CADTH OPTIMAL USE

Dual Antiplatelet Therapy Following Percutaneous Coronary Intervention: Clinical and Economic Impact of Standard versus Extended Duration

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Abbreviations

ACS	Acute coronary syndrome
ASA	Acetylsalicylic acid
BARC	Bleeding Academic Research Consortium
BES	Biolimus-eluting stent
BMS	Bare-metal stent
CI	Confidence interval
DAPT	Dual antiplatelet therapy
DES	Drug-eluting stent
EES	Everolimus-eluting stent
ESC	The European Society of Cardiology
GUSTO	Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries
ICUR	Incremental cost utility ratio
HR	Hazard ratio
LY	Life year
MACCE	Major adverse cardiac and cerebrovascular event
MI	Myocardial infarction
NA	Not applicable
NR	Not reported
NSTEMI	Non-ST-elevation myocardial infarction
PCI	Percutaneous coronary intervention
PES	Paclitaxel-eluting stent
QALY	Quality adjusted life year
RCT	Randomized controlled trial
RR	Relative risk
SD	Standard deviation
SES	Sirolimus-eluting stent
STEMI	ST-elevation myocardial infarction
TIA	Transcient ischemic attack
TIMI	Thrombolysis in myocardial infarction
ZES	Zotarolimus-eluting stent

EXECUTIVE SUMMARY

Rationale and Policy Issues

Dual antiplatelet therapy (DAPT), the combination of a P2Y12 inhibitor (clopidogrel, prasugrel, ticagrelor) with acetylsalicylic acid (ASA), is routinely given following percutaneous coronary intervention (PCI) with stenting with the aim of preventing stent thrombosis and other major adverse cardiac and cerebrovascular events (MACCE). Current guidelines recommend tailoring the length of DAPT depending on individual patient characteristics. Prescribing DAPT for six to 12 months is generally accepted as being standard practice following PCI with stenting. However, given the risk of developing stent thrombosis and de-novo recurrent ischemic events, evidence assessing the impact of extending the duration of DAPT beyond 12 months has been increasing over the last few years. It would appear that some benefits may be derived from such practice, though clinicians also need to consider the associated bleeding risk. It is therefore important for clinicians to identify patients most likely to benefit from extended DAPT therapy as well as rule out those who may derive more harm than good from using such an approach. Also, in some jurisdictions, reimbursement of P2Y12 inhibitors after coronary stenting may be limited to 12 months, particularly reimbursement of prasugrel and ticagrelor. On the other hand, where restrictions have been lifted, in particular for clopidogrel, it may be important to ensure extended therapy will result in optimal outcomes for post-PCI patients, and not result in more harm. Accordingly, given the current uncertainty about the benefits and harms of extended DAPT therapy beyond one year, further elucidation of the available evidence, including assessment of both clinical and economic impact, is required to inform health care decision-makers, policy-makers, clinicians, and patients.

Policy and research questions

There were two policy questions for this project. The first question sought to determine whether it may be cost-effective to extend DAPT duration following PCI with stent insertion. The second question sought to determine whether the choice of P2Y12 inhibitor may impact the cost-effectiveness of extending DAPT.

Policy Question 1: Among patients who underwent PCI with bare metal stent (BMS) or drug eluting stent (DES) insertion, what is the cost-effectiveness of using a P2Y12 inhibitor (i.e., clopidogrel, prasugrel, ticagrelor) in combination with ASA, beyond 12 months?

Policy Question 2: Among patients who underwent PCI with BMS or DES insertion, what is the comparative cost-effectiveness of individual P2Y12 inhibitors (i.e., clopidogrel, prasugrel, ticagrelor) in combination with ASA beyond 12 months, compared with shorter treatment duration (6 to 12 months)?

In order to address these policy questions, four research questions were developed. The first two aim to inform Policy Question 1 whereas the last two aim to inform Policy Question 2:

1) What is the comparative clinical efficacy and safety of shorter duration (6 to 12 months) versus longer duration (i.e. > 12 months) of DAPT following PCI with BMS or DES insertion in:
   - All post-PCI patients;
   - Those with a prior myocardial infarction (MI);
   - Those presenting with acute coronary syndrome (ACS) at time of PCI;
   - Those with diabetes;
   - Different age subgroups;
   - Those who smoke?

2) What is the comparative cost-effectiveness of shorter duration (6 to 12 months) versus longer duration (i.e. > 12 months) of DAPT following PCI with BMS or DES insertion in:
   • All post-PCI patients;
   • Those with a prior MI;
   • Those presenting with ACS at time of PCI;
   • Those with diabetes;
   • Different age subgroups;
   • Those who smoke?

3) Compared with shorter treatment duration (6 to 12 months), what is the comparative clinical efficacy and safety of ASA plus clopidogrel, prasugrel, or ticagrelor, when used for longer (i.e. > 12 months) duration of DAPT following PCI with BMS or DES insertion in:
   • All post-PCI patients;
   • Those with a prior MI;
   • Those presenting with ACS at time of PCI;
   • Those with diabetes;
   • Different age subgroups;
   • Those who smoke?

4) Compared with shorter treatment duration (6 to 12 months), what is the comparative cost-effectiveness of ASA plus clopidogrel, prasugrel, or ticagrelor, when used for longer (i.e. > 12 months) duration of DAPT following PCI with BMS or DES insertion in:
   • All post-PCI patients;
   • Those with a prior MI;
   • Those presenting with ACS at time of PCI;
   • Those with diabetes;
   • Different age subgroups;
   • Those who smoke?

Of note, Research Questions 1 and 3 were answered by the clinical review while Research Questions 2 and 4 were answered by the economic evaluation.

Clinical Review

Methods

We performed a systematic review of published randomized controlled trials (RCTs) that assessed the benefits and harms associated with extending DAPT beyond 12 months. Trials were selected for inclusion if they involved adult participants who received DAPT after stenting for six to 12 months compared with more than 12 months. The primary outcomes of the review are all-cause, cardiovascular, and non-cardiovascular death. Secondary outcomes are MI, stroke, stent thrombosis, urgent target vessel revascularization, MACCE, and bleeding (major, minor, gastrointestinal). Subgroup data were obtained for clinically relevant patient subgroups (prior MI, ACS at presentation, diabetes, smokers, and aged more or less than 75 years). The quality of the included RCTs was evaluated by use of the Cochrane Risk of Bias Tool.

Summary of Evidence

The systematic review identified 13 unique RCTs that met the inclusion criteria. Of these, seven RCTs provided usable data to assess the benefits and harms associated with extending DAPT beyond 12 months following PCI with stenting in clinically important patient subgroups (Research Question 1). Clopidogrel was used by majority of participants in the RCTs, and limited data were available to address Research Question 3 (effect of individual P2Y12 inhibitors).

Research Question 1:
Data from seven RCTs were identified to address this research question. Extending DAPT beyond 12 months was associated with a reduced risk of MI and probable or definite stent thrombosis compared with DAPT for 6-12 months (Table A); these benefits were associated with an increased risk of bleeding, and one large RCT (DAPT) reported a significant increase in non-cardiovascular death among participants who received DAPT for more than 12 months. Results were similar among the subset of participants with an implanted DES. Limited data were available for participants with an implanted BMS. Subgroup data based on clinically important characteristics are summarized below in Table A.

Table A: Summary of Findings: Outcomes

Outcome	> 12 vs. 6–12 months		
	All patients	Patients with BMS	Patients with DES
All-cause death	↔ (N = 25,982)	↔ (N = 2,179)	↔ (N = 24,285)
Cardiovascular death	↔ (N = 21,561)	↔ (N = 492)	↔ (N = 21,561)
Noncardiovascular death	↑[b] **(N = 14,666)**	NA	↑[b] **(N = 14,666)**
Myocardial infarction	↓ **(N = 24,534)**	↔ (N = 2,179)	↓ **(N = 22,847)**
Stroke	↔ (N = 24,534)	↔ (N = 2,179)	↔ (N = 22,847)
Stent thrombosis: Definite	↔ (N = 20,825)	↔ (N = 2,179)	↔ (N = 19,138)
Stent thrombosis: Probable or definite	↓ **(N = 19,489)**	↔ (N = 2,179)	↓ **(N = 17,802)**
Urgent revascularization	↔ (N = 3,136)	NA	↔ (N = 3,136)
MACCE[a]	↔ (N = 21,227)	↔ (N = 2,179)	↔ (N = 19,590)
Gastrointestinal bleeding	↔ (N = 3,773)	NA	↔ (N = 3,773)
TIMI Major bleeding	↔ (N = 9,579)	NA	↔ (N = 9,579)
TIMI Minor bleeding	↔ (N = 3,248)	NA	↔ (N = 3,248)
GUSTO Moderate bleeding	↑ **(N = 13,046)**	↔ (N = 1,687)	↑ **(N = 11,359)**
GUSTO Severe bleeding	↔ (N = 13,046)	↔ (N = 1,687)	↔ (N = 11,359)
GUSTO Moderate or severe bleeding	↑ **(N = 13,046)**	↔ (N = 1,687)	↑ **(N = 11,359)**
BARC Type 3 bleeding	↔ (N = 16,353)	↑ **(N = 1,687)**	↔ (N = 14,666)
BARC Type 5 bleeding	↔ (N = 16,353)	↔ (N = 1,687)	↔ (N = 14,666)
BARC Type 2,3,5 bleeding	↔ (N = 1,398)	↑ **(N = 1,687)**	↔ (N = 11,359)

BARC = Bleeding Academic Research Consortium; DAPT = dual antiplatelet therapy; GUSTO = Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries; MACCE = major adverse cardiac and cerebrovascular events; TIMI = thrombolysis in myocardial infarction; vs. = versus.
Notes:
↓: Risk of an event is lower with extended DAPT compared to shorter-duration DAPT.
↑: Risk of an event is higher with extended DAPT compared to shorter-duration DAPT.
↔: No significant difference between extended and shorter-duration DAPT.
NA: No evidence was available to inform the comparison.
[a] Composite of all-cause death, myocardial infarction, or stroke.
[b] Inconsistent findings across studies. One large RCT (DAPT trial) reported a significant increase in non-cardiovascular death among patients who received extended DAPT, while two smaller RCTs (OPTIDUAL, NIPPON) reported no significant difference between DAPT durations.

Prior myocardial infarction

Compared with DAPT for 6–12 months, extending DAPT for more than 12 months may reduce the risk of MI, probable or definite stent thrombosis, and MACCE but increase the risk of moderate bleeding among participants with a prior MI. An increased in the risk of all-cause death and moderate bleeding was observed in study participants without prior MI. A decreased risk of MI and probable or definite stent thrombosis was also observed in this population (Table B).

Table B: Summary of Findings: Prior Myocardial Infarction

Outcome	> 12 vs. 6–12 months	
	Prior MI	No prior MI
All-cause death	↔ (N = 5,622)	**↑ (N = 6,308)**
Cardiovascular death	↔ (N = 282)	NA
Noncardiovascular death	NA	NA
Myocardial infarction	**↓ (N = 5,622)**	**↓ (N = 6,308)**
Stroke	↔ (N = 5,340)	↔ (N = 6,308)
Stent thrombosis: Definite	NA	NA
Stent thrombosis: Probable or definite	**↓ (N = 5,340)**	**↓ (N = 6,308)**
Urgent revascularization	↔ (N = 282)	NA
MACCE[a]	**↓ (N = 5,340)**	↔ (N = 6,308)
Gastrointestinal bleeding	NA	NA
TIMI Major bleeding	NA	NA
TIMI Minor bleeding	↔ (N = 282)	NA
GUSTO Moderate bleeding	**↑ (N = 5,340)**	**↑ (N = 6,308)**
GUSTO Severe bleeding	↔ (N = 5,340)	↔ (N = 6,308)
GUSTO Moderate or severe bleeding	**↑ (N = 5,340)**	↑ (N = 6,308)
BARC Type 3 bleeding	NA	NA
BARC Type 5 bleeding	NA	NA
BARC Type 2,3,5 bleeding	**↑ (N = 5,340)**	**↑ (N = 6,308)**

BARC = Bleeding Academic Research Consortium; DAPT = dual antiplatelet therapy; GUSTO = Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries; MACCE = major adverse cardiac and cerebrovascular events; MI = myocardial infarction; TIMI = thrombolysis in myocardial infarction; vs. = versus.

Notes:

↓: Risk of an event is lower with extended DAPT compared to shorter-duration DAPT.

↑: Risk of an event is higher with extended DAPT compared to shorter-duration DAPT.

↔: No significant difference between extended and shorter-duration DAPT.

NA: No evidence was available to inform the comparison.

[a] Composite of all-cause death, myocardial infarction, or stroke.

Acute Coronary Syndrome at Time of PCI

Compared with DAPT for 6–12 months, extending DAPT for more than 12 months may reduce the risk of MI and probable or definite stent thrombosis, but increase the risk of bleeding among participants with at ACS at presentation. Limited data were available for participants without ACS (Table C).

Table C: Summary of Findings: Acute Coronary Syndrome

Outcome	> 12 vs. 6–12 months	
	ACS	No ACS
All-cause death	↔ (N = 4,382)	NA
Cardiovascular death	↔ (N = 806)	NA
Noncardiovascular death	NA	NA
Myocardial infarction	**↓ (N = 4,382)**	NA
Stroke	↔ (N = 3,576)	NA
Stent thrombosis: Definite	NA	NA
Stent thrombosis: Probable or definite	**↓ (N = 3,576)**	NA
Urgent revascularization	↔ (N = 806)	NA
MACCE[a]	↔ (N = 6,639)	↔ (N = 1,982)
Gastrointestinal bleeding	NA	NA
TIMI Major bleeding	NA	NA
TIMI Minor bleeding	↔ (N = 806)	NA
GUSTO Moderate bleeding	**↑ (N = 3,576)**	NA
GUSTO Severe bleeding	↔ (N = 3,576)	NA
GUSTO Moderate or severe bleeding	**↑ (N = 3,576)**	NA
BARC Type 3 bleeding	NA	NA
BARC Type 5 bleeding	NA	NA
BARC Type 2,3,5 bleeding	**↑ (N = 3,576)**	NA

ACS = acute coronary syndrome; BARC = Bleeding Academic Research Consortium; DAPT = dual antiplatelet therapy; GUSTO = Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries; MACCE = major adverse cardiac and cerebrovascular events; TIMI = Thrombolysis in Myocardial Infarction; vs. = versus.

Notes:

↓: Risk of an event is lower with extended DAPT compared to shorter-duration DAPT.

↑: Risk of an event is higher with extended DAPT compared to shorter-duration DAPT.

↔: No significant difference between extended and shorter-duration DAPT.

NA: No evidence was available to inform the comparison.

[a] Composite of all-cause death, myocardial infarction, or stroke.

Diabetes

Among those with diabetes, extending DAPT for more than 12 months may increase the risk of bleeding with little benefit (Table D).

Among those without diabetes, extended DAPT may reduce the risk of MI, probable or definite stent thrombosis, and MACCE, with an increased risk of bleeding (Table D).

Table D: Summary of Findings: Diabetes

Outcome	> 12 vs. 6–12 months	
	Diabetes	No diabetes
All-cause death	↔ (N = 4,076)	↔ (N = 8,257)
Cardiovascular death	↔ (N = 4,076)	NA
Noncardiovascular death	↔ (N = 3,391)	NA
Myocardial infarction	↔ (N = 4,076)	**↓ (N = 8,257)**
Stroke	↔ (N = 3,391)	NA
Stent thrombosis: Definite	↔ (N = 3,391)	NA
Stent thrombosis: Probable or definite	↔ (N = 3,391)	**↓ (N = 8,257)**
Urgent revascularization	↔ (N = 685)	NA
MACCE[a]	↔ (N = 3,391)	**↓ (N = 8,257**[b]**)**
Gastrointestinal bleeding	NA	NA
TIMI Major bleeding	NA	NA
TIMI Minor bleeding	↔ (N = 685)	NA
GUSTO Moderate bleeding	↔ (N = 3,391)	NA
GUSTO Severe bleeding	↔ (N = 3,391)	NA
GUSTO Moderate or severe bleeding	↔ (N = 3,391)	**↑ (N = 8,257)**
BARC Type 3 bleeding	**↑ (N = 3,391)**	NA
BARC Type 5 bleeding	↔ (N = 3,391)	NA
BARC Type 2,3,5 bleeding	**↑ (N = 3,391)**	NA

BARC = Bleeding Academic Research Consortium; DAPT = dual antiplatelet therapy; GUSTO = Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries; MACCE = major adverse cardiac and cerebrovascular events; TIMI = Thrombolysis in Myocardial Infarction; vs. = versus.

Notes:

↓: Risk of an event is lower with extended DAPT compared to shorter-duration DAPT.

↑: Risk of an event is higher with extended DAPT compared to shorter-duration DAPT.

↔: No significant difference between extended and shorter-duration DAPT.

NA: No evidence was available to inform the comparison.

[a] Composite of all-cause death, myocardial infarction, or stroke.

Age

Among those aged more than 75 years, extending DAPT for more than 12 months may increase the risk of stroke and bleeding (Table E).

Among those aged less than 75 years, extended DAPT may reduce the risk of MI and probable or definite stent thrombosis though the supporting evidence is inconsistent for both outcomes. Extended DAPT is also associated with an increased risk of bleeding (Table E).

Table E: Summary of Findings: Age

Outcome	> 12 vs. 6–12 months	
	> 75 yr	< 75 yr
All-cause death	↔ (N = 848)	↔ (N = 1,383)
Cardiovascular death	↔ (N = 848)	↔ (N = 1,383)
Noncardiovascular death	NA	NA
Myocardial infarction	↔ (N = 848)	**↓[b] (N = 1,383)**
Stroke	**↑ (N = 587)**	↔ (N = 1,383)
Stent thrombosis: Definite	↔ (N = 587)	↔ (N = 1,383)
Stent thrombosis: Probable or definite	↔ (N = 587)	**↓[c] (N = 1,383)**
Urgent revascularization	↔ (N = 261)	NA
MACCE[a]	↔ (N = 587)	↔ (N = 1,383)
Gastrointestinal bleeding	NA	NA
TIMI Major bleeding	NA	NA
TIMI Minor bleeding	↔ (N = 261)	NA
GUSTO Moderate bleeding	NA	NA
GUSTO Severe bleeding	NA	NA
GUSTO Moderate or severe bleeding	**↑ (N = 587)**	**↑ (N = 1,383)**
BARC Type 3 bleeding	↔ (N = 587)	↔ (N = 1,383)
BARC Type 5 bleeding	NA	NA
BARC Type 2,3,5 bleeding	**↑ (N = 587)**	**↑ (N = 1,383)**

BARC = Bleeding Academic Research Consortium; DAPT = dual antiplatelet therapy; GUSTO = Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries; MACCE = major adverse cardiac and cerebrovascular events; TIMI = Thrombolysis in Myocardial Infarction; vs. = versus; yr = year

Notes:

↓: Risk of an event is lower with extended DAPT compared to shorter-duration DAPT.

↑: Risk of an event is higher with extended DAPT compared to shorter-duration DAPT.

↔: No significant difference between extended and shorter-duration DAPT.

NA: No evidence was available to inform the comparison.

[a] Composite of all-cause death, myocardial infarction, or stroke.

[b] Inconsistent evidence: One large RCT (DAPT trial) reported a significantly lower risk of myocardial infarction among participants aged less than 75 years who received extended DAPT (HR 0.46, 95%CI 0.36 to 0.60), while two smaller RCTs (ITALIC, PRODIGY) reported no significant difference (pooled RR 1.48, 95%CI 0.63 to 3.47).

[c] Inconsistent evidence: One large RCT (DAPT trial) reported a significantly lower risk of definite or probable stent thrombosis among participants aged less than 75 years who received extended DAPT (HR 0.29, 95%CI 0.17 to 0.49), while one smaller RCT (PRODIGY) reported no significant difference (RR 0.72, 95%CI 0.20 to 2.51).

Smoking

Among smokers, extending DAPT for more than 12 months may reduce the risk of myocardial infarction, definite or probable stent thrombosis, and MACCE (Table F).

Among non-smokers, extending DAPT for more than 12 months may reduce the risk of MI and definite or probable stent thrombosis, but increase the risk of bleeding (Table F).

Table F: Summary of Findings: Smoking

Outcome	> 12 vs. 6–12 months	
	Smoking	No smoking
All-cause death	↔ (N = 469)	↔ (N = 1,493)
Cardiovascular death	NA	NA
Noncardiovascular death	NA	NA
Myocardial infarction	↓ **(N = 2,432)**	↓ **(N = 7,426)**
Stroke	NA	NA
Stent thrombosis: Definite	NA	NA
Stent thrombosis: Probable or definite	↓ **(N = 2,432)**	↓ **(N = 7,426)**
Urgent revascularization	NA	NA
MACCE[a]	↓ **(N = 2,901)**	↔ (N = 8,919)
Gastrointestinal bleeding	NA	NA
TIMI Major bleeding	NA	NA
TIMI Minor bleeding	NA	NA
GUSTO Moderate bleeding	NA	NA
GUSTO Severe bleeding	NA	NA
GUSTO Moderate or severe bleeding	↔ (N = 2,432)	↑ **(N = 7,426)**
BARC Type 3 bleeding	NA	NA
BARC Type 5 bleeding	NA	NA
BARC Type 2,3,5 bleeding	↔ (N = 469)	↑ **(N = 1,493)**

BARC = Bleeding Academic Research Consortium; DAPT = dual antiplatelet therapy; GUSTO = Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries; MACCE = major adverse cardiac and cerebrovascular events; TIMI = Thrombolysis in Myocardial Infarction; vs. = versus.
Notes:
↓: Risk of an event is lower with extended DAPT compared to shorter-duration DAPT.
↑: Risk of an event is higher with extended DAPT compared to shorter-duration DAPT.
↔: No significant difference between extended and shorter-duration DAPT.
NA: No evidence was available to inform the comparison.
[a] Composite of all-cause death, myocardial infarction, or stroke.

Research Question 3

The majority (90% to 100%) of recruited participants in the included RCTs were administered clopidogrel. Because the analyses intended to address Research Question 1 primarily involved participants with clopidogrel, no additional analyses were performed to address the effect of this drug in Research Question 3.

Four of the included RCTs involved use of prasugrel by 0.1% to 35% of study participants. Of these, one RCT (DAPT) provided subgroup data for participants who received prasugrel (N = 3456) Among participants who received prasugrel in the DAPT trial, those who received DAPT for more than 12 months (i.e. 1745 of the 3456 participants on prasugrel) were at lower risk of MI, definite or probable stent thrombosis, and MACCE compared with those who received DAPT for 6-12 months, and a higher risk of GUSTO moderate or severe bleeding. No data were available for death, stroke, urgent revascularization, or TIMI bleeding.

Of the included RCTs, ticagrelor was an eligible P2Y12 inhibitor in one RCT (ITALIC); however, no participants in the 24 month DAPT group and 0.1% of participants in the 6 month DAPT group received ticagrelor. As such, there were insufficient data available to assess the benefits and harms of extended DAPT involving ticagrelor. One large RCT (PEGASUS-TIMI 54) was identified during the review which involved randomization of participants with a prior MI to ticagrelor but it did not meet the eligibility criteria. The main reasons for excluding this trial were: i) not all included patients had undergone PCI before randomization (main inclusion criteria was prior history of MI), ii) uncertainty about the proportion of participants who received a P2Y12 inhibitor prior to randomization; ii) the duration of potential DAPT

before randomization which was longer than the eligibility criteria for the present review. However, because the PEGASUS-TIMI 54 trial represents the only identified RCT to assess the benefits and harms of long-term ticagrelor use, the findings from this RCT are briefly discussed in section 5.1.9 and summarized in Appendix 12.

