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Systematic Review/Meta-analysis

Optimal Duration of Dual Antiplatelet Therapy Following Percutaneous Coronary Intervention: An Umbrella Review

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ABSTRACT

Background: The optimal duration of dual antiplatelet therapy (DAPT) after percutaneous coronary intervention with stenting requires consideration of patient characteristics, and decision makers require a comprehensive overview of the evidence.

Methods: We performed an umbrella review of systematic reviews (SRs) of randomized controlled trials of extended DAPT (> 12 months) compared with DAPT for 6 to 12 months after percutaneous coronary intervention with stenting. Outcomes of interest were death, myocardial infarction (MI), stroke, stent thrombosis, major adverse cardiac and cerebrovascular events, bleeding, and urgent revascularization. We aimed to assess the evidence of benefits and harms among clinically important subgroups (eg, elderly patients, those with diabetes, prior MI, acute coronary syndrome). We assessed the quality of the included reviews by use of **A** **M**easurement **T**ool to **A**ssess **S**ystematic **R**eviews (AMSTAR).

Results: Sixteen SRs involving 8 randomized controlled trials were included. Most scored 7 or more points on the AMSTAR checklist. There was no significant difference in outcomes with extended DAPT

RÉSUMÉ

Contexte : Pour déterminer la durée optimale de la bithérapie antiplaquettaire après la pose d'une endoprothèse par intervention coronarienne percutanée, il faut tenir compte des caractéristiques du patient et avoir une bonne vue d'ensemble des données probantes.

Méthodologie : Nous avons examiné l'ensemble des revues systématiques des essais contrôlés avec répartition aléatoire comparant la bithérapie antiplaquettaire prolongée (> 12 mois) et la bithérapie antiplaquettaire d'une durée de 6 à 12 mois après la pose d'une endoprothèse par intervention coronarienne percutanée. Les paramètres d'intérêt étaient le décès, l'infarctus du myocarde (IM), l'accident vasculaire cérébral, la thrombose de l'endoprothèse, les événements vasculaires cérébraux et cardiaques majeurs, l'hémorragie et la nécessité d'une revascularisation d'urgence. Notre objectif était d'évaluer les données à l'appui des bienfaits et des effets nocifs observés dans différents sous-groupes d'importance clinique (p. ex., patients âgés, atteints de diabète, ayant déjà subi un IM ou présentant un syndrome coronarien aigu). Nous avons évalué la qualité des revues incluses dans notre examen à

Dual antiplatelet therapy (DAPT; a P2Y12 inhibitor [eg, clopidogrel, prasugrel, ticagrelor] plus acetylsalicylic acid) is routinely given after percutaneous coronary intervention (PCI) with stenting to prevent stent thrombosis and major adverse cardiovascular (CV) events;[1] however, selecting the optimal duration of DAPT continues to be challenging for practicing physicians and requires balancing the potential benefits and harms for individual patients. Canadian guidelines support an individualized approach to selecting DAPT duration,[2] with different recommendations for patients with acute coronary syndrome (ACS) or non-ACS indications. Similarly, the American College of Cardiology/American Heart Association[1] and the European Society of Cardiology guidelines[3] also recommend tailoring the duration of DAPT based on patient characteristics.

Systematic reviews (SRs) and meta-analyses are generally considered to provide the highest level of evidence to guide evidence-based medicine. Previous SRs have assessed the benefits and harms of extended DAPT after PCI with stenting;[4-14] however, key problems in these SRs include

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compared with 6 months of DAPT in most SRs, with the exception of an increased risk of major bleeding. Compared with 12 months, extended DAPT may reduce the risk of MI and stent thrombosis; however, the findings were not consistent across all reviews. There have been conflicting reports of an increased risk of death with extended DAPT. Few SRs assessed outcomes among patient subgroups.

Conclusions: Extended DAPT may reduce the risk of MI and stent thrombosis but increase the risk of major bleeding and death. Whether the effects of extended DAPT are consistent across patient subgroups is unclear, and future SRs should address this knowledge gap.

l'aide de l'outil AMSTAR (***A Measurement Tool to Assess Systematic Reviews***).

