular accident; DAPT: Dual Antiplatelet Therapy; DES LATE: Duration of Clopidogrel Therapy After Drug-Eluting Stent; DM: Diabetes Mellitus; EXCELLENT: The Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting; HTN: Hypertension; I LOVE IT: Evaluate Safety and Effectiveness of the Tivoli DES and the Firebird DES for Treatment of Coronary Revascularization; ISAR-SAFE: Safety And Efficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation and Interruption Versus Continuation of Double Antiplatelet Therapy; PVD: Peripheral vascular disease; PRODIGY: Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia; RISE: Second-Generation Drug-Eluting Stent Implantation Followed by 6- Versus 12-Month Dual Antiplatelet Therapy; SECURITY: Second-Generation Drug-Eluting Stent Implantation Followed by 6- Versus 12-Month Dual Antiplatelet Therapy; STEMI: ST-elevation myocardial infarction.

*number of both previous PCI and CABG.
2.5. Outcomes

The primary outcome was the incidence of major adverse cardiac events (MACE) and incidence of major bleeding between different durations of DAPT. The definitions of MACE and major bleeding events are shown in supplementary material Tables S1.

2.6. Data synthesis

We conducted our network meta-analysis using the Markov Chain Monte Carlo (MCMC) simulation with a little informative prior distributions and likelihood function to derive the posterior distribution of the parameter. We assessed convergence using the Brooks-Gelman-Rubin method as well as the Monte-Carlo error to check if the error was <5% of the standard deviation of the effect estimates and between-study variance. Random effects for the consistency model were reported as odds ratios (ORs) and Bayesian 95% credible intervals (CI). We converted the relative treatment effects to a probability of the best, second best, third best, and so on, as well as the ranking of each treatment. We combined both results to estimate the surface under the cumulative ranking curve (SUCRA). Inconsistency was assessed by comparing the deviance residuals and deviance information criteria (DIC) statistics in fitted consistency and inconsistency models to identify any loops in the treatment network where inconsistency was present. We analyzed our data using NetMetaXL v1.6.1 and WinBUGS software v1.4.3 (Imperial College and Medical Research Council).

3. Results

Sixteen RCTs were included in the analysis with a total of 42,993 patients; 30.1% were treated for 3–6 mo, 46.9% for 12 mo, and 23% for 24–48 mo. The baseline demographics are shown in Table 2. The mean age of patients included in the trials was 63.1 ± 10.1 years. Overall, 31.3% of patients had diabetes and 67.3% had hypertension. The procedural characteristics of each RCT are shown in supplementary material Tables S2. The most stented artery was the left anterior descending (LAD) artery. Both first- and second-generation stents were used, in various proportions, in these RCTs.

There was a significant improvement in MACE in patients treated with DAPT for 24–48 mo following DES when compared with those treated for 3–6 mo (OR 0.75; 95% CI [0.58–0.97]). In contrast, improvement in MACE was not significantly different when those treated with 24–48 mo of DAPT following DES were compared with those treated with 12 mo of DAPT (OR 0.86; 95% CI [0.69–1.08]). Also, there was no significant improvement in MACE in patients treated with 12 months of DAPT when compared with patients treated with DAPT for 3–6 months (OR 0.87, 95% CI [0.72–1.05]), as illustrated in Figure 2.

![Figure 2. Forest plots summarizing the major adverse cardiac events between the competing treatments duration. Random effects model was used to report the odds ratios (ORs) with 95% credible intervals (CIs).](image-url)
The effect of duration of DAPT following DES on the bleeding risk was also studied. Compared with patients treated with 24–48 mo of DAPT following DES, those treated with either 3–6 mo (OR 0.32, 95% CI [0.17–0.54]) or 12 months of DAPT (OR 0.43, 95% CI [0.27–0.63]) experienced lower bleeding risk. On the other hand, there was no significant improvement in risk of major bleeding when 12 months of DAPT was compared with 3–6 months of DAPT (OR 0.75, 95% CI [0.50–1.10]), as illustrated in Figure 3.

4. Discussion

In the present network meta-analysis of 16 RCTs to evaluate the safety and efficacy of various DAPT durations in DES-treated PCI patients, we had several notable findings [12–15,20–31]. First, long-duration DAPT (≥24 mo) reduces the composite ischemic vascular events significantly when compared with short-duration DAPT (3–6 mo). Second, there is a trend of improved composite ischemic vascular events with longer DAPT as 12 mo was better than 3–6 mo and ≥24 mo was better than both 3–6 mo and 12 mo. Third, there is a higher bleeding risk when longer duration DAPT is used, as there was a significant increase in major bleeding with long-duration DAPT (≥24 mo) when compared with shorter duration DAPT (3–6 mo and 12 mo). Thus, our findings support the use of long-duration DAPT in patients with high risk of thrombotic events and short-duration DAPT in high bleeding-risk patients.