Economic Analysis

Methods

A cost-utility analysis using a two-phase Markov cohort model was conducted to address the health economic research questions. The first phase of the model (extended DAPT phase) was built to reflect the results of the meta-analysis and the endpoints from the studies, i.e., all-cause mortality, non-fatal MI, non-fatal stroke, probable or definite stent thrombosis, urgent revascularization, and bleeding. The cohort received ASA or extended DAPT for a number of monthly cycles reflective of the treatment duration of the various studies included in the meta-analysis (i.e., 12 to 36 months beyond the initial six to 12 months of DAPT). Once the cohort completed the extended DAPT phase, they moved into the second phase of the model (post-extended DAPT phase) which reflected the rest of their life, i.e., up to 100 years of age. In the post-extended DAPT phase, additional health states were included to reflect the possibility of having subsequent cardio-vascular events (e.g., stroke or second MI in an MI patient, MI or second stroke in stroke patients). Published literature supplemented results from our meta-analysis for the post-extended DAPT phase of the model. A lifetime time horizon was taken to capture long-term consequences. Costs, life-years (LYs) and quality-adjusted life years (QALYs) were discounted at 1.5% per annum (0% and 3% in sensitivity analyses). In order to complement the base case analysis, a number of additional sensitivity and exploratory analyses were conducted.

Summary of Findings

In view of the limited clinical data available, economic analyses to answer Research Question 4 could not be performed. The economic evaluation therefore focused on Research Question 2.

According to our base case, extended DAPT was dominant (i.e., more effective and less costly) compared with the six to 12 months DAPT strategy. Both the lifetime incremental benefit, (0.0154 QALYs) and savings ($908) were small. The incremental benefits associated with extended DAPT came largely (98.0%) from the lifetime analysis. When the analysis was limited to the duration of the trials included in the meta-analysis (i.e., average of 19 months beyond the initial 6 to 12 month-DAPT), the incremental benefit of extended DAPT was only 0.0003 QALYs with incremental costs of $957, resulting in an incremental cost-utility ratio (ICUR) of $545,805 per QALY. Uncertainty exists regarding the impact of extended DAPT beyond the duration of studies included in the meta-analysis (i.e., 3 to 5 years). The benefits of extended DAPT once treatment is stopped are not known. Furthermore, several assumptions were required (such as in some instances using data from non-PCI patients) to inform the risk of events in the lifetime analysis.

Sensitivity analyses were performed to address the uncertainty in the post extended DAPT phase of the model as well as the uncertainty related to some inputs (Table 1). In most sensitivity analyses, extended DAPT remained dominant, i.e., more effective and less costly. However, in four scenarios, the ICUR was above $25,000 per QALY. This was observed when ticagrelor was assumed to be the sole P2Y12 inhibitor used in the DAPT regimen, when the analysis was performed on a shorter time horizon (i.e., 19 months beyond the initial 6 to 12 month DAPT), and when using efficacy and safety from studies with an extended DAPT duration of 24 to 30 and 36 to 48 months.

Analyses conducted in patient subgroups should only be considered as exploratory as data to inform these analyses were obtained from few studies (one or two) and required additional assumptions to be made (Table 1). These exploratory analyses indicate that extended DAPT is dominant (i.e., more effective and less costly) in patients with a prior MI and those presenting with an ACS. In patients below 75 years old, the ICUR was $37,269. However, extended DAPT is not the preferred option in patients with diabetes and those above 75 years old as it is less effective and more costly.

Table 1: Key results of the economic analysis

Scenario	6 to 12 month-DAPT		Extended DAPT		Incremental (vs ExtendedDAPT)		
	Costs	QALY	Costs	QALY	ΔCosts	ΔQALY	ICUR
Base case	$42,213	13.63	$41,306	13.65	-$908	0.0154	Extended DAPT dominant
Alternative proportion for anti-platelet agents							
a) 100% clopidogrel	$42,173	13.64	$41,099	13.65	-$1,074	0.0151	Extended DAPT dominant
b) 100% prasugrel	$42,126	13.63	$41,955	13.65	-$171	0.0151	Extended DAPT dominant
c) 100% ticagrelor	$42,263	13.65	$42,745	13.66	$481	0.0150	$32,092
Shorter time horizon (19 months)	$796	1.24	$957	1.24	$161	0.0003	$545,805
DAPT duration in control: 6 months	$30,229	14.05	$30,241	14.08	$254	0.0257	$448
DAPT duration in control: 12 months	$46,104	13.50	$44,564	13.52	-$1,540	0.0161	Extended DAPT dominant
Extended DAPT duration: 18 months	$29,221	14.12	$29,058	14.22	-$162	0.1049	Extended DAPT dominant
Extended DAPT duration: 24 to 30 months	$48,533	13.43	$47,376	13.43	-$1,157	-0.0046	$253,873
Extended DAPT duration: 36 to 48 months	$31,866	14.00	$31,280	14.00	-$586	-0.0077	$75,641
Rebound effect							
a) Maximal rebound at 3 months	$42,274	13.65	$41,701	13.65	-$573	0.0082	Extended DAPT dominant
b) Rates reaching control rates at 6 months	$42,248	13.64	$42,136	13.64	-$113	-0.0067	$16,846
Prior MI	$60,090	12.93	$57,597	12.99	-$2,494	0.0577	Extended DAPT dominant
No prior MI	$49,232	13.48	$47,926	13.42	-$1,307	-0.0578	6 to 12 month-DAPT dominant
ACS	$52,803	13.19	$50,737	13.25	-$2,066	0.0683	Extended DAPT dominant
Diabetes	$54,445	13.14	$54,274	13.08	-$171	-0.0631	6 to 12 month-DAPT dominant
No diabetes	$48,552	13.42	$46,959	13.44	-$1,594	0.0167	Extended DAPT dominant
Above 75 years old	$10,199	6.50	$15,056	6.46	$4,858	-0.0391	6 to 12 month-DAPT dominant
Below 75 years old	$34,292	14.00	$38,300	14.11	$4,008	0.1075	$37,269

QALY: quality adjusted life year; ΔCosts: incremental costs; ΔQALY: incremental QALY; DAPT: dual anti-platelet therapy

Discussion

For the clinical review, there are a number of key limitations; these are:

- Limited data were available for clinically important subgroups included in this review; accordingly these results are associated with uncertainty. Interpretation of results from subgroup analyses should therefore be made with caution.
- The majority of participants in the included RCTs received clopidogrel, with limited data available for prasugrel and none for ticagrelor.
- There were important differences in the inclusion criteria among the RCTs, and some high-risk participants may have been excluded.
- Earlier RCTs involved participants who had received first-generation DES's, which may limit generalizability to current clinical practice.
- The timing of the randomization of participants varied between RCTs, with some participants being randomized within the first 30 days after stenting, while other trials randomized participants who completed six to 12 months of DAPT with no adverse events. This may have excluded some high-risk participants who may have obtained a larger benefit from extended DAPT.
- Outcome definitions varied among the included RCTs, especially for MACCE and major bleeding. To increase homogeneity, we analyzed data separately for different bleeding classification systems and MACCE definitions.

Overall, the clinical review indicates that using DAPT beyond 12 months after PCI is mainly beneficial in reducing MI and probable or definite stent thrombosis. This strategy is however also associated with increased bleeding risk. These are important considerations for clinicians in particular the need to identify which patients are at higher risk for bleeding. Clinicians may also consider other factors in determining which patients would benefit most from extended DAPT, e.g. age, presence of diabetes, smoking status, previous MI.

As the economic analysis used the results of our meta-analysis, the identified limitations to the meta-analysis also apply to the economic analysis. The fact that studies varied in DAPT treatment duration both for the control arm and the extended DAPT arm is another limitation. This is compounded by the lack of evidence on the long-term (i.e., beyond the 3 to 5 years study duration) impact of extended DAPT which required assumptions to be made on the risk of events such as death post-MI or stroke or secondary MI or stroke in the post extended DAPT phase of the model. Although most sensitivity analyses using a lifetime horizon resulted in similar conclusions (i.e., extended DAPT is more effective and less costly than a six to 12 month-DAPT strategy), the ICUR of extended DAPT is $545,805 when the analysis is limited to the duration of the trials included in the meta-analysis. All results from the subgroup analyses should be considered as exploratory only in light of the limited data available to inform the analyses.

Conclusion and Implications for Decision-Making

Overall, extended DAPT beyond 12 months after PCI was predominantly beneficial in reducing MI and probable or definite stent thrombosis; however, this benefit was accompanied by increased risk of bleeding. Given most study participants received clopidogrel, these findings mainly apply to clopidogrel and ASA based DAPT regimens. Similar results were however found for participants using prasugrel. Indeed, among participants who received this P2Y12 inhibitor, DAPT for > 12 months was associated with a lower risk of MI, definite or probable stent thrombosis and MACCE, but higher risk of moderate or severe bleeding, compared with those who received DAPT for six to 12 months. We were unable to compare extended DAPT using ticagrelor versus standard ticagrelor-based DAPT in post-PCI patients due to lack of data. Of note, an increased risk of death was observed among participants without prior MI and the increased risk of stroke among those aged more than 75 years who received extended clopidogrel-based DAPT. In general, from a clinical perspective, patients with prior MI, those with ACS at presentation, no diabetes, or aged less than 75 years may derive the most benefit from extended DAPT, provided bleeding risks are also accounted for when deciding to extend DAPT duration.

From an economic perspective, extending DAPT beyond the initial six to 12 months was more effective and less costly than using ASA only. Exploratory analyses suggest that extended DAPT might be more effective and less costly, and hence preferred, in patients who had a prior MI and those presenting with an ACS. However, it may be less effective and more costly, and hence not preferred, in patients with diabetes and patients above 75 years old. As such, our economic findings are in line with our clinical findings and call for careful selection of patients that may benefit most from extended DAPT in order to ensure extending DAPT beyond 12 months leads to improved clinical and economic outcomes.

1 RATIONALE AND POLICY ISSUES

1.1 Background and Rationale

Dual antiplatelet therapy (DAPT; combination of a P2Y12 inhibitor [clopidogrel, prasugrel, or ticagrelor] with acetylsalicylic acid [ASA]) is generally given for 6 to 12 months following percutaneous coronary intervention (PCI) with stenting, with the aim of preventing stent thrombosis and major adverse cardiac and cerebrovascular events (MACCE). However, debate is ongoing about the optimal duration of DAPT; importantly, patient characteristics may be an important factor in duration decisions.[1] In some settings, DAPT for less than six months may be appropriate (e.g., patients with high risk of bleeding), while other patients may derive greater benefit from extended DAPT (e.g., high risk of stent thrombosis and low risk of bleeding).[2] Previous reviews have reported an increased risk of death among patients who received DAPT for more than 12 months following PCI with stenting,[3,4] but whether this risk is consistent across all patient subgroups is unclear.

Current guidelines recommend tailoring the length of DAPT depending on patient characteristics. The American College of Cardiology/American Heart Association (ACC/AHA)[2] guidelines recommend DAPT for 6 months following PCI for patients with stable coronary artery disease and for 12 months in patients with acute coronary syndrome (ACS), with the consideration of extended DAPT beyond 12 months if potential thrombotic risk is high and bleeding risk is deemed low. Particularly, the use of the DAPT score as a potential means of identifying high-risk patients was emphasized. Similarly, the European Society of Cardiology (ESC) updated guidelines[5] in 2017 also supported a 1-year minimum duration of DAPT for patients with ACS. Recent Canadian guidelines also support an individualized approach to selecting DAPT duration,[6] with different recommendations for patients with ACS or non-ACS indications at the time of PCI.

Previous systematic reviews have attempted to determine the optimal duration of DAPT;[3,4,7-15] however, there is a paucity of data on the impact of specific patient characteristics or type of P2Y12 inhibitor on the effect estimate. One review[4] reported that extending DAPT beyond 12 months reduced the risk of stent thrombosis in patients without, but not with, ACS; however, no significant differences were reported in the risk of cardiovascular death or myocardial infarction (MI). A recent network meta-analysis (NMA) found that, among patients randomized to ticagrelor, prasugrel, or clopidogrel, the risk of major adverse cardiac events and MI were lower with both ticagrelor and prasugrel compared with clopidogrel.[16] Shah and colleagues[16] reported a reduced risk of all-cause and cardiovascular death among patients randomized to ticagrelor compared with clopidogrel. However, whether these results are consistent at all durations of DAPT is unknown.

To make appropriate decisions, clinicians require a transparent and comprehensive review of the evidence to evaluate the potential benefits and harms associated with extending DAPT beyond 12 months after stenting to potentially personalize therapy and reach best patient outcomes; such information may also inform P2Y12 inhibitor reimbursement policies by insurers because such policies may be limited to 12 months, in particular in the public sector. On the other hand, when no limit of reimbursement prevails for P2Y12 inhibitors, it is still important to ensure extended DAPT will lead to optimal outcomes for patients. In this study, we evaluated the comparative clinical effectiveness of different DAPT durations by performing a comprehensive systematic review to assess the benefits and harms associated with extending DAPT beyond 12 months following PCI with stenting in all participants, as well as in clinically relevant patient subgroups, including age, history of MI, ACS at presentation, diabetes, and smoking status. We also aimed to assess the impact of individual P2Y12 inhibitors on the benefits and harms of extended DAPT. The patient subgroups were selected based on the clinical components of the DAPT Score[17] combined with consideration of findings from a recent clinical review[18] which found different effects between shorter and longer DAPT duration for some subgroups. The results of the systematic review were used to inform a de novo cost-utility analysis examining the cost-effectiveness of extended DAPT from the perspective of a Canadian public health care payer.

1.2 Patient Group Input Summary

At the onset of this project, late winter 2018, the list of studies proposed for inclusion in the clinical review was posted for feedback by stakeholders; patient groups were also invited to provide feedback. No feedback was received from patient groups at that time.

1.3 Objectives

The objective of this project was to evaluate the clinical benefits and harms, as well as the cost-effectiveness, of extended DAPT beyond 12 months in clinically relevant subgroups of patients who recently underwent PCI with stenting.

2 POLICY QUESTIONS

There were two policy questions for this project. The first question sought to determine whether it may be cost-effective to extend DAPT duration following PCI with stent insertion. The second question sought to determine whether the choice of P2Y12 inhibitor may impact the cost-effectiveness of extending DAPT.

Policy Question 1: Among patients who underwent PCI with bare metal stent (BMS) or drug eluting stent (DES) insertion, what is the cost-effectiveness of using a P2Y12 inhibitor (i.e., clopidogrel, prasugrel, ticagrelor) in combination with ASA, beyond 12 months?

Policy Question 2: Among patients who underwent PCI with BMS or DES insertion, what is the comparative cost-effectiveness of individual P2Y12 inhibitors (i.e., clopidogrel, prasugrel, ticagrelor) in combination with ASA beyond 12 months, compared with shorter treatment duration (6 to 12 months)?

3 RESEARCH QUESTIONS

There were four research questions for this project. The first two aim to inform Policy Question 1 whereas the last two aim to inform Policy Question 2. Also, research questions 1 and 3 were answered in the clinical review whereas research questions 2 and 4 were answered in the economic evaluation of this report:

1) What is the comparative clinical efficacy and safety of shorter duration (6 to 12 months) versus longer duration (i.e. > 12 months) of DAPT following PCI with BMS or DES insertion in:
   - All post-PCI patients;
   - Those with a prior MI;
   - Those presenting with ACS at time of PCI;
   - Those with diabetes;
   - Different age subgroups;
   - Those who smoke?

2) What is the comparative cost-effectiveness of shorter duration (6 to 12 months) versus longer duration (i.e. > 12 months) of DAPT following PCI with BMS or DES insertion in:
   - All post-PCI patients;
   - Those with a prior MI;
   - Those presenting with ACS at time of PCI;
   - Those with diabetes;
   - Different age subgroups;
   - Those who smoke?

3) Compared with shorter treatment duration (6 to 12 months), what is the comparative clinical efficacy and safety of ASA plus clopidogrel, prasugrel, or ticagrelor, when used for longer (i.e. > 12 months) duration of DAPT following PCI with BMS or DES insertion in:
   • All post-PCI patients;
   • Those with a prior MI;
   • Those presenting with ACS at time of PCI;
   • Those with diabetes;
   • Different age subgroups;
   • Those who smoke?

4) Compared with shorter treatment duration (6 to 12 months), what is the comparative cost-effectiveness of ASA plus clopidogrel, prasugrel, or ticagrelor, when used for longer (i.e. > 12 months) duration of DAPT following PCI with BMS or DES insertion in:
   • All post-PCI patients;
   • Those with a prior MI;
   • Those presenting with ACS at time of PCI;
   • Those with diabetes;
   • Different age subgroups;
   • Those who smoke?

4 METHODS - CLINICAL

The protocol for the clinical review was developed a priori and was registered in PROSPERO (No. CRD42018082587). The protocol and review follows the methods of the Cochrane Handbook for Systematic Reviews for Interventions and the PRISMA checklist for systematic reviews.[19]

4.1 Clinical Evaluation

4.1.1 Literature Search Methods

The literature search was performed by an information specialist using a peer-reviewed search strategy Appendix 1.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946 to the present, including epub ahead of print, in-process records & daily updates) via Ovid; Embase (1974 to the present) via Ovid; The Cochrane Library via Wiley; and PubMed. The search strategy included both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were dual anti-platelet therapy (DAPT) [Intervention] and patients requiring percutaneous coronary intervention (PCI) or stents [Population].

Methodological filters were applied to limit retrieval to randomized controlled trials (RCTs). Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or language. Conference abstracts and opinion pieces were excluded.

Regular alerts were run until project completion; only citations retrieved before January 2, 2018 were incorporated into the analysis. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matter), i.e., ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform (ICTRP) search portal.

4.1.2 Selection Criteria and Methods

Studies were selected for inclusion that met the population, intervention, comparator, and study design criteria. Studies were not included or excluded on the basis of reported outcomes.

Table 1: Selection Criteria

Inclusion criteria	
Population(s)	Adult patients who have undergone PCI with any type of stent and who are receiving DAPT.
Intervention(s)	DAPT following PCI with stenting for an extended duration (more than 12 months). DAPT may involve any type of P2Y12 inhibitor (clopidogrel, prasugrel, ticagrelor) in combination with ASA.
Comparator(s)	DAPT for 6 to 12 months. DAPT may involve any type of P2Y12 inhibitor (clopidogrel, prasugrel, ticagrelor) in combination with ASA.
Outcome(s)*	Primary outcome: death (cardiovascular, all-cause, noncardiovascular). Secondary outcomes: bleeding (major, minor, gastrointestinal), urgent target vessel revascularization, major adverse cardiac and cerebrovascular events, myocardial infarction, stroke, and stent thrombosis.
Study Design(s)	Randomized controlled trials.

Note: ASA = acetylsalicylic acid, DAPT = dual anti-platelet therapy, PCI = percutaneous coronary intervention.
*Studies were not selected for inclusion based on reported outcomes.

4.1.2.1.1 Population and subgroups

The population of interest is adult patients (aged ≥ 18 yr) who have undergone PCI with any type of stent and who are receiving DAPT. Patients receiving DAPT in the absence of stenting are beyond the scope of this review, and studies involving less than 85% of patients who underwent stent implantation were excluded, unless data were reported separately for patients who underwent stenting.

The subgroups of interest were based on clinically important patient characteristics: patients with a prior MI, those presenting with ACS, those with diabetes, those who smoke, and those in different age subgroups. Age subgroups were limited to patients aged more or less than 75 years. Where available, diabetes was dichotomized as Type 1 or Type 2 diabetes.

4.1.2.1.2 Intervention and comparators

***Intervention*:** DAPT following PCI with stenting for an extended duration (> 12 months). DAPT may involve any type or dose of P2Y12 inhibitor (clopidogrel, prasugrel, ticagrelor) in combination with ASA at any dose.

Comparators: DAPT (involving combining a P2Y12 inhibitor [clopidogrel, prasugrel, or ticagrelor] with ASA at any dose) for 6 to 12 months. Other DAPT regimens or durations are beyond the scope of this review.

4.1.2.1.3 Outcomes definition

The primary outcome of interest is death (all-cause, cardiovascular, non-cardiovascular).

The secondary outcomes are urgent target vessel revascularization, MACCE, MI, stroke, stent thrombosis, as well as major, minor and gastrointestinal bleeding, as defined by the individual study protocols and/or publications. A range of MACCE and bleeding classifications and definitions were expected and encountered. Data for MACCE and bleeding outcomes were extracted based on the definitions provided by the study authors; however, data were pooled for MACCE when the components of the composite outcome were deemed sufficiently similar, and data for bleeds were analyzed separately by classification type (e.g., TIMI [Thrombolysis in Myocardial Infarction], BARC [Bleeding Academic

Research Consortium], GUSTO [Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries]). Studies were not included or excluded on the basis of reported outcomes.

Data from studies that included events that occurred during the early DAPT period (0–6 months after PCI) were not pooled with data from studies that reported outcome data from the period starting six to 12 months after PCI.

4.1.2.1.4 Study designs

Randomized controlled studies that meet the above population, intervention and comparator criteria were eligible for inclusion.

4.1.2.1.5 Study selection process

Two independent reviewers applied the eligibility criteria to each title and abstract identified in the literature search. All records deemed potentially relevant by at least one reviewer were obtained in full-text format. The eligibility criteria were applied to the full-text records by both reviewers independently, and a final decision about eligibility was made. Conflicts were resolved by discussion. The reviewers were not blinded to study authors or centre of publication prior to study selection. Study screening and assessment of eligibility was facilitated and standardized through the use of DistillerSR (Evidence Partners).

4.1.3 Quality assessment

We applied The Cochrane Collaboration's Risk of Bias tool (ROB v. 2.0)[20] to each of the included RCTs that reported at least one outcome of interest. The ROB tool addresses six specific domains; sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and "other issues."

Each domain includes one or more specific entries in an ROB table, and a form was created in line with the Cochrane Collaboration's ROB template. The first part of the form involves describing what was reported to have happened in the study; and the second part involves assigning a judgment relating to the ROB for that entry by answering a pre-specified question about the adequacy of the study in relation to the entry, including a judgment of "LOW", "HIGH," or "UNCLEAR" risk of bias.

For each unique RCT, we assessed the quality of the original primary publication with additional details sought from supporting literature (e.g., published protocol, ClinicalTrials.gov records) if necessary. Assessments were performed by one reviewer, and verified by a second reviewer. Disagreements were resolved by consensus.

Publication bias was assessed by visual inspection of funnel plots for outcomes that involved data from more than 10 studies.[21]

4.1.4 Data extraction

Data were extracted by one reviewer by use of piloted and standardized data abstraction forms, and the extracted data were checked for accuracy by a second reviewer. Any disagreements were resolved by consensus.