Résultats : Seize revues systématiques portant sur 8 essais contrôlés avec répartition aléatoire ont été incluses dans l'examen. La plupart ont obtenu 7 points ou plus au questionnaire de contrôle de la qualité de l'outil AMSTAR. Aucune différence significative n'a été relevée entre les résultats obtenus sous bithérapie antiplaquettaire prolongée et sous bithérapie antiplaquettaire d'une durée de 6 mois dans la plupart des revues systématiques, sauf en ce qui concerne le risque accru d'hémorragie majeure. Comparativement à un traitement sur une période de 12 mois, la bithérapie antiplaquettaire prolongée peut réduire le risque d'IM et de thrombose de l'endoprothèse; cependant, les constatations des différentes revues ne concordaient pas toujours. Les données rapportées en ce qui concerne le risque accru de décès chez les patients recevant une bithérapie antiplaquettaire prolongée sont contradictoires. Peu de revues systématiques ont évalué les résultats dans différents sous-groupes de patients.

Conclusions : Une bithérapie antiplaquettaire prolongée peut réduire le risque d'IM et de thrombose de l'endoprothèse, mais aussi accroître le risque d'hémorragie majeure et de décès. Nous n'avons pas pu déterminer avec certitude si les effets d'une bithérapie antiplaquettaire prolongée sont les mêmes dans tous les sous-groupes de patients; d'autres revues systématiques s'imposent afin de combler cette lacune dans les connaissances.

grouping together all patients regardless of characteristics, discrepant findings for certain reported outcomes, and a lack of reporting of outcomes among clinically important patient subgroups. Given this uncertainty in the evidence base, we performed an umbrella review to comprehensively evaluate the evidence to support clinical decision-making. Umbrella reviews are ideally situated to synthesize the findings of multiple SRs, highlight contradictory findings, and explore discrepant findings.[15] Specifically, we sought to address the following questions: (1) What are the benefits and harms of extended DAPT beyond 12 months compared with 6 to 12 months after PCI with stenting? (2) Are there specific subgroups of patients for whom the optimal duration of DAPT is different? (3) Is there a rebound effect after withdrawal of DAPT?

Materials and Methods

This review has been registered (PROSPERO no. CRD42016047735) and the protocol has been published.[16] The review was performed following the protocol without deviation; however, here we report data only from the included SRs (ie, not from the randomized controlled trials [RCTs] included within the SRs). Briefly, we performed an umbrella review of the published and grey literature to identify SRs that included RCTs that addressed the benefits or harms of extended DAPT (> 12 months) compared with shorter DAPT (6-12 months). The comparison of less than 6 months with more than 12 months of DAPT was beyond the scope of this review.

Search strategy, study selection, and data extraction

We searched Embase, Ovid MEDLINE, Cochrane Library, and PubMed (2011 to August 13, 2016; the search was updated on May 10, 2018). We also searched grey literature sources (eg, websites of health technology assessment agencies, professional associations) for unpublished reviews. No language restrictions were applied. The search strategy has been published.[16] Titles and abstracts and full-text records were screened in duplicate by 2 independent reviewers (J.E., Z.B., W.L.). Data were extracted by 1 reviewer using piloted and standardized abstraction forms and verified by a second reviewer (J.E., Z.B., W.L.). We extracted only data pertaining to the comparison of 6 to 12 months with longer than 12 months. The quality of the included SRs was assessed by the use of the **A** **M**ea**s**urement **T**ool to **A**ssess Systematic **R**eviews (AMSTAR) checklist.[17]