Despite the advances in the treatment of coronary artery disease, recurrent stent thromboses remain problematic [32,33]. The introduction of DAPT (aspirin and a P2Y12 receptor antagonist) has mitigated the risk of early and late thrombosis after coronary stent implantation, yet the duration of DAPT remains controversial [34]. Although most of the previously published meta-analyses have supported the use of short-duration DAPT because of the lower associated bleeding risk without an apparent increase in ischemic vascular events, some meta-analyses were consistent with our finding and supported the use of longer durations of DAPT after DES implantation to reduce ischemic vascular events [19,35]. The time-dependent nature of DAPT on risk of ischemic vascular events has also been demonstrated in a previous meta-analysis [36].

Six trials evaluated the efficacy of DAPT when used for more than 12 mo [12,13,23,24,27,31]. All of them showed a lower incidence of composite ischemic events compared to shorter durations of DAPT with the exception of Lee et al and Valgimigli et al, who showed a higher incidence of these events with long DAPT [12,27]. A recently published individual data meta-analysis by Lee et al may explain the unexpected findings in these two studies, however [37]. The majority of deaths in these trials were associated with a higher rate of Type II MI, a condition that is not affected by DAPT,
indicating that many of these deaths may not have been related to a true cardiac event [38]. It should be noted that the DAPT Trial – the largest of these trials – reported a significantly lower incidence of vascular events with long DAPT [13]. Furthermore, a subgroup analysis of patients treated by everolimus-eluting stents – the most commonly used stent – resulted in significant reduction of stent thrombosis and MI [39].

In our study, there was no significant difference in the rate of ischemic events with 12 mo of DAPT, which is the current recommended duration after DES implantation, when compared with using DAPT for 6 mo or less following DES [5]. This result was inconsistent with three of the included trials [21,22,28]. This incongruity could be explained by the inclusion of low-risk patients and short duration of follow-up implemented by these trials. Also, several trials were limited by low event rates, which raise the possibility of bias [22,28]. In contrast, Hahn et al included only patients with acute coronary syndrome (ACS) and showed a lower rate of composite ischemic events in the 12 mo DAPT group [15]. This may highlight the importance of longer duration DAPT in patients with ACS, as they have a higher rate of recurrent ischemic events than patients with stable coronary artery disease [32,33]. More trials with exclusively ACS patients are required, however, before solid conclusions can be made regarding the optimal duration of DAPT after DES implantation in such patients.

In our meta-analysis, the benefit of prolonging DAPT was precluded by a higher risk of bleeding, which was consistent across all of the included trials. Although bleeding risk has been associated with higher mortality, both a recently published analysis by Udell et al and Mauri et al concluded that the risk of fatal bleeding was not significantly higher in a longer duration DAPT arm when compared with a shorter duration DAPT arm [13,16,40]. Furthermore, one study showed a comparable risk of noncardiac death between 6 mo and 12 mo of DAPT, even though the major bleeding risk was higher with longer DAPT [37]. Thus, it remains controversial as to whether or not reported bleeding risk should affect clinical decision-making when it comes to duration of DAPT following DES.

Although our results support longer duration DAPT after DES implantation to reduce risk of ischemic events, it is important to note that there has been a recent influx of new generation DESs, which inherently carry different thrombosis risks, as well as several different combinations of DAPT.

4.1. Limitations

Our analysis has some limitations that should be acknowledged. First, we did not have access to patient-level data. Second, the definition of MACE varied between the clinical trials; however, we could not find any significant heterogeneity in the analysis ($I^2 < 15$). Third, there were inconsistencies in the definition of bleeding events among the included studies. Fourth, the included trials assessed different CAD presentations (stable vs ACS). Finally, clopidogrel was the main thienopyridine used in most of the included trials; therefore, generalizability of the current results to other P2Y12 blockades is limited.

5. Conclusions

In patients who undergo DES implantation, longer durations of DAPT after DES implantation are associated with lower rates of composite ischemic vascular events, especially with durations longer than 24 mo. Longer duration DAPT is associated with a higher rate of bleeding, however.

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No potential conflict of interest was reported by the authors.

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