The original, primary publication for each included RCT was used for data extraction, with supplementary data obtained from companion reports and ClinicalTrials.gov records where necessary to address the research questions. In situations where multiple publications for a unique RCT were available (e.g., supplemental online appendices, companion publications of specific outcomes or populations from the original study), we extracted the most recently adjudicated data for each outcome, with preference given to published records.

Data extraction included: 1) characteristics of studies, including author, year, study design, country of study; 2) key baseline participant characteristics (age, sex, smoking status, diabetes, prior MI, presence of ACS at presentation, history of heart failure; 2) interventions studied, including duration, type of P2Y12 inhibitor; and 3) data related to the outcomes of interest.

If included studies reported multiple time points for outcome assessment, we extracted the event counts for the longest period reported for which the original randomization schedule/allocation was preserved. Because the timing of randomization was variable across studies, we sought to standardize the data by extracting event counts for the treatment period starting six months after randomization, where available.

For all outcomes, we extracted the total number of events during the treatment period and/or the total number of participants who experienced at least one event during that same time period. Because most studies reported the number of people who experienced an event, this formed the basis for the analysis. If the number of events was reported, but not the number of people who experienced an event, we assumed that each person experienced only one event such that the number of events and the number of people with an event were equivalent.

As well as data for all patients, we extracted data separately for clinically important subgroups (prior MI, ACS at presentation, diabetes, smoking, age group). Smoking status may include current, former or never, and the groups for analysis were be based on the reported data. Where available, data were extracted separately for type of P2Y12 inhibitor (clopidogrel, prasugrel, ticagrelor) to address *Research Question 3.*

4.1.5 Data Analysis and Synthesis

A descriptive summary of study selection, quality assessment, and study and patient characteristics is presented for each included RCT that reported at least one outcome of interest.

Data for all participants, as well as for a priori defined subgroups, was analyzed by random-effects pair-wise meta-analysis by use of RevMan (v.5.3; Cochrane Collaboration). The relative risk (RR) and 95% confidence intervals (CIs) for each outcome were determined (i.e., >12 months of DAPT versus. 6–12 months of DAPT). The number of participants randomized to each group was used as the denominator for all analyses.

We assessed clinical heterogeneity by examining the participant characteristics of the included studies, and methodological heterogeneity by assessing the study design characteristics. Statistical heterogeneity was assessed by use of the I^2 statistic, with I^2 values above 75% considered to represent substantial heterogeneity; pooled data are not reported above this threshold. If data are insufficient for meta-analyses or if high heterogeneity was detected, descriptive summaries are presented.

Bayesian NMAs were planned to address Research Question 3 (effect of individual P2Y12 inhibitors at different durations of DAPT); however, insufficient data for NMA were available.

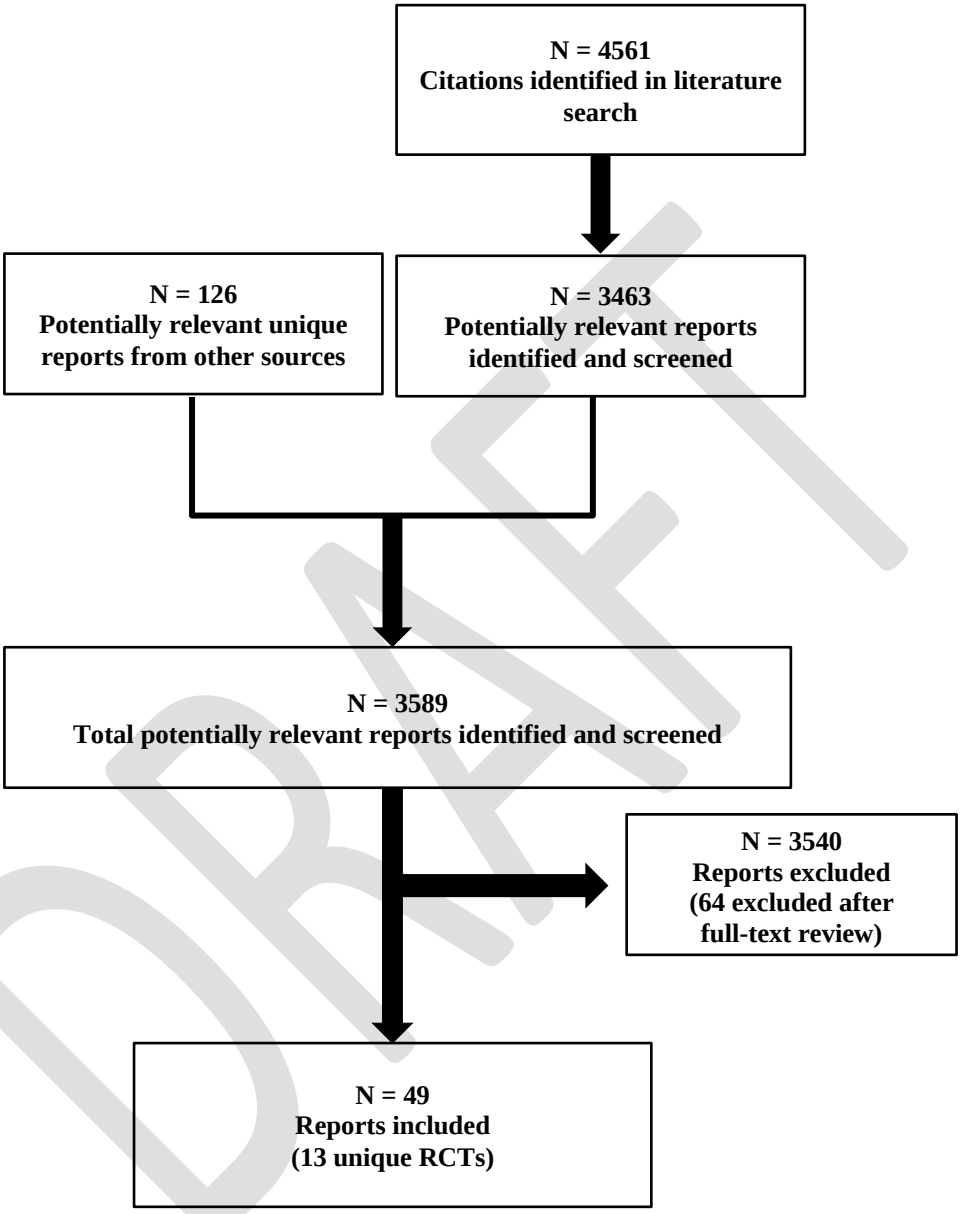
In the following sections, the term “significant” is used to express statistical significance; otherwise, “clinical importance” is used.

5 RESULTS OF CLINICAL EVALUATION

5.1 Selection of Primary Studies

The initial literature search returned 4561 records (Figure 1), with 3463 records remaining after removal of duplicates. An additional 126 unique citations were identified through grey literature searching. Of the 3589 records screened based on titles or abstracts, 118 records were considered potentially relevant; the full text of 5 records could not be located (Appendix 3), and 113 records were examined in full-text format. After full-text review, 49 records corresponding to 13 unique RCTs[22-34] were included. The full list of included and excluded records is available in Appendix 2 and Appendix 3.

Figure 1: PRISMA Flowchart of Selected Reports



The literature search was updated on February 1, 2018; no additional RCTs that met the eligibility criteria were identified.

5.2 Study Characteristics

In total, 13 unique RCTs were included. Of these, no data were reported for five RCTs[22,26,28,29,33]; thus, the evidence base for this review is formed by eight RCTs.[23-25,27,30-32,34] Of the RCTs that did not report data, one was a protocol,[26] while four RCTs were available only as ClinicalTrials.gov registrations.[22,28,29,33]

Of the studies registered in ClinicalTrials.gov but had no results posted, the status of two RCTs is unknown (NCT record last updated prior to 2015; NCT02402491[29]; NCT00954707[33]). One RCT was terminated because of slow enrollment (NCT02494284[28]). The outcomes of participants in one trial were reported as part of the DAPT trial (NCT01106534[22]).

The study characteristics for the eight RCTs that reported study results are summarized in below and are reported in detail in Appendix 4.

The included RCTs were published between 2012 and 2017, and involved between 1,010 and 11,648 participants (Table 2). The largest RCT was the DAPT trial,[24] with initial outcome data published in 2014. None of the included studies were conducted in Canada or the US, although one multi-national study included sites in the US.[24]

Most of the included studies were open-label (k = 7), with one placebo-controlled trials (Table 2). Six of the trials were designed to test whether extended DAPT was more effective than DAPT for a shorter duration (superiority hypothesis), while two studies tested whether extended DAPT was no worse than shorter DAPT (non-inferiority hypothesis). The primary outcome for each study is shown in Appendix 4.

The timing of randomization relative to PCI was variable between studies (Appendix 4). Four of the included RCTs randomized participants during hospitalization for PCI or within the first 30 days after PCI,[23,25,31,32] while the remaining four RCTs randomized participants who completed 6-12 months of DAPT with no adverse events; as such, these patients received six to 12 months of DAPT before randomization. This may have excluded some high-risk participants who may have obtained a larger benefit from extended DAPT.

Table 2: Summary of study characteristics

Trial characteristic	Category	No. of included studies
Publication status	Unique RCTs	13
	Unique RCTs reporting an outcome of interest	8
	Peer-reviewed publication available	9
	Available as a Clinical Trials.gov record only	4
Trial characteristic	**Categories**	**No. of included studies (k = 8)**
No. of countries	Multinational	2
	Single country	6
Study design	Placebo-controlled	1
	Open-label	7
	Superiority	6
	Non-inferiority	2
Stent type	Drug-eluting stent only	5
	Bare-metal stent only	0
	Both drug-eluting and bare-metal stents	3
P2Y12 inhibitor	Clopidogrel only	4
	Prasugrel only	0

	Ticagrelor only	0
	Multiple types of P2Y12 inhibitors	4
Timing of randomization	At or within 30 days of PCI	4
	6 to 12 months following PCI	4
Publication year		Range: 2012 to 2017
Randomized sample size		Range: 1,010 to 11,648

Note: PCI = percutaneous intervention, RCT = randomized controlled trial.

The most frequently used P2Y12 inhibitor was clopidogrel (Table 3). Four RCTs involved only clopidogrel (PRODIGY,[25] DES-LATE,[27] OPTIDUAL,[30] Dadjou 2016[32]), while four RCTs involved more than one type of P2Y12 inhibitor (DAPT,[24] ARCTIC-Interruption,[34] ITALIC,[31] NIPPON[23]). Additional information about the P2Y12 inhibitors, including dose, is provided in Appendix 4.

Table 3: P2Y12 inhibitors used as part of DAPT regimens

Author, year	Group	Eligible P2Y12 inhibitors	No. (%) of participants			
			Clopidogrel	Prasugrel	Ticagrelor	Other P2Y12 inhibitor
Nakamura 2017 (NIPPON)*	6 mo 18 mo	Clopidogrel, ticlopidine	1619 (97.9) 1605 (97.1)	1 (0.1) 3 (0.2)	NA	32 (1.9) 44 (2.7)
Helft 2016 (OPTIDUAL)	12 mo 48 mo	Clopidogrel	100%*	NR	NR	NR
Gilard 2015 (ITALIC)	6 mo 24 mo	Clopidogrel, prasugrel, ticagrelor	902 (98.9) 895 (98.4)	15 (1.6) 16 (1.8)	1 (0.1) 0 (0)	NA
Mauri 2014 (DAPT)‡	12 mo 30 mo	Clopidogrel, prasugrel	3230 (65.4) 3275 (65.2)	1711 (34.6) 1745 (34.8)	NA	NA
Lee 2014 (DES-LATE)	12 mo 24 mo	Clopidogrel	2502 (99.5) 2521 (99.6)	NR	NR	NR
Collet 2014 (ARCTIC-INT)	12 mo 18–30 mo	Clopidogrel, prasugrel	562 (90.1) 569 (89.6)	53 (8.5) 54 (8.5)	NR	NR
Valgimigli 2012 (PRODIGY)	6 mo 24 mo	Clopidogrel	983 (100)† 987 (100)†	NA	NA	NA
Dadjou 2016¶	< 12 mo > 12 mo	Clopidogrel	100%*	NR	NR	NR

Note: DAPT = dual anti-platelet therapy, mo = months, NA = not applicable, NR = not reported.
*Assumed 100% based on description of study treatments.
†At randomization (30 days post PCI). At 6-months post PCI, 83.6% of participants in the 6-month DAPT group were receiving clopidogrel (98.3% among participants with a DES; 39.2% among participants with a BMS), and 99.4% of participants in the 24-month DAPT group.
‡P2Y12 inhibitor use among randomized participants with an implanted DES.

The mean age of the included participants was 60 years or older (Appendix 5). Most of the participants were male (64% to 82%), and about one-third of participants in each RCT had diabetes (24% to 38%). Between 23% and 61% of participants reported current smoking. Prior MI was reported in between 4% and 22% of participants. Heart failure was reported by three trials,[24,25,34] with between 0.6% and 5% of participants reporting a history of heart failure.

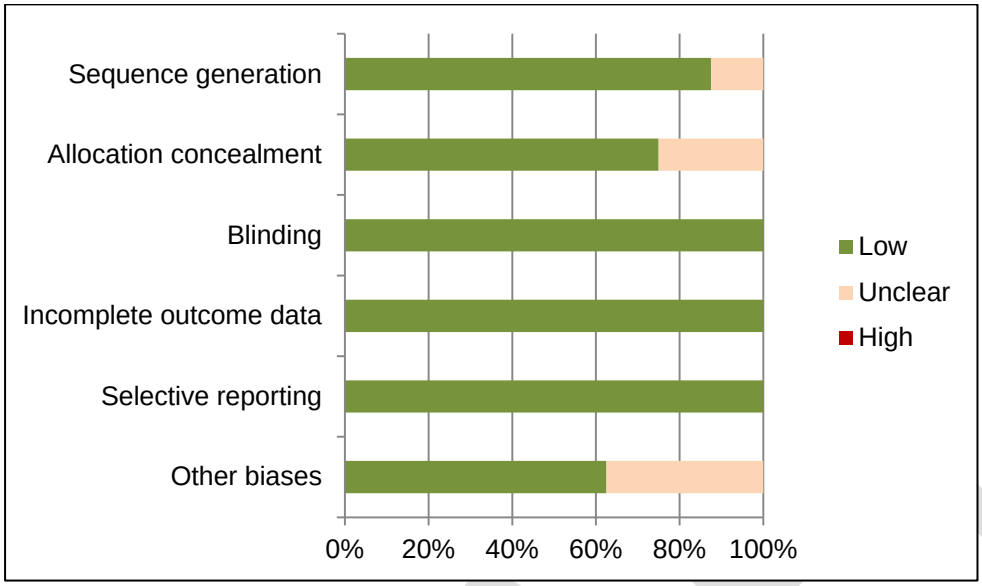
There was wide variation in the percentage of participants with ACS within the RCTs (Appendix 6). Between 0.1% and 33% of participants had ST-elevation MI (STEMI), between 2% and 23% of participants had non-STEMI (NSTEMI), and between 9% and 39% of participants had unstable angina). Two RCTs[32,34] did not report the proportion of participants with STEMI, NSTEMI or unstable angina. Three trials reported the percentage of complex lesions (ACC/ AHA classification as Class B2 or C; 48% to 79%). The wide range in participants with ACS may be due in part to the inclusion and exclusion criteria (Appendix 8). For example, participants with STEMI were excluded from the ITALIC trial,[31] while the PRODIGY trial enrolled "all-comers," including participants with STEMI.[25]

All of the included RCTs involved participants with DES. Commonly included stent types were everolimus, paclitaxel, zotarolimus, and sirolimus (Appendix 7).Three RCTs involved participants with either DES and BMS (PRODIGY,[25] DAPT[24], Dadjou 2016[32]). About 25% of participants in the PRODIGY trial received a BMS,[25] while about 15% of participants in the DAPT trial[24] included participants with a BMS. No studies involved only participants with an implanted BMS.

5.3 Risk of Bias

ROB was assessed by use of the Cochrane Collaboration's ROB tool for all studies that reported at least one outcome of interest (k = 8) (Appendix 9). Overall, the included RCTs were generally at low risk of bias. Most of the included RCTs were judged to be at low risk of bias for adequate sequence generation and allocation concealment (Figure 2), with the exception of DES-LATE[27] and Dadjou 2016,[32] which did not provide sufficient details to permit judgement. Although seven of the eight included RCTs were open-label, we judged the risk of bias to be low for the blinding domain for all RCTs because the outcomes were objective and unblinding would not be expected to have a large impact on the outcomes of interest. The domains "incomplete outcome data" and "selective outcome reporting" were judged to be at low risk of bias for all included RCTs. Three RCTs (ITALIC,[31] OPTIDUAL,[30] NIPPON[23]) were considered to be at unclear risk of "other sources of bias" because all were terminated early. Two RCTs (ITALIC,[31] OPTIDUAL[30]) were terminated for problems with recruitment, while the NIPPON[23] trial was terminated after the first planned interim analysis (after 1,500 participants were followed for 18 months) because of "substantially lower overall event rates in 1 treatment group" and slow recruitment.

Figure 2: Risk of bias assessment of included randomized controlled trials



5.4 Data Synthesis

> ***Research question 1:*** *What are the comparative clinical efficacy and safety of shorter (6 to 12 months) versus longer (i.e. > 12 months) duration of DAPT following PCI with BMS or DES insertion in the following groups: all post-PCI patients; those with a prior myocardial infarction; those presenting with ACS; those with diabetes; those in different age subgroups; and those who smoke?*

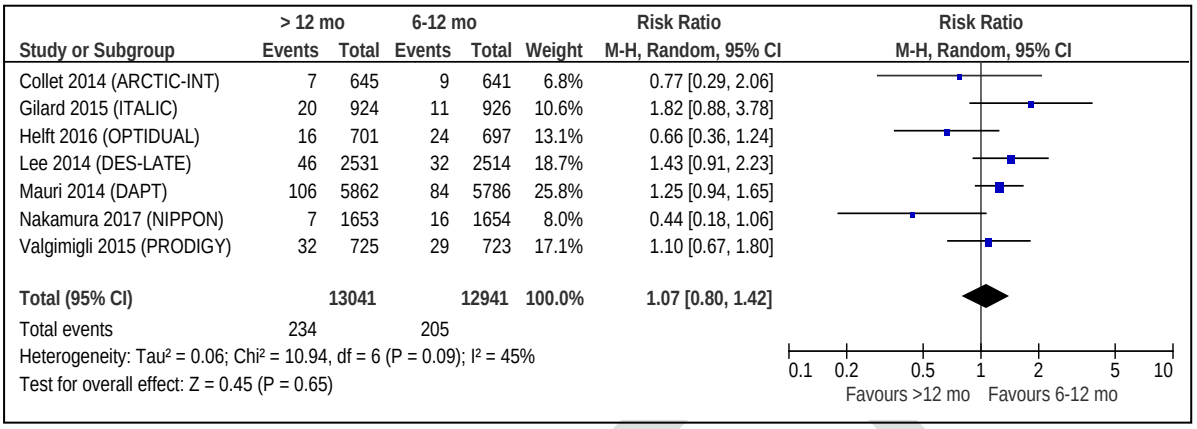
In total, eight of the included RCTs addressed this research question.[23-25,27,30-32,34] The remaining RCTs reported no data (ClinicalTrials.gov records)[22,28,29,33] or were available only as published protocols.[26] Of the eight RCTs that reported data, four randomized participants within 30 days of PCI.[23,25,31,32] Nakamura and colleagues (NIPPON)[23] and Valgimigli and colleagues (PRODIGY)[25] reported outcome data for the entire DAPT period (i.e., from PCI onward), as well as data from six months onward. The data from the first six months of DAPT include participants who were potentially at higher risk of an adverse event. In order to ensure consistency with the data from the remaining trials, which reported data starting from six or 12 months after PCI, we included in the following analyses data from the PRODIGY and NIPPON trials from six months onward, using the number of participants who reached the 6-month milestone as the denominator. Although the ITALIC trial[31] also randomized participants at PCI, those who experienced an event during the first six months were excluded from the analysis, and data are reported for the period from six months to 24 months after PCI. One trial (Dadjou et al.[32]) reported data for the entire study period starting at PCI; because these data include participants at high-risk of an event and to ensure consistency across trials we excluded these data from our analyses. As such, the following analyses are based on data from seven RCTs,[23-25,27,30,31,34] representing the treatment period starting six months after PCI.

5.4.1 All patients

5.1.1.1.1 All-cause death

In total, seven RCTs[23-25,27,30,31,34] involving 25,982 participants assessed all-cause death associated with 6–12 months of DAPT compared with extended DAPT (> 12 months). There was no significant difference in the risk of all-cause death between DAPT durations (RR 1.07, 95%CI 0.80 to 1.42), with moderate heterogeneity between trials (I^2 = 45%) (Figure 3).

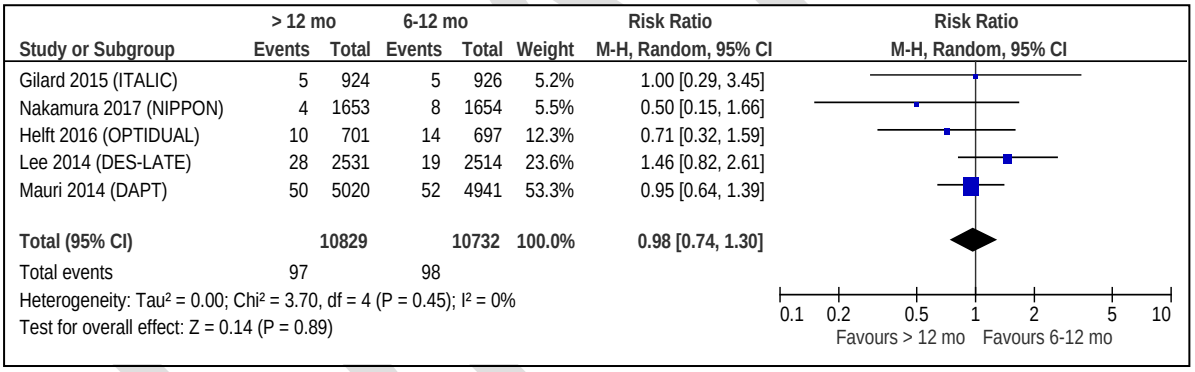
Figure 3: Relative risk of all-cause death



5.1.1.1.2 Cardiovascular death

In total, five RCTs[23,24,27,30,31] involving 21,561 participants assessed cardiovascular death associated with 6–12 months of DAPT compared with extended DAPT (> 12 months). There was no significant difference in the risk of cardiovascular death between DAPT durations (RR 0.98, 95%CI 0.74 to 1.30) (Figure 4).