Outcomes

The primary outcome was death (all-cause mortality, CV, non-CV). Secondary outcomes were myocardial infarction (MI), stroke, stent thrombosis, major adverse cardiac and cerebrovascular events (MACCE), bleeding (major, minor, gastrointestinal), and urgent target vessel revascularization. Bleeding data are reported separately by classification systems (eg, **T**hrombolysis **i**n **MI** [TIMI], **B**leeding **A**cademic **R**esearch **C**onsortium [BARC], **G**lobal **U**se of **S**trategies **t**o **O**pen Occluded Coronary Arteries [GUSTO]) to ensure consistency and clinical relevance; no data are reported for SRs that did not report the classification system or that pooled data across classification systems. Data were extracted from SRs for clinically important subgroups based on patient demographics, clinical, and procedural parameters, including age, sex, smoking status, diabetes, prior MI, history of heart failure, ACS at presentation, vein graft intervention, left main intervention, and lesion complexity, and implanted stent type (drug-eluting stent [DES] or bare-metal stent [BMS]).[16]

Synthesis

Findings from SRs that reported pooled effect estimates were grouped and synthesized using a descriptive approach.

Because the landmark DAPT trial was published in late 2014,[18] data are summarized only from SRs published after the publication of the DAPT trial. The direction of the effect estimates (odds ratio [OR], hazard ratio [HR], relative risk) and confidence intervals (CIs) reported in the original publications were standardized such that the effect estimate reports the risk of an event in the extended DAPT group relative to that in the shorter DAPT group.

Results

Literature search

In total, 1154 records were identified from the literature search (Fig. 1). Of these, 27 records corresponding to 25 unique reviews met our inclusion criteria. Sixteen reviews were published after publication of the DAPT trial[18] and provided outcome data pertaining to short (6-12 months) compared with extended (> 12 months) DAPT (Table 1), forming the evidence base for this umbrella review. The full list of included SRs is available in Supplemental Appendix S1.

Review characteristics

Of the 16 eligible SRs, all included RCTs involving participants who had undergone PCI with a DES (Table 1), whereas 2 RCTs (DAPT,[18] PRODIGY[19]) enrolled participants with either a DES or BMS. Two reviews focused on either second-generation[6] or "newer generation"[14] DES, whereas the remainder included participants with any DES type. Few SRs focused on specific patient populations: 1 review each focused on patients with diabetes mellitus[20] or acute coronary syndrome,[21] and 1 review[11] performed subgroup analyses for patients with or without ACS or aged more or less than 65 years.

Among the SRs, the most recent literature search was performed in March 2017, with the earliest searches performed in November 2014. All included SRs compared DAPT for 6 to 12 months with DAPT for more than 12 months, either as the primary analysis or as a subgroup analysis if additional DAPT durations were considered. Most SRs included a common set of 5 RCTs (DAPT, Optimal Duration of Clopidogrel Therapy With DES to Reduce Late Coronary Arterial Thrombotic Event [DES-LATE], **A**ssessment by a Double **R**andomization of a **C**onventional Antiplatelet Strategy vs a Monitoring-Guided Strategy for Drug-Eluting Stent Implantation and of **T**reatment **I**nterruption vs **C**ontinuation One Year After Stenting [ARCTIC]-Interruption, **Opti**mal **Dual** [OPTIDUAL], Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study [PRODIGY]),[18,19,22-24] which compared DAPT for 6 to 12 months with DAPT for more than 12 months; 1 SR[20] additionally included data from the REAL/ZEST-LATE (pooled analysis of **Real**-World Patients Treated With Drug-Eluting Stent Implantation and **L**ate Coronary **A**rterial **T**hrombotic **E**vents [REAL-LATE] and **Z**otarolimus-**E**luting Stent, **S**irolimus-Eluting Stent, or Pacli**t**axel-Eluting Stent Implantation for Coronary Lesions-**L**ate Coronary **A**rterial **T**hrombotic **E**vents [ZEST-LATE]) trial[25] and/or a trial published in abstract format[26] (Supplemental Appendix S2). Most of the included SRs (75%) scored 7 or more points (of 11 possible points) on the AMSTAR checklist (Supplemental Table S1). Of the 16 reviews, only 1 SR reported having an *a priori* research design[4] and 1 provided a list of both included and excluded studies.[6] Quality of the included RCTs was assessed by all SRs, although 1 SR[8] did not specify the quality assessment tool. Most of the RCTs included in the SRs were judged to be at low risk of bias by the SR authors, although most RCTs were open label.