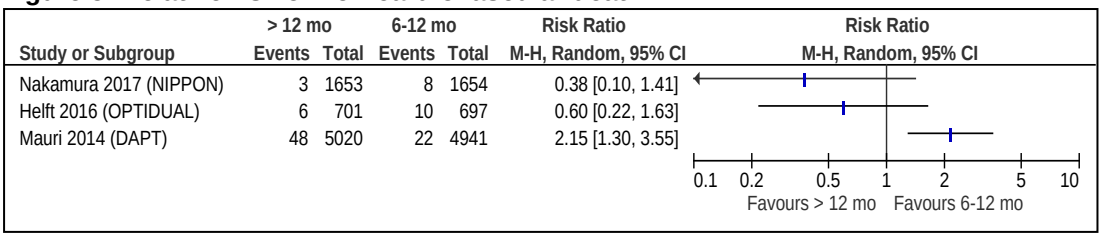
Figure 4: Relative risk of cardiovascular death



5.1.1.1.3 Non-cardiovascular death

In total, three RCTs[23,24,30] involving 14,666 participants assessed non-cardiovascular death associated with 6–12 months of DAPT compared with extended DAPT (> 12 months). No pooled analysis was performed as there was high heterogeneity between trials (I^2 = 79%). Of note, two RCTs (NIPPON,[23] OPTIDUAL[30]) found no significant difference in the risk of non-cardiovascular death, while one RCT (DAPT[24]) reported a significantly higher risk of non-cardiovascular death with DAPT for more than 12 months (RR 2.15, 1.30 to 3.55) (Figure 5).

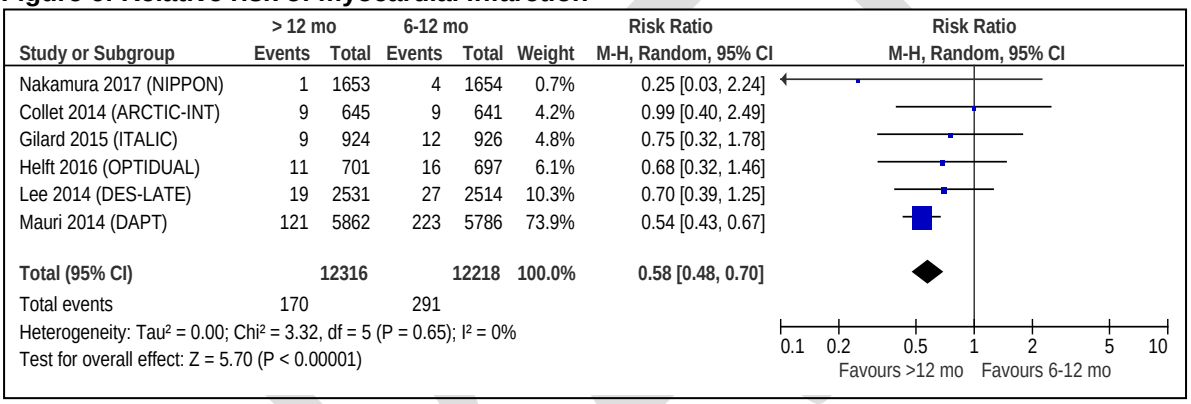
Figure 5: Relative risk of non-cardiovascular death



5.1.1.1.4 Myocardial infarction

In total, six RCTs[23,24,27,30,31,34] involving 24,534 participants assessed MI associated with six to 12 months of DAPT compared with extended DAPT (> 12 months). Participants who received extended DAPT were at lower risk of MI compared with those who received DAPT for six to 12 months (RR 0.58, 95%CI 0.48 to 0.70) (Figure 6).

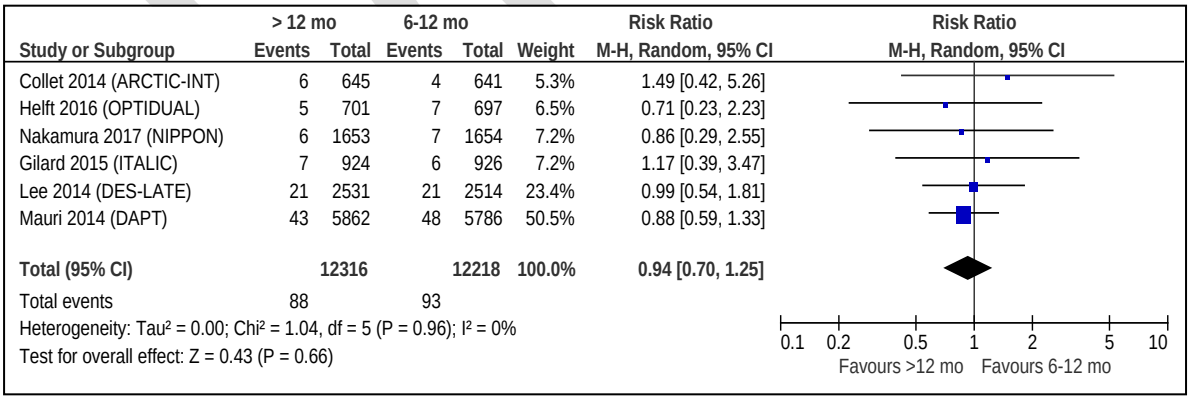
Figure 6: Relative risk of myocardial infarction



5.1.1.1.5 Stroke

In total, six RCTs[23,24,27,30,31,34] involving 24,534 participants assessed stroke associated with six to 12 months of DAPT compared with extended DAPT (> 12 months). There was no significant difference in the risk of stroke between DAPT durations (RR 0.94, 95%CI 0.70 to 1.25) (Figure 7).

Figure 7: Relative risk of stroke

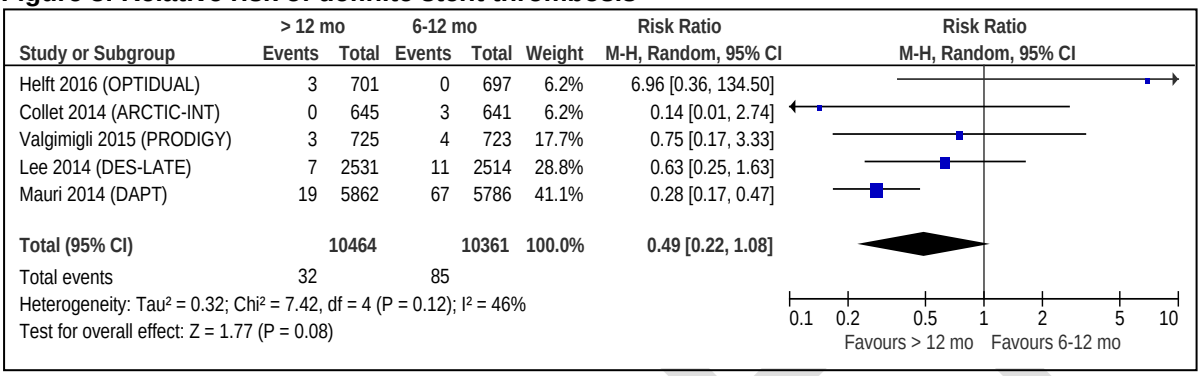


5.1.1.1.6 Stent thrombosis

Definite stent thrombosis

In total, five RCTs[24,25,27,30,34] involving 20,825 participants assessed definite stent thrombosis associated with six to 2 months of DAPT compared with extended DAPT (> 12 months). There was no statistically significant difference in the risk of definite stent thrombosis between DAPT durations (RR 0.49, 95%CI 0.22 to 1.08), with moderate heterogeneity between trials (I^2 = 46%) (Figure 8). Although this result did not reach statistical significance, there may be a protective effect of DAPT for longer than 12 months, as observed in the DAPT trial.

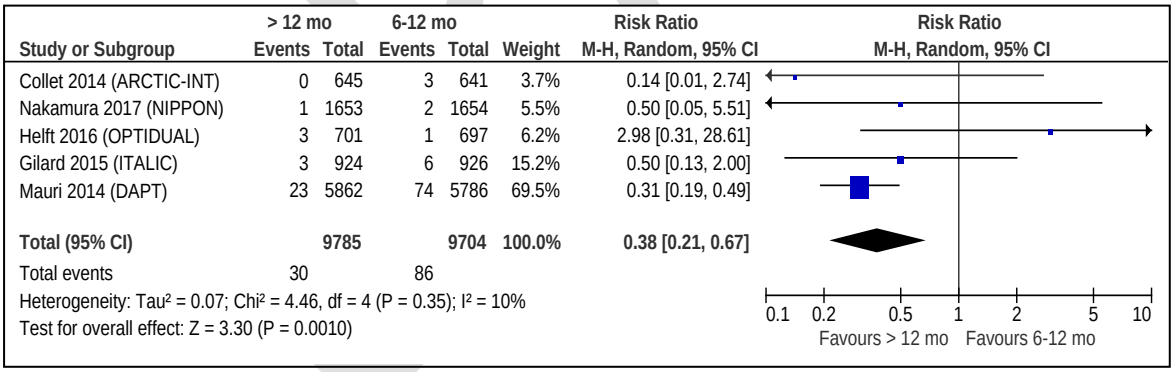
Figure 8: Relative risk of definite stent thrombosis



Definite or probable stent thrombosis

In total, five RCTs[23,24,30,31,34] involving 19,489 participants assessed probable or definite stent thrombosis associated with six to 12 months of DAPT compared with extended DAPT (> 12 months). Participants who received extended DAPT were at lower risk of probable or stent thrombosis compared with those who received DAPT for six to 12 months (RR 0.38, 95%CI 0.21 to 0.67), with low heterogeneity between trials (I^2 = 10%) (Figure 9).

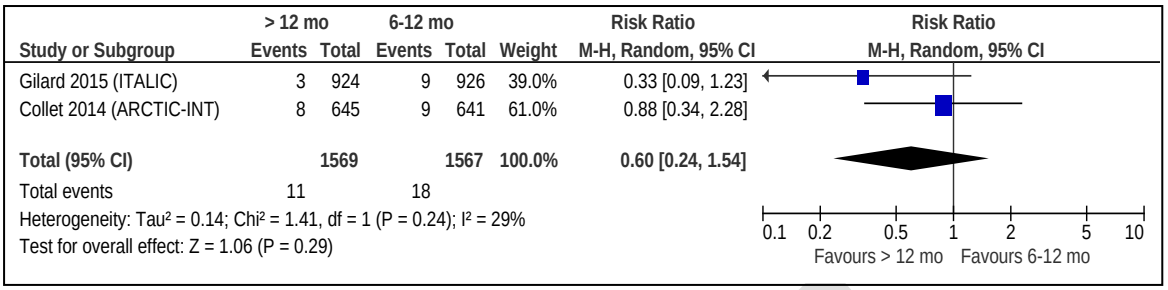
Figure 9: Relative risk of definite or probable stent thrombosis



5.1.1.1.7 Urgent revascularization

Two RCTs[31,34] involving 3,136 participants assessed urgent revascularization associated with six to 12 months of DAPT compared with extended DAPT (> 12 months). There was no significant difference in the risk of urgent revascularization between DAPT durations (RR 0.60, 95%CI 0.24 to 1.54), with moderate heterogeneity between trials (I^2 = 29%) (Figure 10).

Figure 10: Relative risk of urgent revascularization

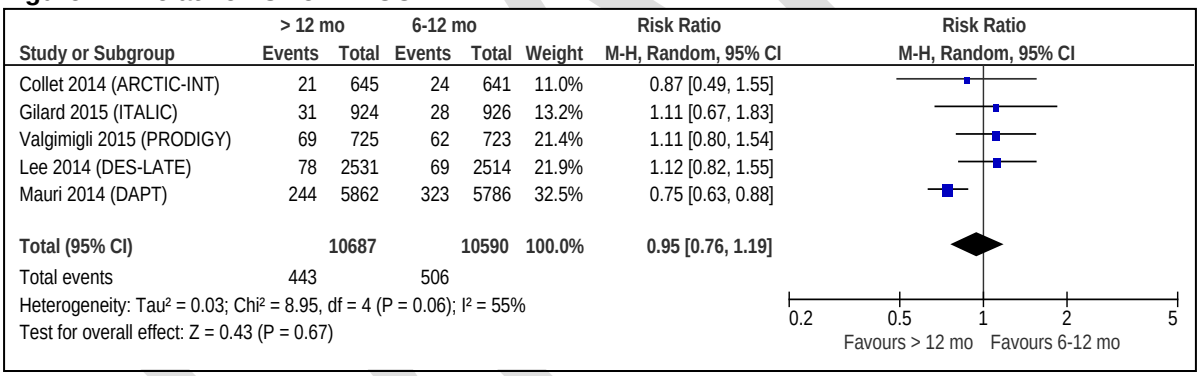


5.1.1.1.8 MACCE

All of the included RCTs assessed the occurrence of MACCE during the treatment period, but there was wide variation in components of the composite outcome across trials. In order to ensure consistency, we pooled data from trials that reported a composite consisting of all-cause death, myocardial infarction, or stroke.

Five RCTs[24,25,27,31,34] reported the occurrence of MACCE during the treatment period, defined as a composite outcome involving death, myocardial infarction or stroke. In total, 21,277 participants were randomized to six to 12 months or >12 months of DAPT. There was no significant difference in the risk of MACCE between DAPT durations (RR 0.95, 95%CI 0.76 to 1.19), with moderate heterogeneity between trials (I^2 = 55%) (Figure 11).

Figure 11: Relative risk of MACCE



Two additional RCTs reported MACCE by use of an alternative definition that included major bleeding (Table 4), with no significant difference in the risk of an event between DAPT for >12 months or 6-12 months.

Table 4: MACCE reported by use of alternative definitions

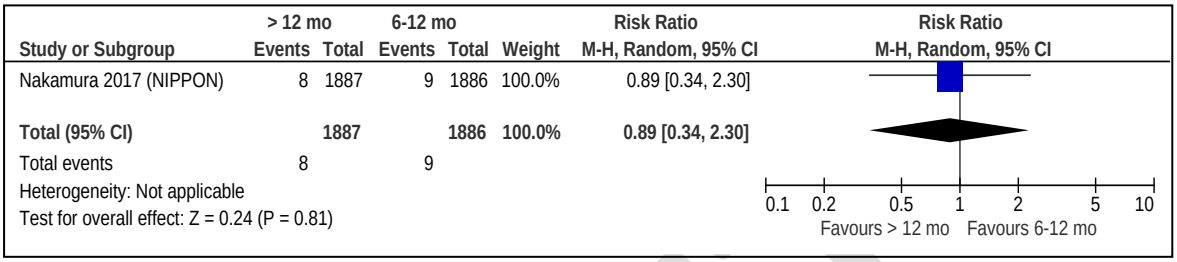
Trial	MACCE definition	No. events/ no. participants	RR (95%CI)
Nakamura 2017 (NIPPON)	All-cause death, Q-wave or non–Q-wave MI, cerebrovascular events, major bleeding	6 mo: 34/1654 18 mo: 24/1653	0.71 (0.42, 1.19)
Helft 2016 (OPTIDUAL)	All-cause death, non-fatal MI, stroke, or major bleeding	12 mo: 52/697 48 mo: 40/701	0.76 (0.51, 1.14)

Note: CI = confidence interval, MACCE = major adverse cardiac and cerebrovascular events, MI = myocardial infarction, mo = months, RR = relative risk.

5.1.1.1.9 Gastrointestinal bleeding

Gastrointestinal bleeding was reported by one RCT,[23] with no significant difference in risk between participants who received DAPT for 6 or 18 months (Figure 12).

Figure 12: Relative risk of gastrointestinal bleeding



5.1.1.1.10 Major bleeding

A variety of bleeding classification systems were used among the included trials to assess bleeding severity (Table 5). The TIMI classification system was most commonly used among the included trials.

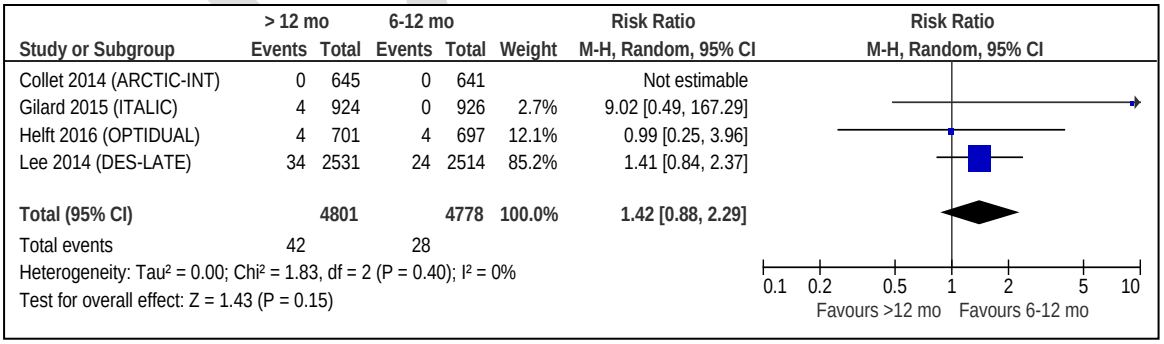
Table 5: Bleeding classification systems used by the included RCTs to assess bleeding severity

Trial	Bleeding classification systems*
Mauri 2014 (DAPT)	GUSTO, BARC
Valgimigli 2012 (PRODIGY)	TIMI, BARC
Collet 2014 (ARCTIC-INT)	TIMI, STEEPLE
Gilard 2015 (ITALIC)	TIMI
Helft 2016 (OPTIDUAL)	TIMI, BARC, GUSTO, ISTH
Nakamura 2017 (NIPPON)	BARC, REPLACE
Lee 2014 (DES-LATE)	TIMI
*Description of each bleeding classification system is available in Appendix 10	

TIMI Major Bleeding

TIMI major bleeds were reported in four RCTs,[27,30,31,34] involving 9,579 participants.
Among RCTs that assessed TIMI major bleeding, there was no significant difference in the risk of TIMI major bleeding between DAPT durations (RR 1.42, 95%CI 0.88 to 2.29) (Figure 13).

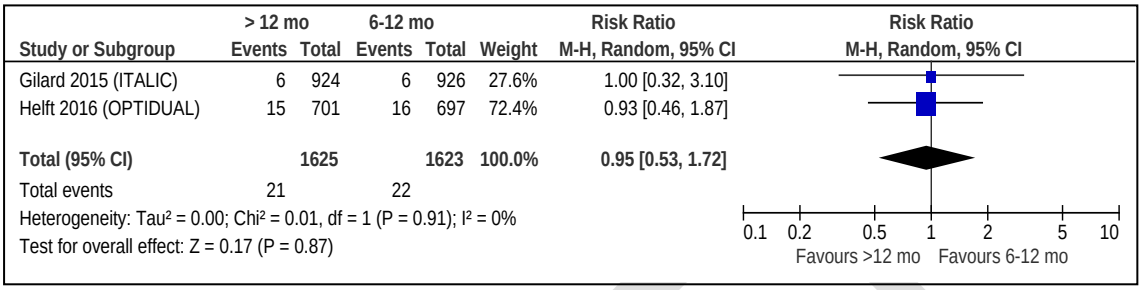
Figure 13: Relative risk of TIMI major bleeding



TIMI Minor Bleeding

TIMI minor bleeds were reported in two RCTs,[30,31] involving 3,248 participants. There was no significant difference in the risk of TIMI minor bleeding between DAPT durations (RR 0.95, 95%CI 0.53 to 1.72) (Figure 13).

Figure 14: Relative risk of TIMI minor bleeding



The DAPT trial, the largest included RCT, did not use the TIMI classification system for bleeding. The DAPT study, plus three other RCTs, assessed bleeding severity by use of an alternative classification system (Table 6). Among these studies, there was no significant difference in risk between DAPT for >12 months and DAPT for 6-12 months for most bleeding outcomes, with the exception of GUSTO Moderate bleeding (RR 1.68, 95%CI 1.22, 2.30) and GUSTO moderate and severe bleeding (RR 1.57 (1.17, 2.11). Results from the DAPT trial suggest that there is a trend toward increased major bleeding with extended DAPT.

Table 6: Relative risk of bleeding, assessed by use of alternative bleeding classification systems

Bleeding classification system*	Trial	No. events/ no. randomized	RR (95%CI); I^2
BARC			
Type 2	DAPT	12 mo: 79/5786 30 mo: 167/5862	1.41 (0.51, 3.90); 69%
	OPTIDUAL	12 mo: 7/697 48 mo: 5/701	
Type 3	DAPT	12 mo: 74/5786 30 mo: 138/5862	1.29 (0.76, 2.22); 58%
	OPTIDUAL	12 mo: 14/697 48 mo: 13/701	
	NIPPON	6 mo: 11/1654† 18 mo: 10/1653†	
Type 5	DAPT	12 mo: 5/5786 30 mo: 7/5862	1.72 (0.62, 4.47); 0%
	OPTIDUAL	12 mo: 0/697 48 mo: 1/701	
	NIPPON	6 mo: 0/1654† 18 mo: 2/1653†	
Type 2,3,5	OPTIDUAL	12 mo: 20/697 48 mo: 18/701	0.89 (0.48, 1.68); NA
GUSTO			
Moderate	DAPT	12 mo: 52/5786 30 mo: 91/5862	**1.68 (1.22, 2.30); 0%**
	OPTIDUAL	12 mo: 8/697	

		48 mo: 11/701	
Severe	DAPT	12 mo: 29/5786 30 mo: 44/5862	1.41 (0.90, 2.20); 0%
	OPTIDUAL	12 mo: 4/697 48 mo: 3/701	
Moderate or severe	DAPT	12 mo: 80/5786 30 mo: 135/5862	**1.57 (1.17, 2.11); 7%**
	OPTIDUAL	12 mo: 12/697 48 mo: 13/701	
Replace			
Major	NIPPON	6 mo: 11/1654† 18 mo: 22/1653†	2.00 (0.97, 4.11); NA
ISTH			
Major	OPTIDUAL	12 mo: 14/697 48 mo: 14/701	0.99 (0.48, 2.07); NA
Minor	OPTIDUAL	12 mo: 7/697 48 mo: 6/701	0.85 (0.29, 2.52); NA
STEEPLE			
Major	ARCTIC-INT	12 mo: 1/641 18-30 mo: 7/645	6.96 (0.86, 56.38); NA
Minor	ARCTIC-INT	12 mo: 2/641 18-30 mo: 5/645	2.48 (0.48, 12.76); NA

Note: CI = confidence interval, mo = months, NA = not applicable, RR = relative risk.
*Definitions for each bleeding classification system are available in Appendix 10.
†No. randomized who reached the 6-month landmark without experiencing the primary outcome.

5.4.2 Patients with an implanted BMS

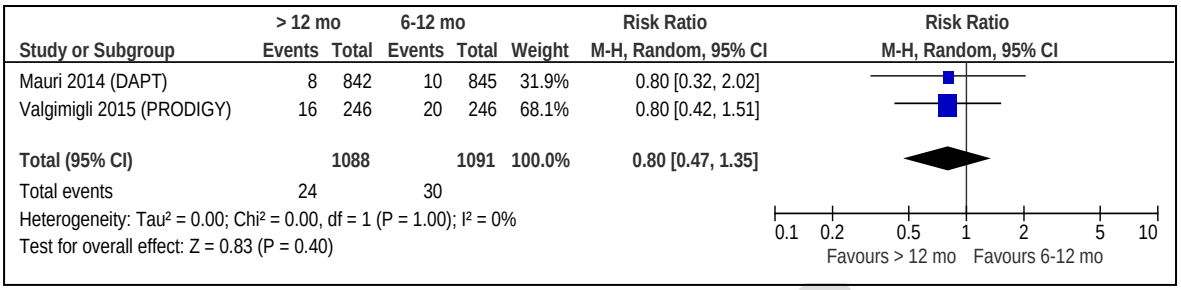
Two of the included RCTs involved participants with an implanted BMS (PRODIGY,[25] DAPT trial[24]) or DES. About 25% of participants in the PRODIGY trial received a BMS,[25] while about 15% of participants in the DAPT trial[24] included participants with a BMS. These RCTs each reported data separately for participants with a BMS and form the evidence base for this subgroup.

In the PRODIGY trial[25] participants were randomized within 30 days of PCI, and data were presented in two ways: 0–24 months of DAPT or 6–24 months of DAPT. For participants with a BMS, subgroup data were provided for the period from 0–24 months of DAPT. Based on the reported number of participants included at each stage of the study, less than 10 people experienced an event during the first 6 months. In the following analyses, the included data from the PRODIGY trial includes these participants. Hazard ratios for the risk of an event during the period from 6 months onward (i.e., excluding participants who experienced an early event) were available for some outcomes and are reported below.

5.1.1.1.11 All-cause death

Two RCTs[24,25] involving 2,179 participants with a BMS assessed all-cause death. Among those with an implanted BMS, there was no significant difference in the risk of all cause death between DAPT durations (RR 0.80, 95%CI 0.47 to 1.35) (Figure 15).

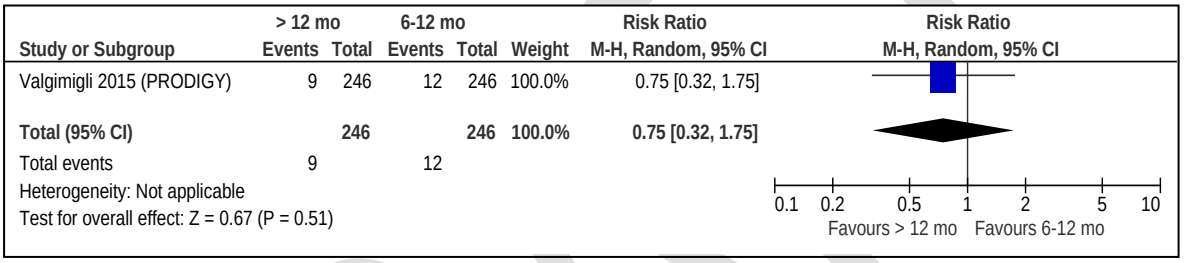
Figure 15: Relative risk of all-cause death among participants with an implanted BMS



5.1.1.1.12 Cardiovascular death

One RCT[25] involving 492 participants with a BMS assessed cardiovascular death. Among those with an implanted BMS, there was no significant difference in the risk of cardiovascular death between DAPT durations (RR 0.75, 95%CI 0.32 to 1.75) (Figure 16).

Figure 16: Relative risk of cardiovascular death among participants with an implanted BMS



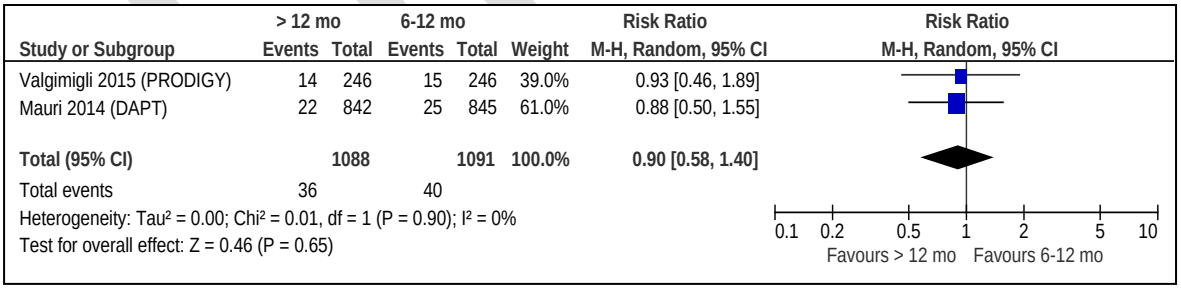
5.1.1.1.13 Non-cardiovascular death

No studies assessed non-cardiovascular death among participants with an implanted BMS.

5.1.1.1.14 Myocardial infarction

Two RCTs[24,25] involving 2,179 participants with a BMS assessed MI. Among those with an implanted BMS, there was no significant difference in the risk of MI between DAPT durations (RR 0.90, 95%CI 0.58 to 1.40) (Figure 17).

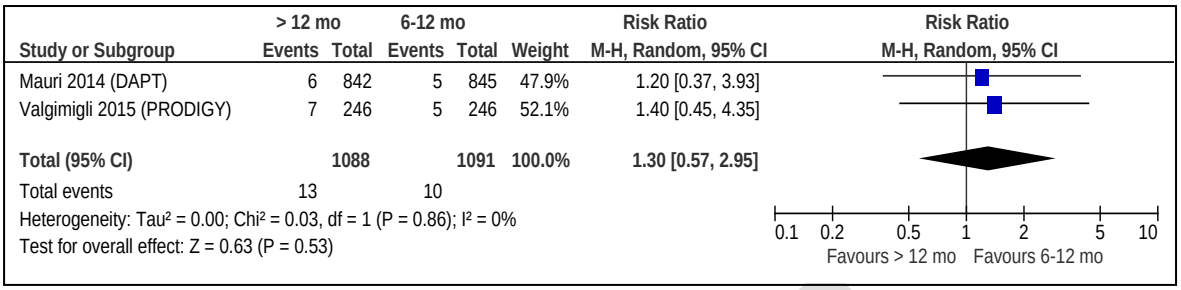
Figure 17: Relative risk of myocardial infarction among participants with an implanted BMS



5.1.1.1.15 Stroke

Two RCTs[24,25] involving 2,179 participants with a BMS assessed stroke. Among those with an implanted BMS, there was no significant difference in the risk of stroke between DAPT durations (RR 1.30, 95%CI 0.57 to 2.95) (Figure 18).

Figure 18: Relative risk of stroke among participants with an implanted BMS



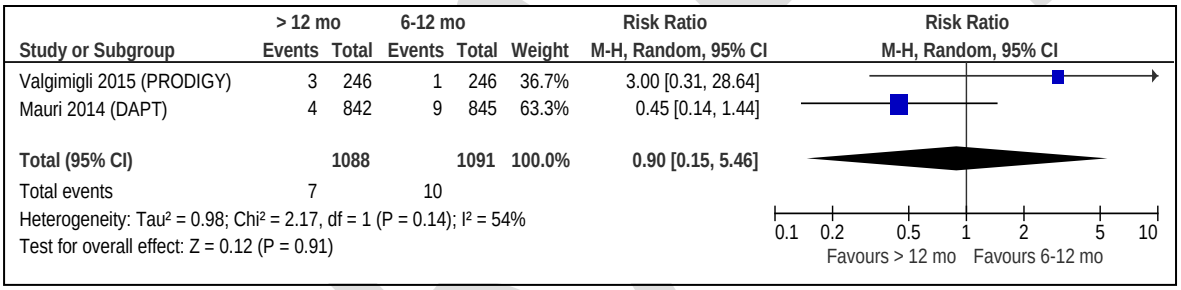
5.1.1.1.16 Stent thrombosis

Two RCTs[24,25] involving 2,179 participants with a BMS assessed stent thrombosis.

Definite stent thrombosis

Among those with an implanted BMS, there was no significant difference in the risk of definite stent thrombosis between DAPT durations (RR 0.90, 95%CI 0.15 to 5.46), with moderate heterogeneity between trials (I^2 = 54%) (Figure 19).

Figure 19: Relative risk of definite stent thrombosis among participants with an implanted BMS

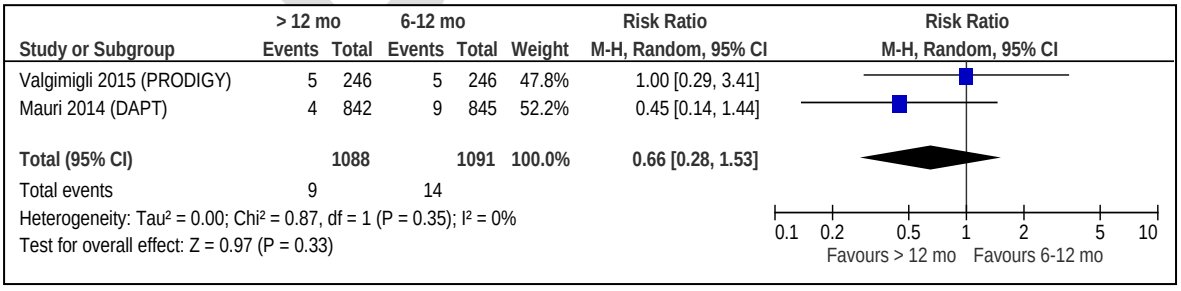


In the PRODIGY trial,[25] the hazard ratio for definite stent thrombosis during the period from six to 24 months was 1.04 (95%CI 0.56, 1.95).

Definite or probable stent thrombosis

Among those with an implanted BMS, there was no significant difference in the risk of definite or probable stent thrombosis between DAPT durations (RR 0.66, 95%CI 0.28 to 1.53) (Figure 20).

Figure 20: Relative risk of definite or probable stent thrombosis among participants with an implanted BMS



In the PRODIGY trial,[25] the hazard ratio (HR) for definite or probable stent thrombosis during the period from six to 24 months was 1.31 (95%CI 0.30, 5.83).

5.1.1.1.17 Urgent revascularization

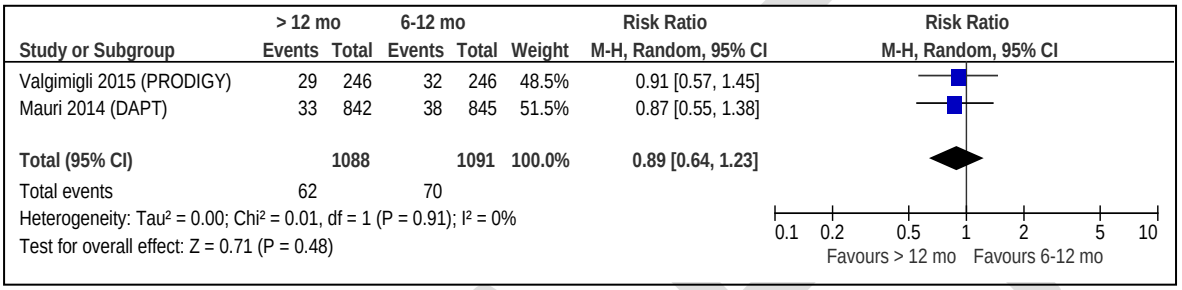
No studies assessed urgent revascularization among participants with an implanted BMS.

5.1.1.1.18 MACCE

Two RCTs[24,25] involving 2179 participants with a BMS assessed MACCE by use of the same composite outcome definition (all-cause death, MI, stroke).

Among those with an implanted BMS, there was no significant difference in the risk of MACCE between DAPT durations (RR 0.89, 95%CI 0.64 to 1.23) (Figure 21).

Figure 21: Relative risk of MACCE among participants with an implanted BMS



In the PRODIGY trial,[25] the hazard ratio for MACCE during the period from six to 24 months was 1.04 (95%CI 0.56, 1.95).

5.1.1.1.19 Gastrointestinal bleeding

No studies assessed gastrointestinal bleeding among participants with an implanted BMS.

5.1.1.1.20 Major and minor bleeding

Neither of the RCTs involving participants with an implanted BMS assessed bleeding by use of the TIMI classification system.

Among participants in the DAPT trial with an implanted BMS, there was a significantly higher risk of BARC Type 2 bleeding, Type 3 bleeding, and Type 2,3,5 bleeding among participants who received DAPT for more than 12 months compared with those who received DAPT for six to 12 months (Table 7). There were no statistically significant differences between DAPT durations for GUSTO moderate or severe bleeding or BARC Type 5 bleeding among those with a BMS. No bleeding data were reported by the PRODIGY trial[25] for participants with a BMS.

Table 7: Relative risk of bleeding among participants with an implanted BMS

Trial	Bleeding classification system*	No. events/ no. participants	RR (95%CI)
Mauri 2014 (DAPT)	GUSTO Moderate/severe	12 mo: 7/845 30 mo: 16/842	2.29 (0.95, 5.55)
	Gusto Severe	12 mo: 3/845 30 mo: 6/842	2.01 (0.50, 8.00)
	Gusto Moderate	12 mo: 4/845 30 mo: 10/842	2.51 (0.79, 7.97)
	BARC Type 2, 3, 5	12 mo: 14/845 30 mo: 38/842	**2.72 (1.49, 4.99)**
	BARC Type 2	12 mo: 7/845 30 mo: 22/842	**3.15 (1.35, 7.34)**

	BARC Type 3	12 mo: 6/845 30 mo: 16/842	**2.68 (1.05, 6.81)**
	BARC Type 5	12 mo: 1/845 30 mo: 0/842	0.33 (0.1, 8.20)

Note: BMS = bare-metal stent, CI = confidence interval, mo = months, RR = relative risk
*Definitions for each bleeding classification system are available in Appendix 10.

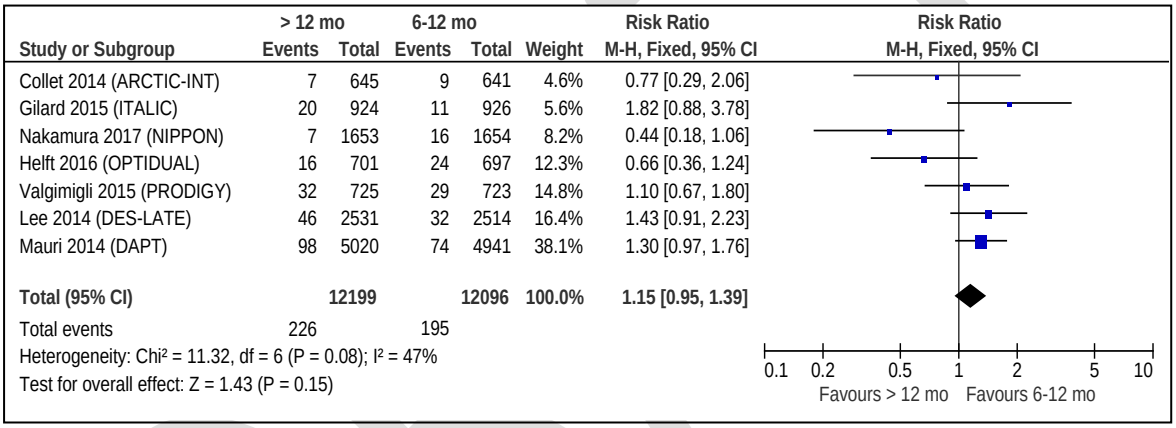
5.4.3 Participants with an implanted DES

Of the included RCTS, five involved only participants with an implanted DES.[23,27,30,31,34] Two additional RCTs[24,25] provided subgroup data for participants with a DES. These seven RCTs form the evidence base to address this subgroup.

5.1.1.1.21 All-cause death

Seven RCTs[23-25,27,30,31,34] involving 24,285 participants with a DES assessed all-cause death. Among those with an implanted DES, there was no significant difference in the risk of all-cause death between DAPT durations (RR 1.15, 95%CI 0.95 to 1.39), with moderate heterogeneity (I^2 = 47%) (Figure 22).

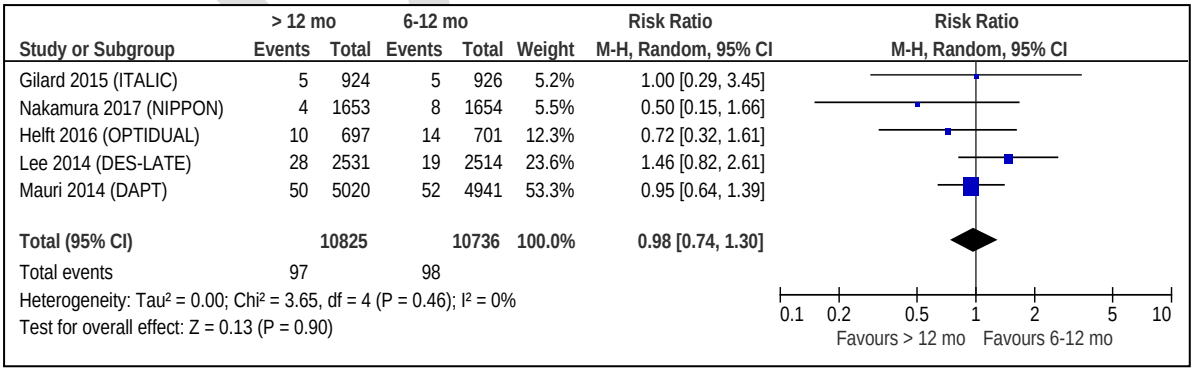
Figure 22: Relative risk of all-cause death among participants with an implanted DES



5.1.1.1.22 Cardiovascular death

Five RCTs[23,24,27,30,31] involving 21,561 participants with a DES assessed cardiovascular death. Among those with an implanted DES, there was no significant difference in the risk of cardiovascular death between DAPT durations (RR 0.98, 95%CI 0.74 to 1.30) (Figure 23).

Figure 23: Relative risk of cardiovascular death among participants with an implanted DES



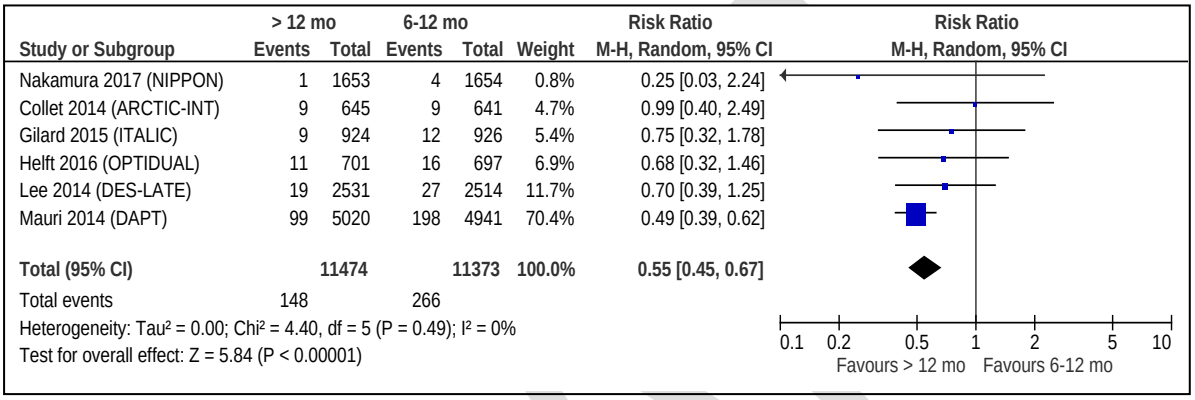
5.1.1.1.23 Non-cardiovascular death

Three RCTs[23,24,30] involving 14,666 participants assessed non-cardiovascular death associated with six to 12 months of DAPT compared with extended DAPT (> 12 months). When pooled, there was high heterogeneity between trials (I^2 = 79%). Of note, two RCTs (NIPPON,[23] OPTIDUAL[30]) found no significant difference in the risk of non-cardiovascular death, while one RCT (DAPT[24]) reported a significantly higher risk of non-cardiovascular death with DAPT for more than 12 months (RR 2.15, 1.30 to 3.55) (Figure 5).

5.1.1.1.24 Myocardial infarction

Six RCTs[23,24,27,30,31,34] involving 22,847 participants with a DES assessed MI. Among those with an implanted DES, DAPT for >12 months was associated with a lower risk of MI compared with DAPT for six to 12 months (RR 0.55, 95%CI 0.45 to 0.67) (Figure 24).

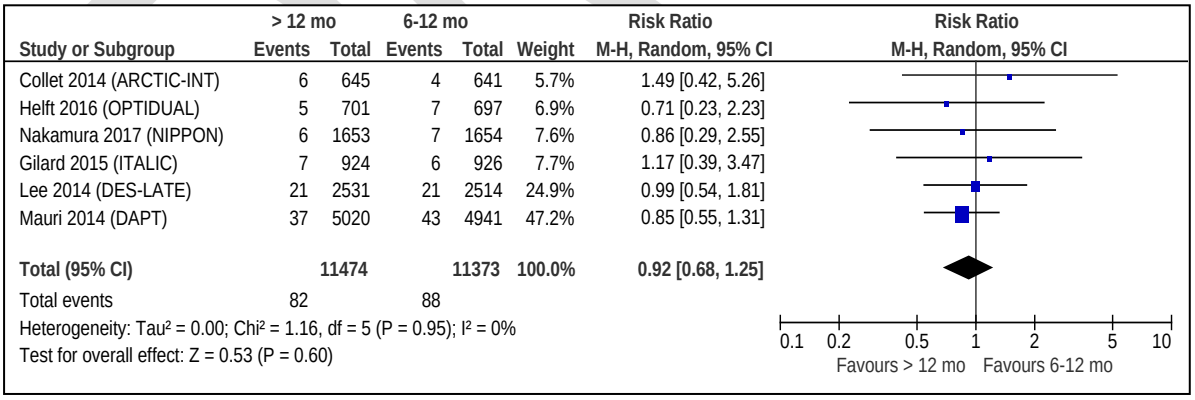
Figure 24: Relative risk of myocardial infarction among participants with an implanted DES



5.1.1.1.25 Stroke

Six RCTs[23,24,27,30,31,34] involving 22,847 participants with a DES assessed stroke. Among those with an implanted DES, there was no significant difference in the risk of stroke between DAPT durations (RR 0.92, 95%CI 0.68 to 1.25) (Figure 25).

Figure 25: Relative risk of stroke among participants with an implanted DES



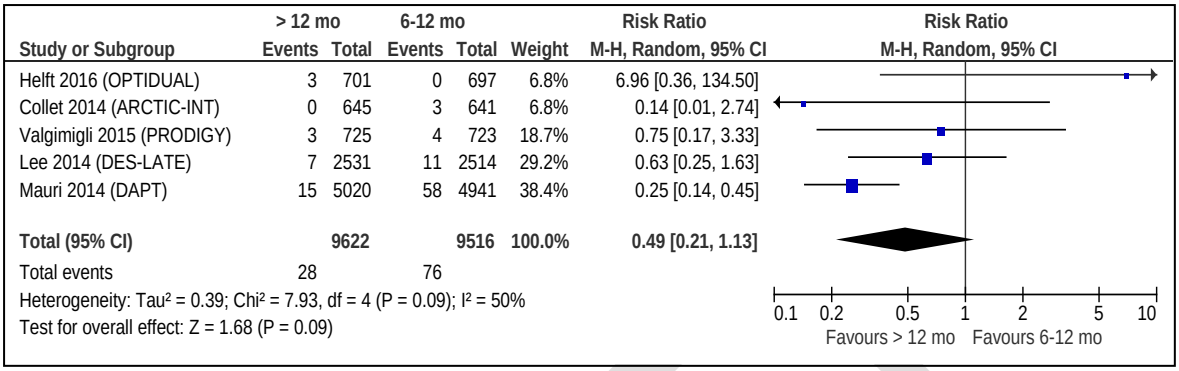
5.1.1.1.26 Stent thrombosis

Definite stent thrombosis

Five RCT[24,25,27,30,34] involving 19,138 participants with a DES assessed definite stent thrombosis. Among those with an implanted DES, there was no significant difference in the risk of definite stent thrombosis between DAPT durations (RR 0.49, 95%CI 0.21 to 1.13), with moderate heterogeneity (I^2 = 50%) (Figure

26). Results from the DAPT trial suggest a protective effect of extended DATP on stent thrombosis; however, these results were not replicated in the smaller RCTs.