Among the core set of 5 RCTs,[18,19,22-24] the mean participant age was more than 60 years in each study (Supplemental Table S2). Most participants were male (69% to 82%), and diabetes was common (24% to 38%). There was wide variation in the proportion of patients with ACS: between 0.1% and 34% of patients had ST-segment elevation MI, between 7% and 23% of patients had non−ST-segment elevation MI, and between 9% and 39% of patients had unstable angina.

Summary of outcomes

In the following sections, we describe the findings from the included SRs for all participants as well as for patient subgroups, where data were available. Figure 2 provides an overview of the main findings, highlighting discrepant findings between the SRs. None of the included SRs assessed minor bleeding, gastrointestinal bleeding, or urgent target vessel revascularization. Few SRs reported outcomes among patient subgroups, and none assessed outcomes by sex or among patients with prior MI, heart failure, smoking, complex lesions, unstable angina, peripheral artery disease, vein graft intervention, or left main intervention. No reviews reported outcomes among participants with an implanted BMS.

All-cause death. All 16 SRs[4-14,20,21,27-29] assessed all-cause death with different durations of DAPT (Supplemental Table S3). No significant differences were reported in the risk of all-cause death for extended DAPT compared with DAPT for 6 months (5 SRs[4,6,7,10,12]) or 6-12 months (3 SRs[8,9,14]). The findings were mixed among reviews that compared 12 months with extended DAPT: 7 SRs[4,5,7,10,11,13,27] reported an increased risk of death associated with extended DAPT compared with DAPT for 12 months, whereas 6 SRs reported no significant difference in risk,[6,12,20,21,28,29] including 1 network meta-analysis,[12] which found no significant difference in risk between 12 and 24, 30, or 36 months of DAPT. Two SRs addressed the risk of all-cause death among patient subgroups, reporting no significant difference in the risk of death between 12 month and extended DAPT among participants with diabetes[20] or ACS.[21]

CV death. Fourteen SRs[4-11,13,20,21,27-29] assessed CV death (Supplemental Table S3). No significant differences in the risk of CV death were reported for extended DAPT compared with DAPT for 6 months (4 SRs[4,6,7,10]), 6-12 months (2 SRs[8,9]), or 12 months (12 SRs[4-7,10,11,13,20,21,27-29]). Among patient subgroups, there was no reported difference in the risk of CV death among participants with diabetes (1 SR[20]), with ACS (2 SRs[11,21]), without ACS (1 SR[11]), or among

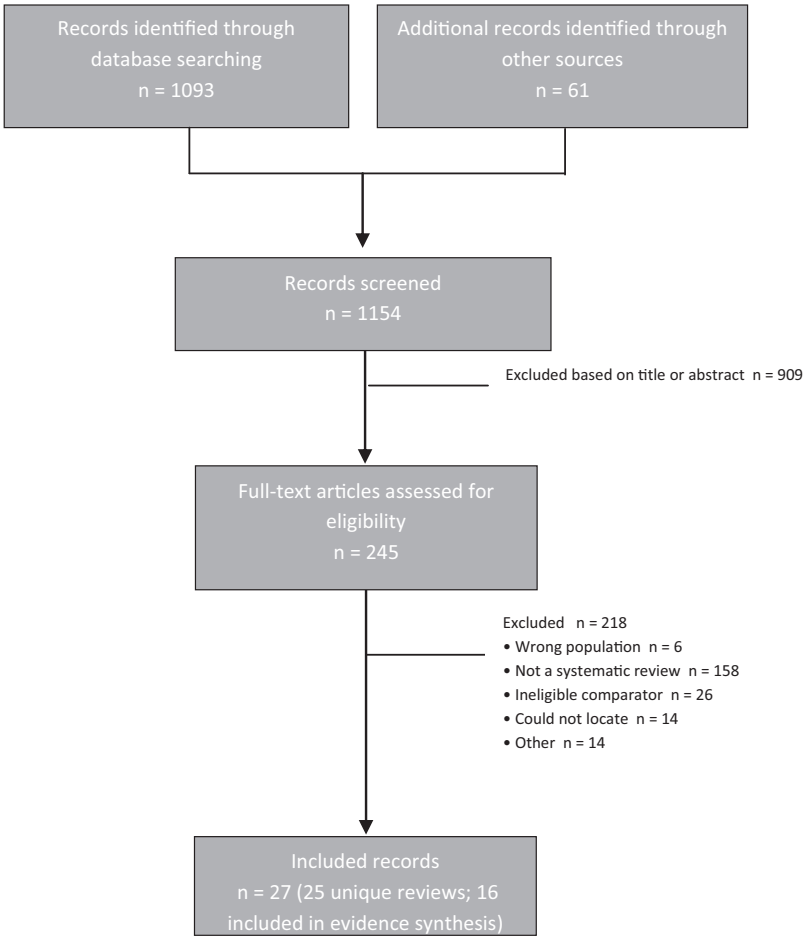


Figure 1. PRISMA diagram showing selection of included systematic reviews.

participants aged more or less than 65 years (1 SR[11]) (Supplemental Tables S3 and S4).

Non-CV death. One SR[10] assessed the risk of non-CV death, finding no significant difference in the risk between extended DAPT and DAPT for 6 months (hazards ratio [HR], 1.11; 95% CI, 0.61, 2.04) (Supplemental Table S3). However, compared with 12 months of DAPT, extended DAPT was associated with a significantly higher risk of non-CV death (HR, 1.89; 95% CI, 1.27, 2.78; 1 SR[10]). No SRs addressed the risk of non-CV death among patient subgroups.

Myocardial infarction. All 16 SRs[4-14,20,21,27-29] assessed MI (Supplemental Table S5). Three SRs[4,6,7] reported no significant difference in the odds of MI between 6 months of DAPT and extended DAPT, and 1 network meta-analysis[12] reported no difference in risk between 24, 30, or 36 months compared with 6 months of DAPT.

Compared with 6 to 12 months of DAPT, extended DAPT beyond 12 months was reported to be associated with a lower risk of MI in 3 SRs (Supplemental Table S5).[8,9,14] Similarly, a lower risk of MI was reported between extended DAPT and 12 months of DAPT (11 SRs[4-7,10,11,13,21,27-29]). One network meta-analysis[12] reported no significant difference in the odds of MI between extended DAPT for 24 vs 30 months, 24 vs 36 months, or 30 vs 36 months.

Among participants with ACS, 1 SR[21] reported a significantly lower risk of MI with extended DAPT,[21] whereas 1 SR[11] reported no significant difference in the risk of MI among those with or without ACS (Supplemental Tables S4 and S5). There was no significant difference in the risk of MI with extended DAPT among participants with diabetes (1 SR[20]) or among those aged more or less than 65 years (1 SR[11]; Supplemental Table S4).

Stroke. Eight SRs[4,5,7,13,20,27-29] assessed the risk of stroke (Supplemental Table S5). No significant differences were reported in the risk of stroke between extended DAPT and DAPT for 6 months (2 SRs[4,7]) or 12 months of DAPT (8 SRs[4,5,7,13,20,27-29]). No SRs assessed the risk of stroke for extended DAPT compared with 6 to 12 months of DAPT. One SR reported no significant difference in the risk of stroke among participants with diabetes.[20]

Stent thrombosis. Stent thrombosis was assessed by 15 SRs[4-14,20,21,27,29] (Supplemental Table S5). No differences were reported in the risk of definite or probable stent