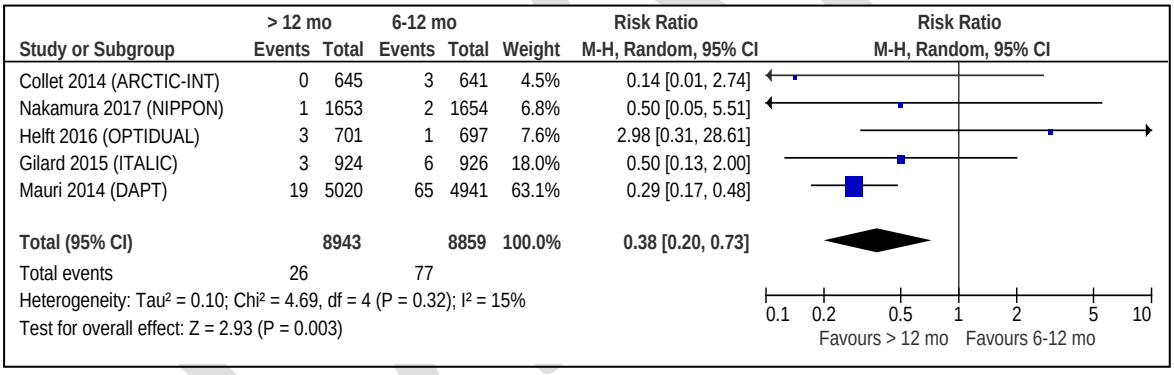
Figure 26: Relative risk of definite stent thrombosis among participants with an implanted DES



Definite or probable stent thrombosis

Five RCTs[23,24,30,31,34] involving 17,802 participants with a DES assessed definite or probable stent thrombosis. Among those with an implanted DES, DAPT for >12 months was associated with a lower risk of definite or probable stent thrombosis compared with DAPT for 6-12 months (RR 0.38, 95%CI 0.20 to 0.73) (Figure 27).

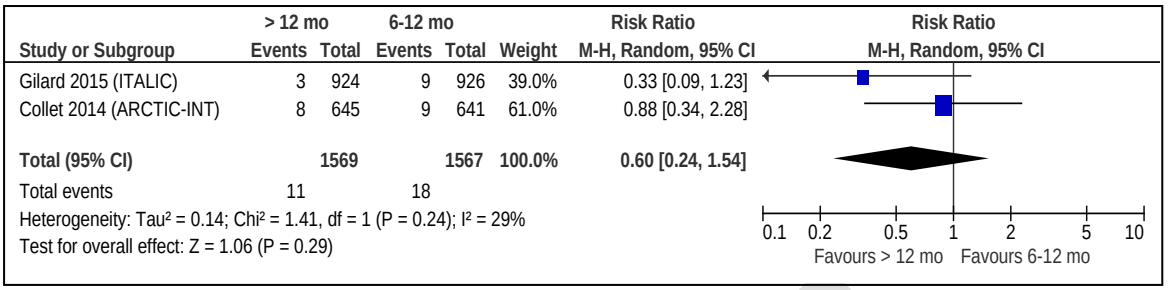
Figure 27: Relative risk of definite or probable stent thrombosis among participants with an implanted DES



5.1.1.1.27 Urgent revascularization

Two RCTs[31,34] involving 3,136 participants assessed urgent revascularization among participants with an implanted DES. There was no significant difference in the risk of urgent revascularization between DAPT durations (RR 0.60, 95%CI 0.24 to 1.54), with moderate heterogeneity between trials (I^2 = 29%) (Figure 28).

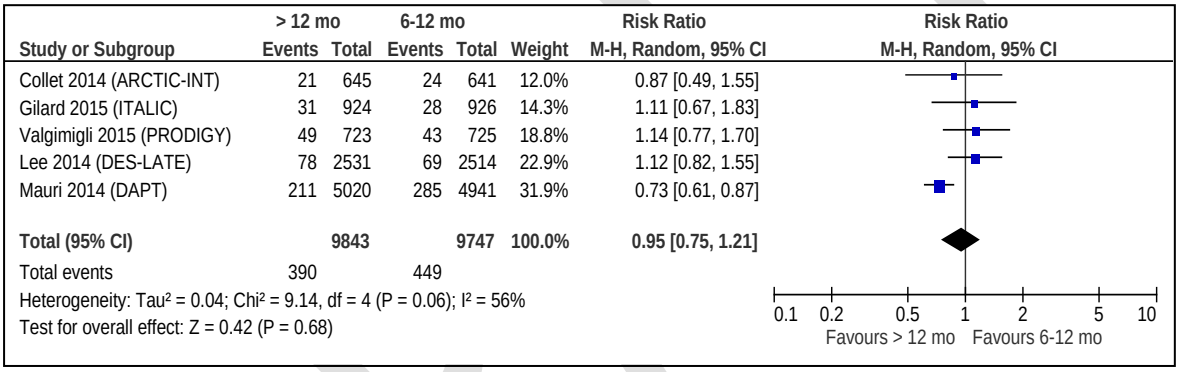
Figure 28: Relative risk of urgent revascularization among participants with an implanted DES



5.1.1.1.28 MACCE

Five RCTs[24,25,27,31,34] involving 19,590 participants assessed MACCE by use of a comparable definition (all-cause death, MI, stroke) among participants with an implanted DES. There was no significant difference in the risk of MACCE between DAPT durations (RR 0.95, 95%CI 0.75 to 1.21), with moderate heterogeneity between trials (I^2 = 56%) (Figure 29).

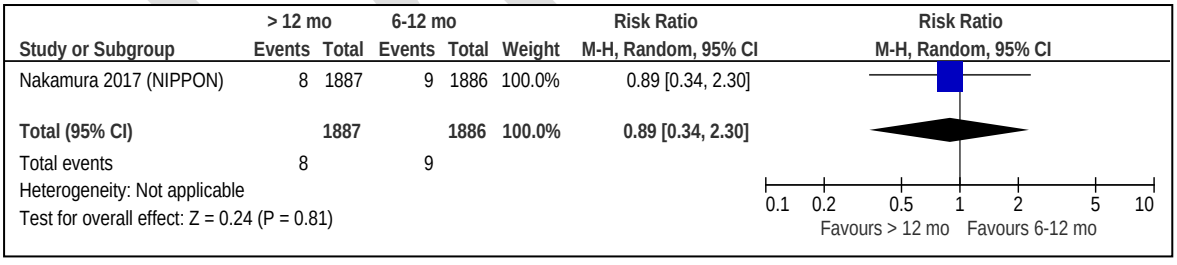
Figure 29: Relative risk of MACCE among participants with an implanted DES



5.1.1.1.29 Gastrointestinal bleeding

Gastrointestinal bleeding was reported by one RCT[23] involving 3773 participants with a DES, with no significant difference in risk between participants who received DAPT for 6 or 18 months (Figure 30).

Figure 30: Relative risk of gastrointestinal bleeding among participants with an implanted DES

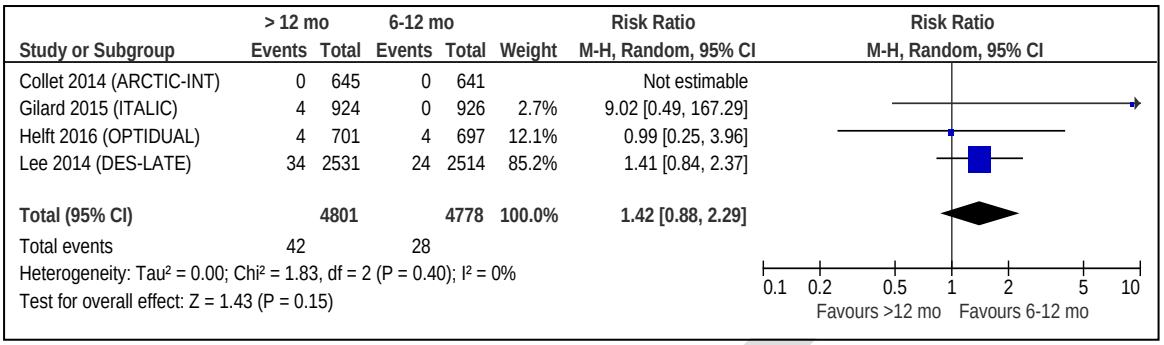


5.1.1.1.30 Major and minor bleeding

TIMI Major Bleeding

TIMI major bleeds were assessed in four RCTs,[27,30,31,34] involving 9579 participants; the DAPT trial did not assess major bleeding by use of the TIMI scale . Among trials that used the TIMI system, there was no significant difference in the risk of TIMI major bleeding between DAPT durations (RR 1.42, 95%CI 0.88 to 2.29) (Figure 31).

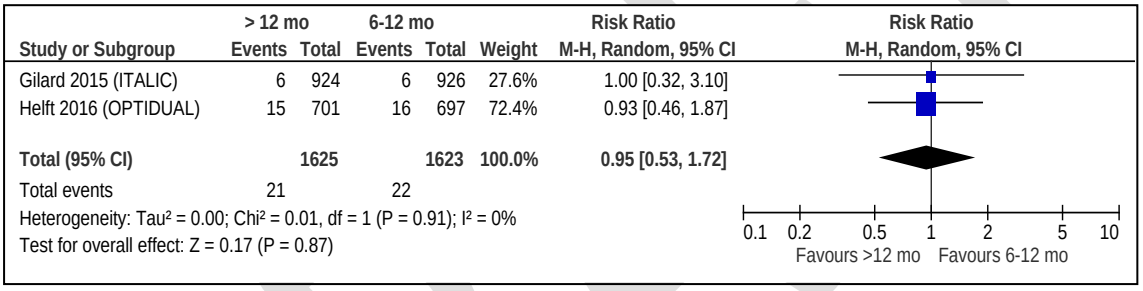
Figure 31: Relative risk of TIMI major bleeding among participants with an implanted DES



TIMI Minor Bleeding

TIMI minor bleeds were assessed in two RCTs,[30,31] involving 3248 participants. There was no significant difference in the risk of TIMI minor bleeding between DAPT durations (RR 0.95, 95%CI 0.53 to 1.72) (Figure 32).

Figure 32: Relative risk of TIMI minor bleeding among participants with an implanted DES



Alternative classification systems

Four RCTs, including the DAPT trial, assessed bleeding severity among participants with an implanted DES by use of an alternative classification system (Table 8). There was no statistically significant difference in risk between DAPT for >12 months and DAPT for six to 12 months for most bleeding outcomes, with the exception of GUSTO moderate bleeding (RR 1.62, 95%CI 1.16, 2.25) and moderate or severe bleeding (RR 1.53, 95% CI 1.17, 2.00). Results from the DAPT trial suggest that there is a trend toward increased major and minor bleeding with extended DAPT.

Table 8: Relative risk of bleeding, assessed by use of alternative bleeding classification systems, among participants with an implanted DES

Bleeding classification system*	Trial	No. events/ no. randomized	RR (95%CI); I^2
BARC			
Type 2	DAPT	12 mo: 72/4941 30 mo: 145/5020	1.39 (0.53, 3.62); 66%
	OPTIDUAL	12 mo: 7/697 48 mo: 5/701	
Type 3	DAPT	12 mo: 68/4941 30 mo: 122/5020	1.29 (0.78, 2.12); 51%
	OPTIDUAL	12 mo: 14/697 48 mo: 13/701	
	NIPPON	6 mo: 11/1654† 18 mo: 10/1653†	

Type 5	DAPT	12 mo: 4/4941 30 mo: 7/5020	2.08 (0.71, 6.07); 0%
	OPTIDUAL	12 mo: 0/697 48 mo: 1/701	
	NIPPON	6 mo: 0/1654† 18 mo: 2/1653†	
Type 2,3,5	DAPT	12 mo: 137/4941 30 mo: 263/5020	1.38 (0.67,2.85); 80%
	OPTIDUAL	12 mo: 20/697 48 mo: 18/701	
GUSTO			
Moderate	DAPT	12 mo: 48/4941 30 mo: 81/5020	**1.62 (1.16, 2.25); 0%**
	OPTIDUAL	12 mo: 8/697 48 mo: 11/701	
Severe	DAPT	12 mo: 26/4941 30 mo: 38/5020	1.35 (0.84, 2.16); 0%
	OPTIDUAL	12 mo: 4/697 48 mo: 3/701	
Moderate or severe	DAPT	12 mo: 73/4941 30 mo: 119/5020	**1.53 (1.17, 2.00); 0%**
	OPTIDUAL	12 mo: 12/697 48 mo: 13/701	
Replace			
Major	NIPPON	6 mo: 11/1654† 18 mo: 22/1653†	2.00 (0.97, 4.11); NA
ISTH			
Major	OPTIDUAL	12 mo: 14/697 48 mo: 14/701	0.99 (0.48, 2.07); NA
Minor	OPTIDUAL	12 mo: 7/697 48 mo: 6/701	0.85 (0.29, 2.52); NA
STEEPLE			
Major	ARCTIC-INT	12 mo: 1/641 18-30 mo: 7/645	6.96 (0.86, 56.38); NA
Minor	ARCTIC-INT	12 mo: 2/641 18–30 mo: 5/645	2.48 (0.48, 12.76); NA

Note: CI = confidence interval, DES = drug-eluting stent, mo = months, NA = not applicable, RR = relative risk.
*Definitions for each bleeding classification system are available in Appendix 10.
†No. randomized who reached 6 month landmark without experiencing the primary outcome.

5.4.4 Participants with a prior MI

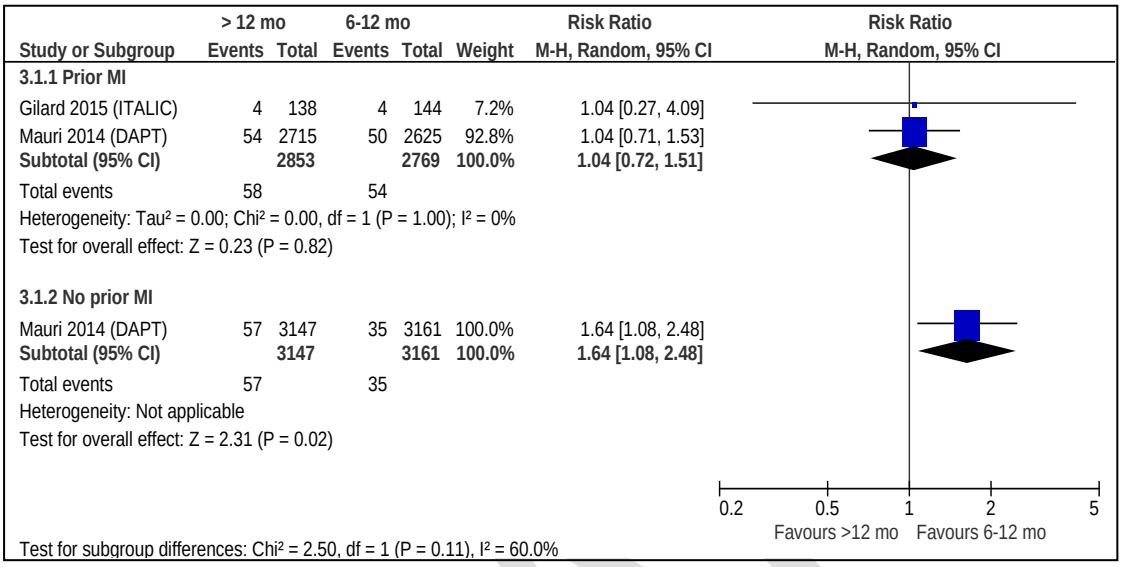
Two RCTs[24,31] reported outcome data among participants with a prior MI. The DAPT trial[24] reported data for any previous MI, prior MI (more than 72 hours before PCI), index MI (within 72 hours of PCI), and both prior and index MI. For consistency with the ITALIC trial, which reported data for participants with a "history of MI", we included in the analysis data for "any MI" from the DAPT trial.

5.1.1.1.31 All-cause death

Two RCTs[24,31] involving 5622 participants reported all-cause death among participants with a history of MI. Among participants with a prior MI, there was no significant difference in the risk of all-cause death between DAPT for six to 12 months or >12 months (RR 1.04, 95%CI 0.72 to 1.51) (Figure 33).

One RCT[24]involving 6308 participants with no history of MI reported a statistically significant increase in all-cause death among participants who received more than 12 months of DAPT following PCI (RR 1.64, 95%CI 1.08 to 2.48) (Figure 33).

Figure 33: Relative risk of all-cause death among participants with or without a history of myocardial infarction

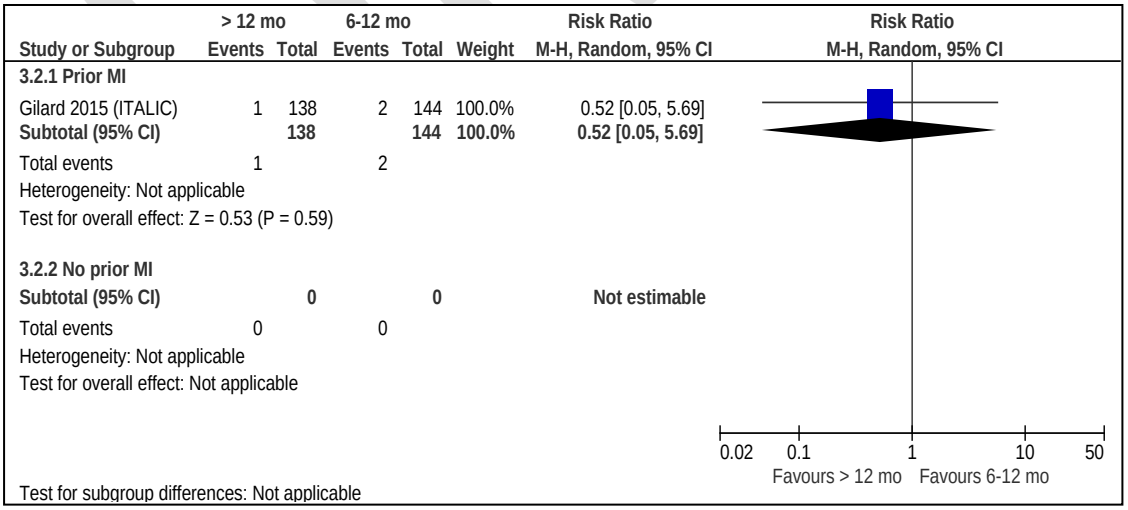


No studies assessed all-cause death among participants with or without a history of MI by stent type (BMS or DES).

5.1.1.1.32 Cardiovascular death

One RCT[31] involving 282 participants with a history of MI reported no significant difference in the risk of cardiovascular death between 6–12 months and > 12 months of DAPT (RR 0.52, 95%CI 0.05, 5.69) (Figure 34). No RCTs assessed cardiovascular death among participants with no history of MI.

Figure 34: Relative risk of cardiovascular death among participants with or without a history of myocardial infarction



No studies assessed cardiovascular death among participants with or without a history of MI by stent type (BMS or DES).

5.1.1.1.33 Non-cardiovascular death

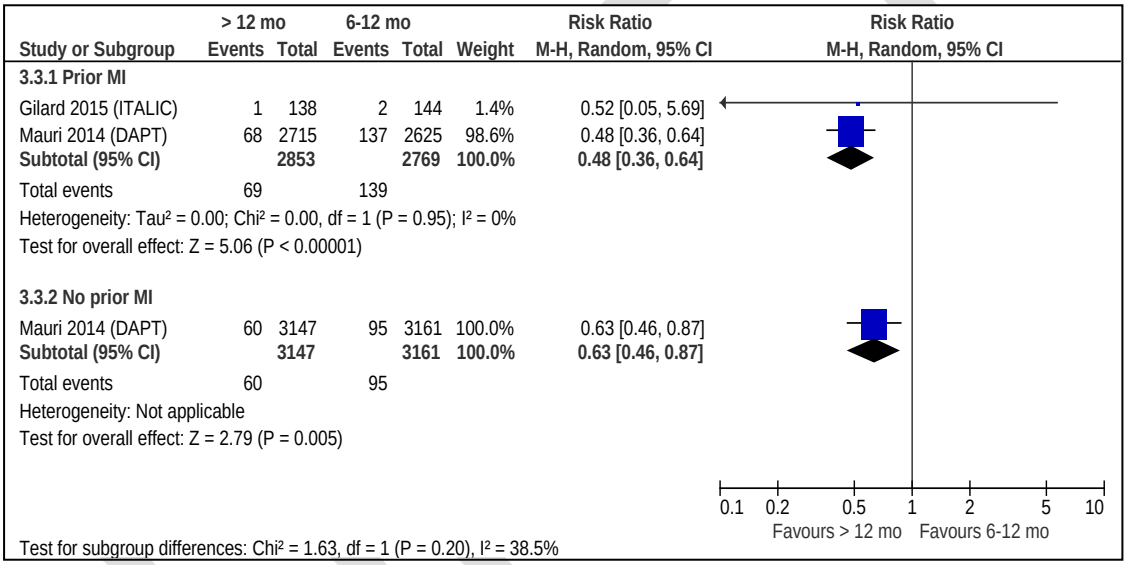
None of the included RCTs assessed non-cardiovascular death among participants with or without prior MI.

5.1.1.1.34 Myocardial infarction

Two RCTs[24,31] involving 5,622 participants reported the new occurrence of MI. Among participants with a prior MI, participants who received DAPT for >12 months were at lower risk of new MI compared with those who received six to 12 months of DAPT (RR 0.48, 95%CI 0.36 to 0.64) (Figure 35).

One RCT[24]involving 6,308 participants with no history of MI reported a significant lower risk of new MI among participants who received more than 12 months of DAPT compared with those who received six to 12 months of DAPT (RR 0.63, 95%CI 0.46 to 0.87) (Figure 35).

Figure 35: Relative risk of new myocardial infarction among participants with or without a history of myocardial infarction

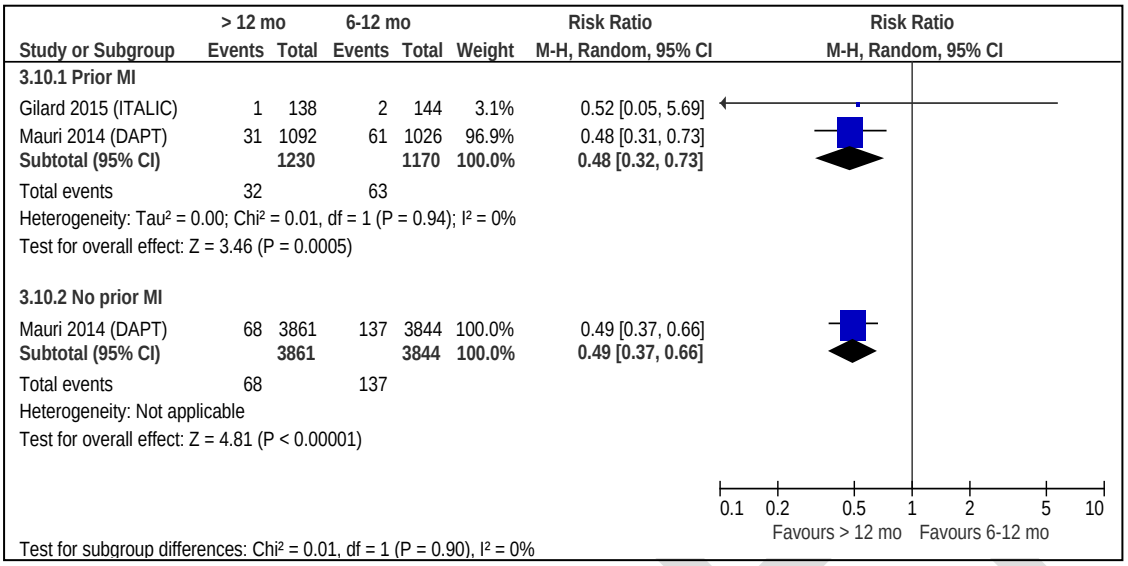


Drug eluting stents

Two RCTs[24,31] assessed myocardial infarction among participants with an implanted DES and with or without a history of MI.