Table 1. Summary of systematic reviews included in the evidence synthesis

Systematic review	Country	Funding source	Search date	Population	DAPT durations of interest compared	AMSTAR score
Ferrante et al., 2017[28]	Italy	NR	March 2016	Patients who underwent PCI with DES	12 vs > 12 mo	8
Huang et al., 2016[20]	China	No funding	June 2016	Patients with diabetes mellitus who received DAPT after PCI with DES	12 vs > 12 mo	7
Bavishi et al., 2017[21]	United States	No funding	March 1, 2017	Patients with acute coronary syndromes undergoing PCI	12 vs > 12 mo	7
Wang et al., 2017[29]	China	NR	May 2016	Patients who underwent PCI with DES or BMS	12 vs > 12 mo	8
Tang et al., 2016[27]	China	Nonpharma	January 4, 2015	Patients with coronary artery disease with an implanted DES	12 vs > 12 mo	7
Fei et al., 2016[4]	China	No funding	January 28, 2016	Patients who underwent PCI with DES	6 vs > 12 mo, 12 vs > 12 mo	8
Palla et al., 2015[5]	United States	NR	February 15, 2015	Patients who underwent PCI with DES	12 vs >12 mo	7
D'Ascenzo et al., 2016[6]	Italy	NR	April 2015	Patients who underwent PCI with second-generation DES	6 vs > 12mo, 12 vs > 12 mo	9
Tsoi et al., 2015[7]	China	NR	November 18, 2014	Patients who underwent PCI with DES	6 to > 12 mo, 12 vs > 12 mo	7
Verdoia et al., 2016[8]	Italy	Pharma	November 2014	Patients who underwent PCI with DES	6-12 vs > 12 mo	6
Cassese et al., 2015[9]	Germany	NR	January 10, 2015	Patients who underwent PCI with DES	6-12 vs > 12 mo	7
Palmerini et al., 2015[10]	United States	No funding	November 20, 2014	Patients who underwent PCI with DES	6 vs > 12 mo, 12 vs > 12 mo	7
Navarese et al., 2015[11]	Germany	Nonpharma	February 16, 2015	Patients who underwent PCI with DES	12 vs > 12 mo	7
Xie et al., 2016[12]	China	Nonpharma	December 31, 2014	Patients who underwent PCI with DES	6 vs >12 mo*	6
Zhang et al., 2015[13]	China	No funding	November 18, 2014	Patients who underwent PCI with DES	12 vs > 12 mo	6
Bittl et al., 2016[14]	United States	NR	NR	Patients who underwent PCI with "newer generation" DES	6-12 vs > 12 mo	5

AMSTAR, **A** **M**ea**s**urement **T**ool to **A**ssess Systematic **R**eviews; BMS, bare-metal stent; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; MI, myocardial infarction; NR, not reported; PCI, percutaneous coronary intervention.

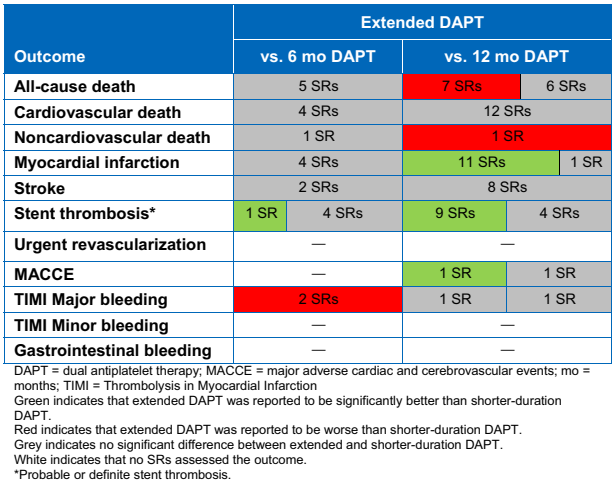
*Network meta-analysis.

thrombosis between 6 months and extended DAPT (3 SRs[4,6,7]). One network meta-analysis[12] reported that extended DAPT for 30 months was associated with a lower risk of definite or probable stent thrombosis compared with 6 months, but no significant differences in risk between 6 months and 24 or 36 months of DAPT. Compared with 6 to 12 months of DAPT, extended DAPT was associated with a lower risk of definite or probable stent thrombosis (3 SRs[8,9,14]). Similarly, extended DAPT was associated with a lower risk of definite or probable stent thrombosis compared with 12 months of DAPT (8 SRs[4,5,7,10,11,13,27,29]). One network meta-analysis[12] reported no significant difference in the risk of definite or probable stent thrombosis between extended DAPT and 24 or 36 months.[12]

Among participants with ACS, there was no reported difference in the risk of stent thrombosis among those with extended DAPT (2 SRs[11,21]); however, 1 SR[11] reported a reduced risk of stent thrombosis among those without ACS (Supplemental Tables S4 and S5). Similarly, the risk of stent thrombosis was reported to be lower among those aged less than, but not more than, 65 years (1 SR[11]; Supplemental Table S4). There was no reported difference in the risk of stent thrombosis with extended DAPT among participants with diabetes[20] (1 SR; Supplemental Table S5).