Among those with an implanted DES, extended DAPT for more than 12 months was associated with a lower risk of MI among those with (RR 0.48, 95%CI 0.32 to 0.73) or without (RR 0.49, 95%CI 0.37 to 0.66) a history of MI (Figure 36).

Figure 36: Relative risk of new myocardial infarction among participants with an implanted DES with or without a history of myocardial infarction



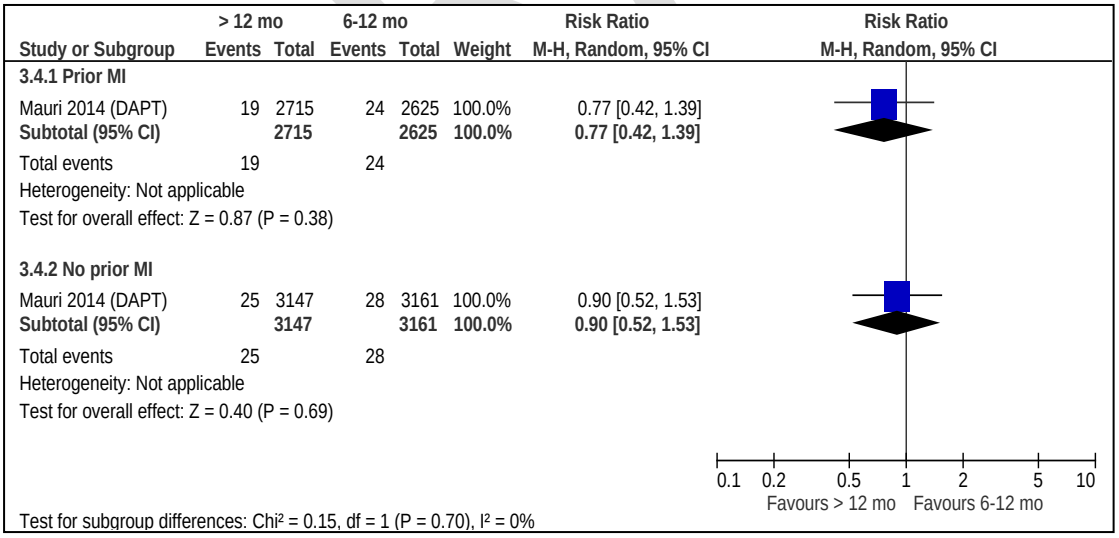
Bare metal stents

No studies assessed MI among participants with or without a history of MI with an implanted BMS.

5.1.1.1.35 Stroke

One RCT[24] reported no significant difference in the risk of stroke among participants with (RR 0.77, 95% CI 0.42 to 1.39) or without (RR 0.90, 95%CI 0.52 to 1.53) prior MI (Figure 37).

Figure 37: Relative risk of stroke among participants with or without a history of myocardial infarction



No studies assessed stroke among participants with or without a history of MI by stent type (BMS or DES).

5.1.1.1.36 Stent thrombosis

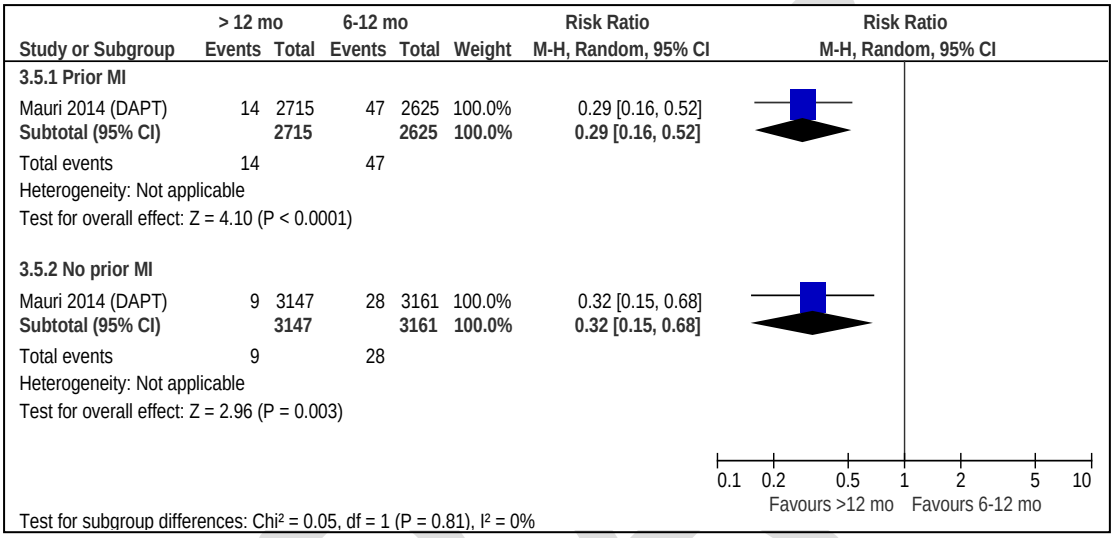
Definite

None of the included RCTs assessed definite stent thrombosis among participants with or without prior MI.

Definite or probable stent thrombosis

One RCT[24] reported a significantly lower risk of definite or probable stent thrombosis among participants with (RR 0.29, 95% CI 0.16, 0.52) or without (RR 0.32, 95%CI 0.15 to 0.68) prior MI (Figure 38).

Figure 38: Relative risk of definite or probable stent thrombosis among participants with or without a history of myocardial infarction

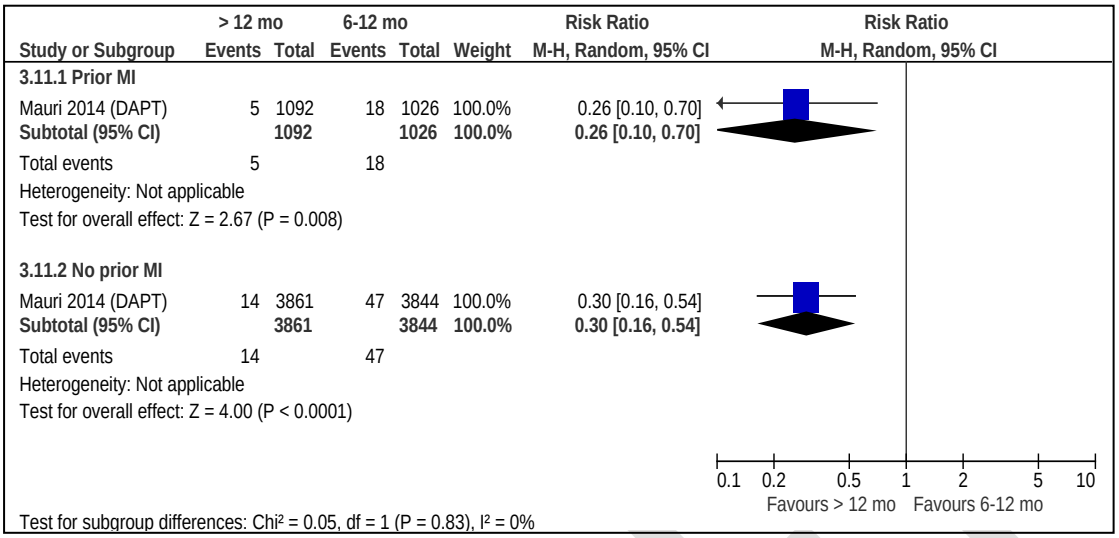


Drug-eluting stents

One RCT[24] assessed probable or definite stent thrombosis among participants with an implanted DES and with or without a history of MI.

Among those with an implanted DES, extended DAPT for more than 12 months was associated with a lower risk of definite or probable stent thrombosis among those with (RR 0.26, 95%CI 0.10 to 0.70) or without (RR 0.30, 95%CI 0.16 to 0.54) a history of MI (Figure 39).

Figure 39: Relative risk of definite or probable stent thrombosis among participants with an implanted DES with or without a history of myocardial infarction



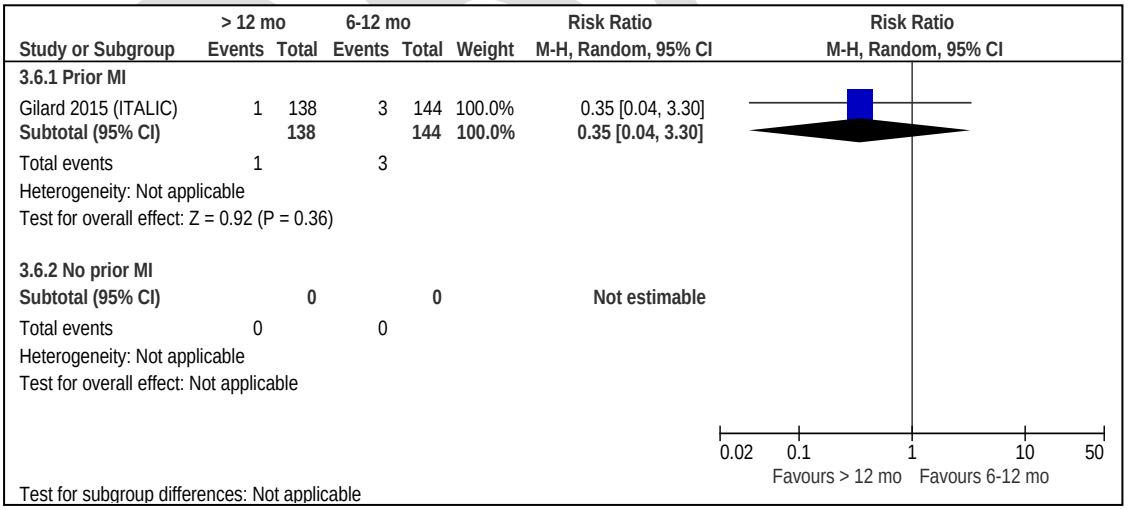
Bare-metal stents

No studies assessed probable or definite stent thrombosis among participants with an implanted BMS with or without a history of MI.

5.1.1.1.37 Urgent revascularization

One RCT[31] involving 282 participants with a history of MI reported no significant difference in the risk of urgent revascularization between 6–12 months and > 12 months of DAPT (RR 0.35, 95%CI 0.04 to 3.30) (Figure 40). No RCTs assessed urgent revascularization among participants with no history of MI.

Figure 40: Relative risk of urgent revascularization among participants with or without a history of myocardial infarction

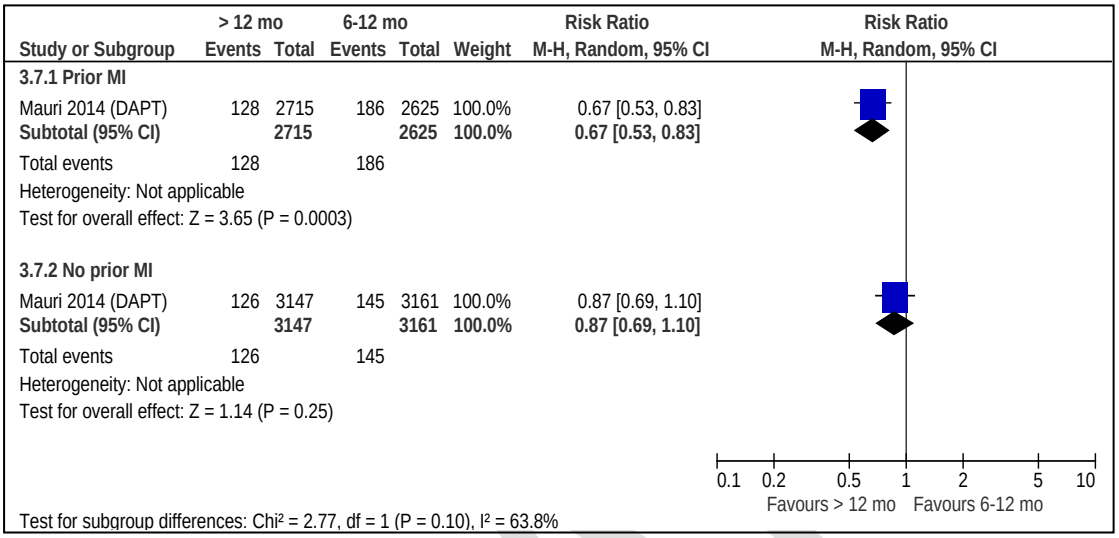


No studies assessed urgent revascularization among participants with or without a history of MI by stent type (BMS or DES).

5.1.1.1.38 MACCE

One RCT[24] reported a significantly lower risk of MACCE (all-cause death, MI, stroke) among participants with prior MI (RR 0.67, 95% CI 0.53 to 0.83), but no significant difference among participants with no history of MI (RR 0.87, 95% CI 0.69, 1.10) (Figure 41).

Figure 41: Relative risk of MACCE among participants with or without a history of myocardial infarction



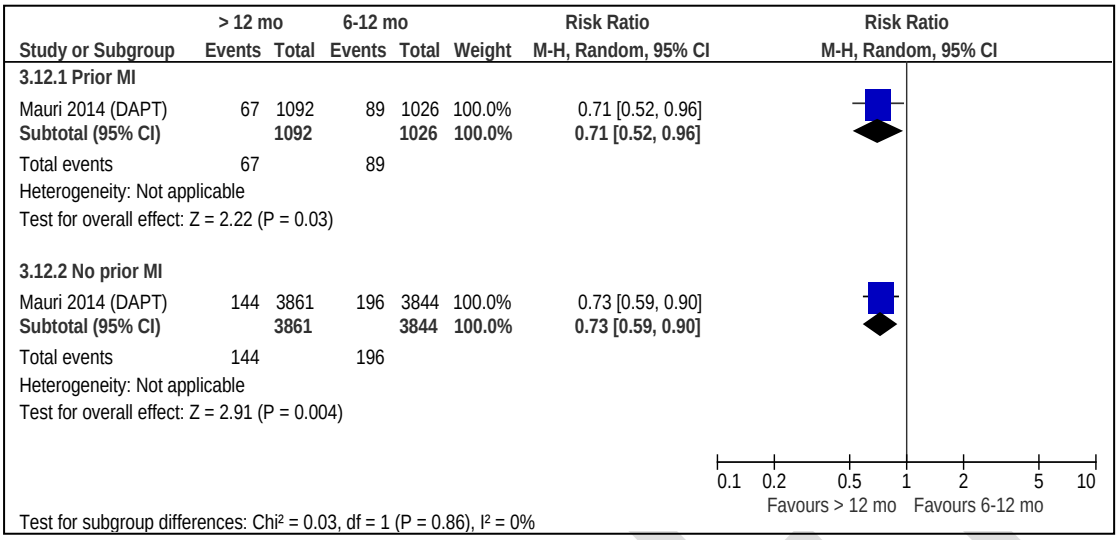
Using an alternative definition of MACCE (all-cause death, MI, stroke, urgent revascularization, major bleeding), one RCT (ITALIC[31]) reported a non-significant difference in risk between DAPT for six to 12 months or DAPT for > 12 months (RR 0.38, 95%CI 0.12 to 1.16) among those with a history of MI. No data were reported for participants without a history of MI.

Drug-eluting stents

One RCT[24] assessed MACCE (all-cause death, MI, stroke) among participants with an implanted DES and with or without a history of MI.

Among those with an implanted DES, extended DAPT for more than 12 months was associated with a lower risk of MACCE among those with (RR 0.71, 95%CI 0.52 to 0.96) or without (RR 0.73, 95%CI 0.59 to 0.90) a history of MI (Figure 42).

Figure 42: Relative risk of MACCE among participants with an implanted DES with or without a history of myocardial infarction



Bare-metal stents
No studies assessed MACCE among participants with an implanted BMS with or without a history of MI.

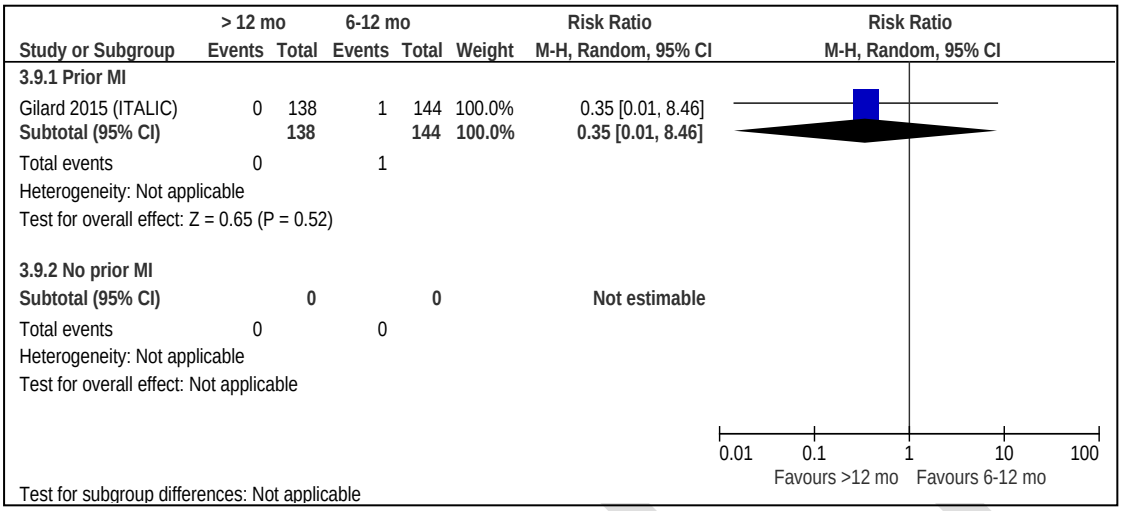
5.1.1.1.39 Gastrointestinal bleeding
No studies reported gastrointestinal bleeding among participants with or without a history of MI.

5.1.1.1.40 Major and minor bleeding

TIMI Major Bleeding
No studies reported TIMI major bleeding among participants with or without a history of MI.

TIMI Minor Bleeding
One RCT[31] reported no significant difference in the risk of TIMI minor bleeding among participants with prior MI (RR 0.35, 95% CI 0.01 to 8.46) (Figure 43). This trial (ITALIC[31]) involved only participants with an implanted DES. No data were available for participants without a history of MI.

Figure 43: Relative risk of TIMI minor bleeding among participants with or without a history of myocardial infarction



Other bleeding

Among participants with either a DES or BMS, the risk of GUSTO moderate or severe bleeding, GUSTO moderate bleeding, and BARC Type 2, 3 or 5 bleeding was significantly higher among those who received extended DAPT compared with DAPT for six to 12 months both with or without a history of MI (Table 9). There was no difference in GUSTO severe bleeding between DAPT durations for either those with or without a history of MI.

Among participants with an implanted DES, there was an increased risk of GUSTO moderate or severe bleeding among those without a history of MI (RR 1.72, 95%CI 1.24 to 2.39), but not among those with a history of MI (RR 1.25, 95%CI 0.68 to 2.29) (Table 9).

Table 9: Bleeding reported by use of alternative classification systems, among participants with or without a history of myocardial infarction

		Prior MI		No prior MI	
Trial	**Bleeding classification system***	**No. events/ no. participants**	**RR (95%CI)**	**No. events/ no. participants**	**RR (95%CI)**
Mauri 2014 (DAPT)†	GUSTO moderate or severe	12 mo: 29/2625 30 mo: 57/2715	**1.89 (1.21, 2.95)**	12 mo: 54/3161 30 mo: 85/3147	**1.58 (1.13, 2.22)**
	GUSTO moderate	12 mo: 16/2625 30 mo: 38/2715	**2.30 (1.28, 4.11)**	12 mo: 38/3161 30 mo: 57/3147	**1.51 (1.00, 2.26)**
	GUSTO severe	12 mo: 13/2625 30 mo: 16/2715	1.19 (0.57, 2.47)	12 mo: 19/3161 30 mo: 28/3147	1.48 (0.83, 2.64)
	BARC 2,3 or 5	12 mo: 55/2625 30 mo: 117/2715	**2.06 (1.50, 2.82)**	12 mo: 101/3161 30 mo: 192/ 3147	**1.91 (1.51, 2.42)**
Mauri 2014 (DAPT)‡	GUSTO moderate or severe	12 mo: 18/1026 30 mo: 24/1092	1.25 (0.68, 2.29)	12 mo: 55/3844 30 mo: 95/3861	**1.72 (1.24, 2.39)**

Note: BMS = bare-metal stent, CI = confidence interval, DES = drug-eluting stent, MI = myocardial infarction, mo = months, RR = relative risk.
*Definitions for each bleeding classification system are available in Appendix 10.
†Participants with either an implanted DES or BMS.
‡Participants with an implanted DES.

5.4.5 Participants with ACS at presentation

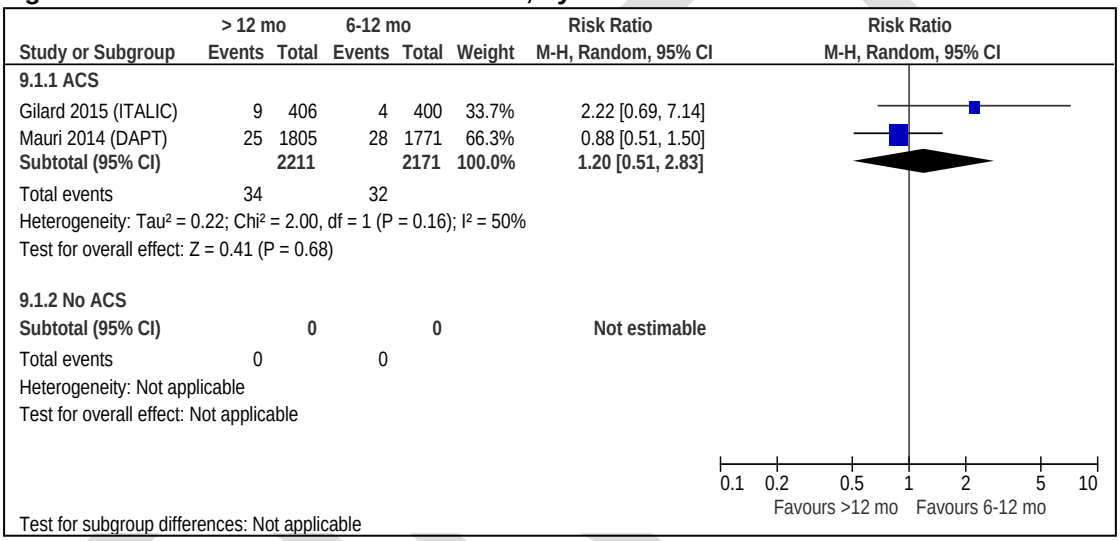
In total, six RCTs[23-25,27,31,34] reported data for participants with ACS. Of these, five trials[23,25,27,31,34] categorized participants as having "ACS" or "No ACS," while one RCT (DAPT) reported data for participants with an index MI (occurring within 72 hours before the index PCI).[24]

Although the PRODIGY trial[25] reported outcomes among those with and without ACS, subgroup data were reported only for the entire DAPT period (i.e., from PCI onward), which is not consistent with the period reported by the other trials (starting 6–12 months after PCI). As such, we did not pool data from PRODIGY with data from the other trials because of differences in the reporting period.