Definite stent thrombosis was assessed by 3 SRs[11,27,28] (Supplemental Table S5). Compared with 12 months of DAPT, extended DAPT was associated with a lower risk of definite stent thrombosis in 2 SRs[11,27]; however, 1 SR[28] that included 1 additional RCT reported no significant difference in risk. No reviews assessed the risk of definite stent thrombosis with extended DAPT.

MACCE. Three SRs[11,14,28] assessed MACCE (Supplemental Table S5); however, the components of this composite outcome varied among the included RCTs (Supplemental Table S6). Bittl et al.[14] pooled the primary outcome of 6 RCTs, which ranged from a composite outcome including death, MI, and stroke to a composite outcome including death, MI, stent thrombosis, stroke or transient ischemic attack, urgent revascularization, finding a lower risk of MACCE with extended DAPT compared with 6 to 12 months (OR, 0.85; 95% CI, 0.72, 1.00) (Supplemental Table S5). Navarese et al.[11] pooled the primary outcome of 3 RCTs, again with dissimilar components of the composite outcome, similarly reporting a lower risk of MACCE with extended DAPT compared with 12 months (OR, 0.78; 95% CI, 0.67, 0.92). In contrast, Ferrante et al.[28] reported no statistically significant difference in the



DAPT = dual antiplatelet therapy; MACCE = major adverse cardiac and cerebrovascular events; mo = months; TIMI = Thrombolysis in Myocardial Infarction
Green indicates that extended DAPT was reported to be significantly better than shorter-duration DAPT.
Red indicates that extended DAPT was reported to be worse than shorter-duration DAPT.
Grey indicates no significant difference between extended and shorter-duration DAPT.
White indicates that no SRs assessed the outcome.
*Probable or definite stent thrombosis.

Figure 2. Summary of evidence from included systematic reviews of extended DAPT (> 12 months) compared with 6 or 12 months of DAPT. SR, systematic review.

risk of MACCE between extended DAPT and 12 months (OR, 0.81; 95% CI, 0.63, 1.06). Differences in findings between the 3 SRs are likely related to the inclusion of different RCTs and differences in the composite outcome between RCTs.

Bleeding. All included SRs aimed to assess the effect of extended DAPT on bleeding; however, only 5 SRs[4,6,7,11,27] specified the bleeding classification system and pooled studies that used the same classification system. Thus, the evidence base for bleeding comprises 4 SRs[4,6,7,11] that assessed TIMI major bleeding and 1 SR[27] that assessed GUSTO severe bleeding (Supplemental Table S5). The risk of TIMI major bleeding was significantly higher among patients who received extended DAPT compared with 6 months of DAPT (2 SRs[4,7]). Compared with 12 months of DAPT, there was no significant difference in the risk of TIMI major bleeding with extended DAPT (2 SRs[6,11]); however, 1 SR[27] reported a higher risk of GUSTO major bleeding among participants who received extended DAPT.

The risk of gastrointestinal bleeding was not assessed by any of the included SRs.

Urgent revascularization

None of the included SRs assessed urgent target vessel revascularization.

Rebound effect

None of the included SRs assessed outcomes after withdrawal of extended DAPT.

Discussion

This review provides a comprehensive summary of the evidence base of the optimal duration of DAPT after PCI with stenting, including in clinically important subgroups. In this umbrella review, we comprehensively searched for and assessed the quality of previously published SRs. Overall, we found fairly consistent evidence that extended DAPT beyond 12 months after PCI with stenting reduces the risk of MI and stent thrombosis compared with 12 months of DAPT. In general, the magnitude and direction of effect estimates across included SRs was consistent, suggesting that extended DAPT, compared with DAPT for 6 to 12 months, is associated with a 32% to 47% relative risk reduction for MI and a 50% to 60% reduction for definite or probable stent thrombosis. However, these benefits may be accompanied by an almost 3-fold increased risk of major bleeding, as well as all-cause death (30% to 43%) and non-CV death (89%), although these findings were inconsistent across included SRs. Despite the importance of selecting the optimal duration of DAPT based on individual patient characteristics, as highlighted by recent clinical practice guidelines, few SRs have assessed the potential benefits and harms among such groups. As such, this is an important gap in the literature that should be addressed in future SRs to provide additional evidence to support clinical decision-making.

An increased risk of death (all-cause, non-CV) with extended DAPT was reported in some, but not all, SRs that compared extended DAPT with 12 months of DAPT (Fig. 2). Interestingly, this increased risk was not observed when extended DAPT was compared with DAPT for 6 months. This discrepancy may be related to which RCTs were included in each comparison. For example, the DAPT trial, which compared 12 months and 30 months of DAPT, found a borderline significant increase in all-cause death (HR, 1.36; 95% CI, 1.00, 1.85) with extended DAPT; however, this increase was not observed in smaller RCTs that compared 6 months of DAPT with extended DAPT.[19,22] Interestingly, a network meta-analysis involving multiple DAPT durations[12] reported no statistically significant difference in the risk of all-cause death with DAPT for 12 months compared with DAPT for 18-48 months. Although this analysis provides some reassurances, it is unclear whether this finding is consistent across patient subgroups, and the currently available SRs do not address this important clinical issue.

Strengths and limitations

In this study, we performed a comprehensive umbrella review of the published and grey literature to identify all SRs that compared the use of extended DAPT for more than 12 months with DAPT for 6-12 months after PCI. The review followed a published protocol[16] and used systematic approaches. However, there are several limitations that must be acknowledged. Because we performed a review of SRs, the limitations of the included SRs and RCTs carry through to our review. First, limited data were available for most clinically important subgroups, precluding assessment of the effects of extended DAPT based on specific patient characteristics. Future SRs would be strengthened by focusing on such subgroups to inform clinical decision making. Second, early RCTs primarily involved the use of first-generation DES, which may limit generalizability to current clinical practice. Third, direct comparison of findings between SRs is hampered by differences in reporting (eg, OR vs HR) and study methodologies (fixed vs random effects meta-analyses). However, for most outcomes, the point estimates from the individual SRs were relatively consistent, with differences in the width of

the CIs. Fourth, for some outcomes, the finding of no significant difference between DAPT durations may have been owing to low statistical power resulting from a low event count. Fifth, most of the included reviews included a common set of 5 RCTs; as such, there are correlated results across the RCTs, increasing the consistency of the findings. Finally, outcome definitions varied among the RCTs, especially for bleeding and MACCE (Supplemental Table S4). Most of the included SRs pooled these data, despite differences in definitions, hindering the interpretation of their findings. Future SRs would benefit from pooling only composite outcome data that include the same components or use the same bleeding classification system.

Conclusions

Overall, evidence from available SRs supports a beneficial role of extended DAPT in reducing the risk of MI and stent thrombosis beyond 12 months after PCI with stenting. This is contrasted, however, by a potential increase in the risk of death and major bleeding, although previous reviews have reported conflicting findings. Few reviews have assessed the benefits and harms of extended DAPT in clinically important subgroups, and future reviews should address this gap in the literature.

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J.E., S.E.K., M.B., D.Y.F.S., and G.A.W. designed the study. B.S. developed and executed the search strategy. J.E., W.L., and Z.B. selected studies for inclusion and extracted data. J.E., S.E.K., D.Y.F.S., and G.A.W. interpreted the data. J.E. wrote the first draft of the manuscript, which was critically revised for intellectual content by all authors. All authors approved the version submitted for publication and agreed to be accountable for all aspects of the study.

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Supplementary Material

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