5.1.1.1.41 All-cause death

Two RCTs[24,31] involving 4,382 participants with ACS reported all-cause death, with no significant difference in the risk of all-cause death between DAPT >12 months or 6–12 months (RR 1.20, 95%CI 0.51 to 2.83) (Figure 44). No data were reported for participants without ACS.

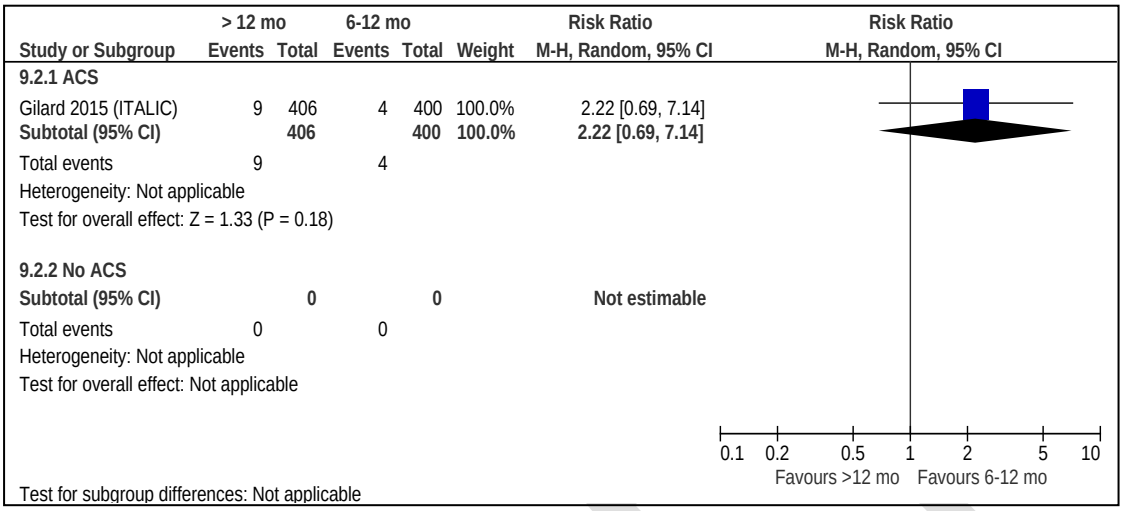
Figure 44: Relative risk of all-cause death, by ACS status



Drug-eluting stents

Among participants with ACS at presentation who received a DES, there was no significant difference in the risk of all-cause death between DAPT for > 12 months and 6-12 months (RR 2.22, 95%CI 0.69 to 7.14) (Figure 45). No data were reported for participants without ACS.

Figure 45: Relative risk of all-cause death among participants with an implanted DES, by ACS status



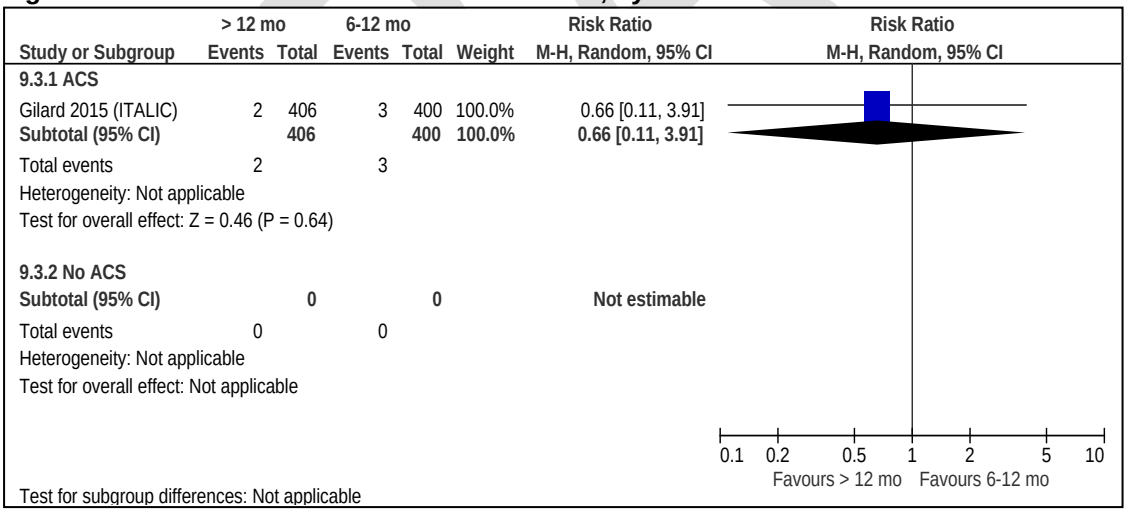
Bare-metal stents

No studies assessed all-cause death among participants with an implanted BMS by ACS status.

5.1.1.1.42 Cardiovascular death

One RCT[31] involving 806 participants with ACS assessed cardiovascular death, with no significant difference in risk between DAPT for >12 months or 6-12 months (RR 0.66, 95%CI 0.11 to 3.91) (Figure 46). No data were reported for participants without ACS.

Figure 46: Relative risk of cardiovascular death, by ACS status



Drug-eluting stents

Among participants with ACS and with a DES, there was no difference in the risk of cardiovascular death between DAPT durations (RR 0.66, 95%CI 0.11 to 3.91) (Figure 46). No data were reported for participants without ACS.

Bare-metal stents

No studies assessed all-cause death among participants with an implanted BMS by ACS status.

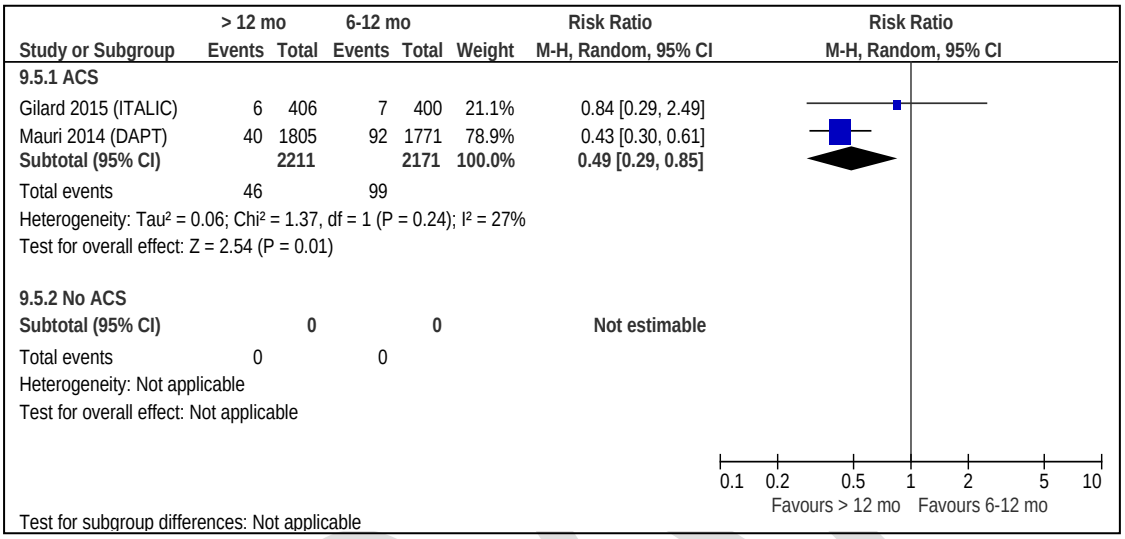
5.1.1.1.43 Non-cardiovascular death

No studies assessed non-cardiovascular death among participants with ACS.

5.1.1.1.44 Myocardial infarction

Two RCTs[24,31] involving 4,382 participants with ACS assessed MI. Among those with ACS at presentation, extended DAPT was associated with a lower risk of MI compared with DAPT for six to 12 months (RR 0.49, 95%CI 0.29 to 0.85) (Figure 47). No data were reported for participants without ACS.

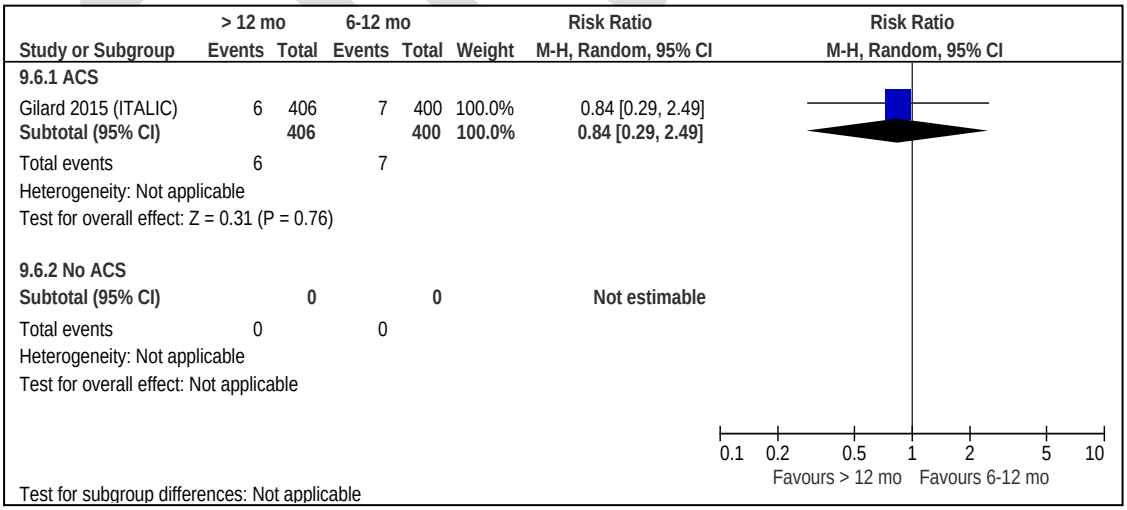
Figure 47: Relative risk of myocardial infarction, by ACS status



Drug-eluting stents

Among participants with ACS and with a DES, there was no difference in the risk of MI death between DAPT durations (RR 0.84, 95%CI 0.29 to 2.49) (Figure 48). No data were reported for participants without ACS.

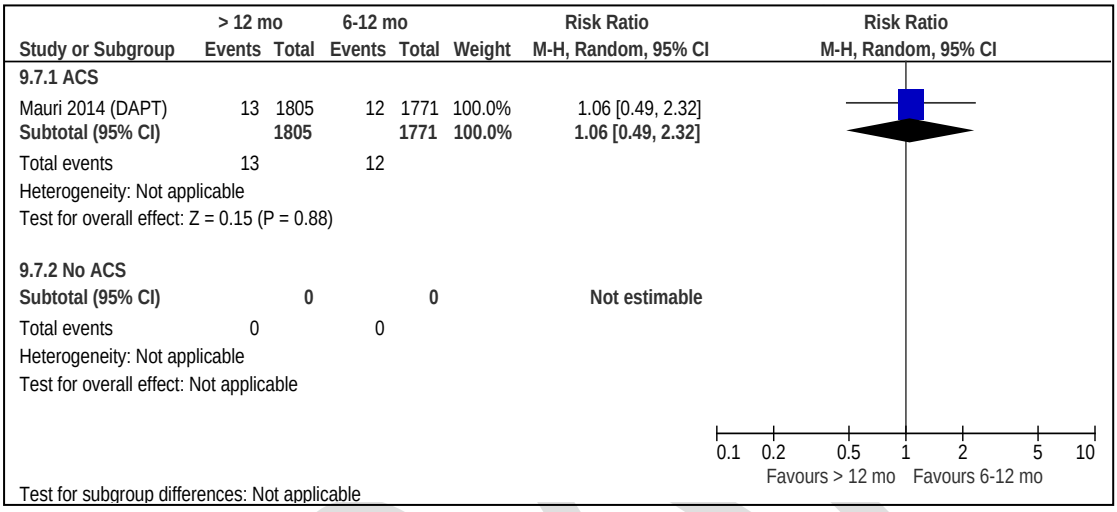
Figure 48: Relative risk of myocardial infarction among participants with an implanted DES, by ACS status



Bare-metal stents
No studies assessed MI among participants with an implanted BMS by ACS status.

5.1.1.1.45 Stroke
One RCT[24] involving 3,576 participants with ACS assessed stroke. Among those with ACS at presentation, there was no significant difference in the risk of stroke between those who received DAPT for > 12 months or 6-12 months (RR 1.06, 95%CI 0.49 to 2.32) (Figure 49). No data were reported for participants without ACS.

Figure 49: Relative risk of stroke, by ACS status

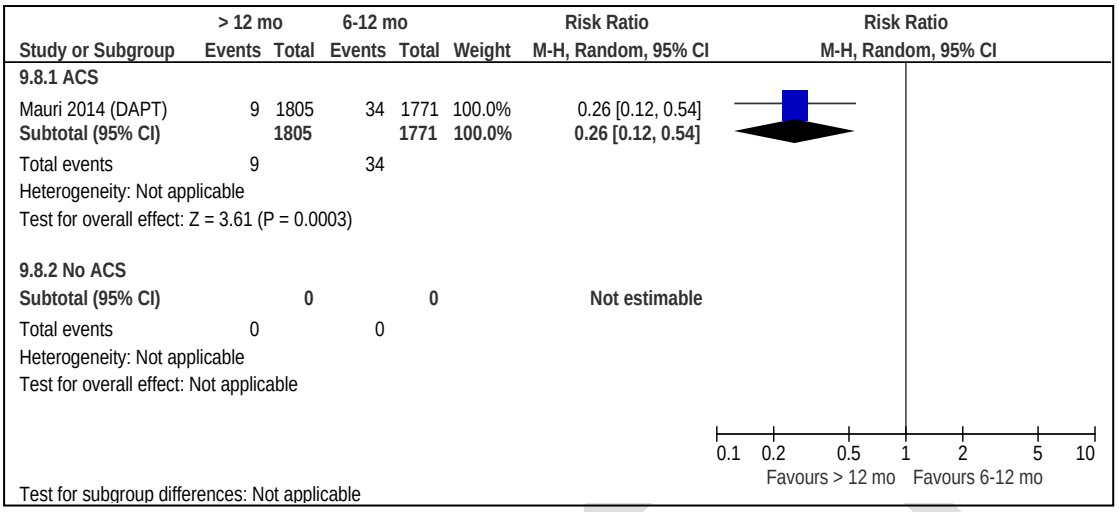


No studies assessed stroke among participants with or without ACS by stent type (BMS or DES).

5.1.1.1.46 Stent thrombosis
Definite stent thrombosis
No studies assessed definite stent thrombosis by ACS status.

Definite or probable stent thrombosis
One RCT[24] involving 3,576 participants with ACS assessed definite or probable stent thrombosis. Among those with ACS at presentation, those who received DAPT for > 12 months were at lower risk of definite or probable stent thrombosis compared with those who received DAPT for 6-12 months (RR 0.26, 95%CI 0.12 to 0.54) (Figure 50). No data were reported for participants without ACS.

Figure 50: Relative risk of definite or probable stent thrombosis, by ACS status



No studies assessed stroke among participants with or without ACS by stent type (BMS or DES).

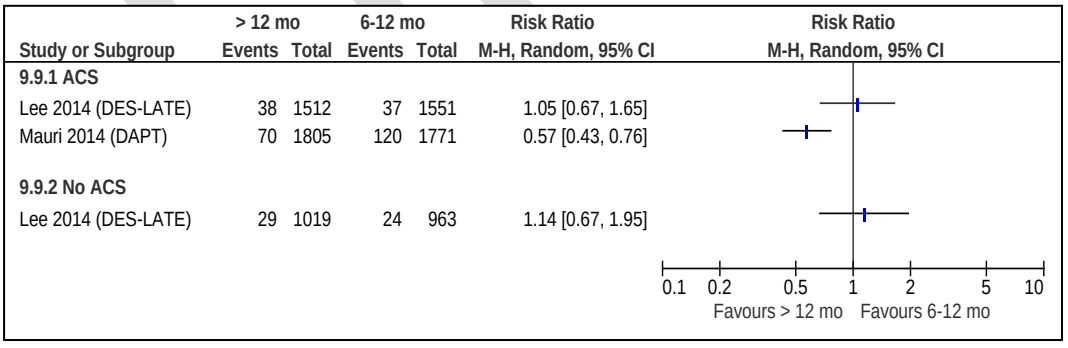
5.1.1.1.47 Urgent revascularization

One RCT[31] reported urgent revascularization among 806 participants with ACS, reporting six events in the extended DAPT group (24 months; n = 406) and no events in the control group (6 months; n = 400) (RR 0.08, 95%CI 0.00 to 1.34).No data were available for participants without ACS.

5.1.1.1.48 MACCE

Two RCTs[24,27] involving 6,639 participants with ACS assessed MACCE by use of a consistent definition (all-cause death, MI, stroke). One RCT (DAPT) reported a statistically significant decrease in MACCE among participants with ACS who received extended DAPT (RR 0.57, 95%CI 0.43 to 0.76). In contrast, a second RCT (DES-LATE) reported no significant difference in MACCE in this group (RR 1.05, 95%CI 0.67 to 1.65). The results of these trials were not pooled because of high heterogeneity (I^2 = 80%). There was also no significant difference in the risk of MACCE between DAPT durations in participants without ACS (RR 1.14, 95% CI 0.67, 1.95).

Figure 51: Relative risk of MACCE, by ACS status



An additional three RCTs[23,31,34] assessed MACCE by use of varied definitions among participants with ACS. Despite differences in definitions across trials, each of the RCTs reported no significant difference in the risk of MACCE between DAPT durations in participants with or without ACS (Table 10).

Table 10: MACCE reported by use of alternative definitions, by ACS status

		ACS		No ACS	
Trial	MACCE definition	No. events/ no. participants	RR (95%CI)	No. events/ no. participants	RR (95%CI)
Nakamura 2017 (NIPPON)	All-cause death, Q-wave or non–Q-wave MI, cerebrovascular events, major bleeding	6 mo: 14/611 18 mo: 7/641	0.48 (0.19, 1.18)	6 mo: 20/1128 18 mo: 17/1104	0.87 (0.46, 1.65)
Gilard 2015 (ITALIC)	All-cause mortality, MI, stroke, urgent revascularization, major bleeding	6 mo: 14/400 24 mo: 17/406	1.20 (0.60, 2.39)	NR	—
Collet 2014 (ARCTIC-INT)	All-cause death, myocardial infarction, stent thrombosis, stroke, urgent revascularisation	12 mo: 8/167 18–30 mo: 6/156	0.80 (0.28, 2.26)	12 mo: 19/457 18 mo: 18/479	0.90 (0.48, 1.70)

Note: ACS = acute coronary syndrome, CI = confidence interval, MACCE = major adverse cardiac and cerebrovascular events, MI = myocardial infarction, mo = months, NR = not reported, RR = relative risk.

5.1.1.1.49 Gastrointestinal bleeding

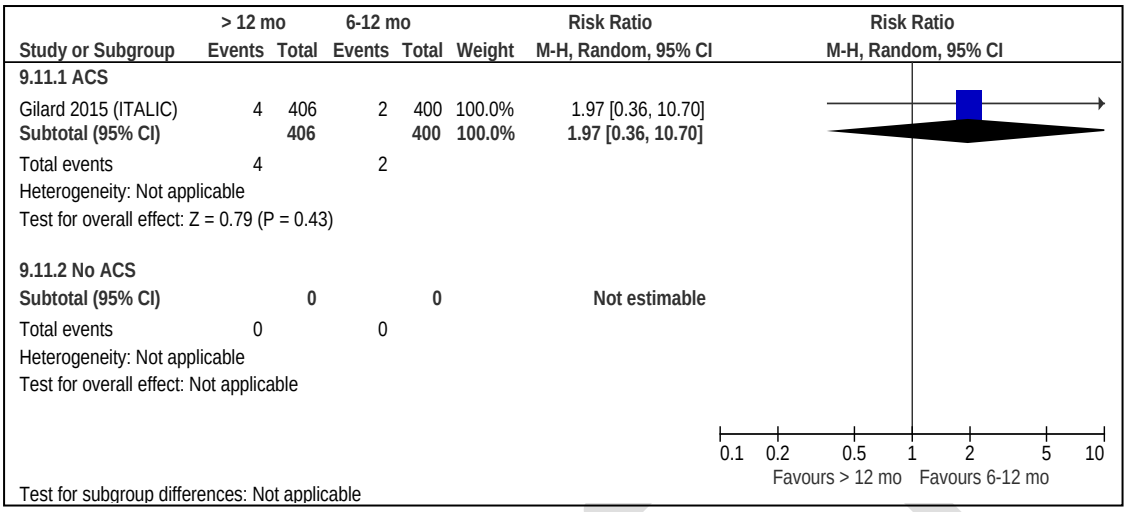
No studies assessed gastrointestinal bleeding by ACS status.

5.1.1.1.50 Major and minor bleeding

TIMI major bleeding
No studies assessed TIMI major bleeding by ACS status.

TIMI minor bleeding
One RCT[31] assessed TIMI minor bleeding among 806 participants with ACS. Among participants with ACS, there was no significant difference in the risk of TIMI minor bleeding between DAPT for > 12 months or 6-12 months (RR 1.97, 95% CI 0.36 to 10.70) (Figure 52); only participants with an implanted DES were eligible for this trial. No data were reported for participants without ACS.

Figure 52: Relative risk of TIMI minor bleeding, by ACS status



Alternative bleeding classification systems

Among participants with ACS, extended DAPT was associated with a significantly higher risk of BARC Type 2,3,or 5 bleeding, GUSTO moderate or severe bleeding, and GUSTO moderate bleeding, but no statistically significant difference in GUSTO severe bleeding (Table 11). No data were available for participants without ACS

Table 11: Bleeding reported by use of alternative classification systems, by ACS status

		ACS		No ACS	
Trial	**Bleeding classification system***	**No. events/ no. participants**	**RR (95%CI)**	**No. events/ no. participants**	**RR (95%CI)**
Mauri 2014 (DAPT)†	GUSTO moderate or severe	12 mo: 14/1771 30 mo: 34/1805	**2.38 (1.28, 4.42)**	NR	—
	GUSTO moderate	12 mo: 5/1771 30 mo: 22/1805	**4.23 (1.64, 11.37)**	NR	—
	GUSTO severe	12 mo: 9/1771 30 mo: 13/1805	1.42 (0.61, 3.31)	NR	—
	BARC 2,3,5	12 mo: 37/1771 30 mo: 78/1805	**2.07 (1.41, 3.04)**	NR	—

Note: ACS = acute coronary syndrome, CI = confidence interval, mo = months, NR = not reported, RR = relative risk.
*Definitions for each bleeding classification system are available in Appendix 10.
†Participants with either an implanted DES or BMS.

5.4.6 Participants with diabetes

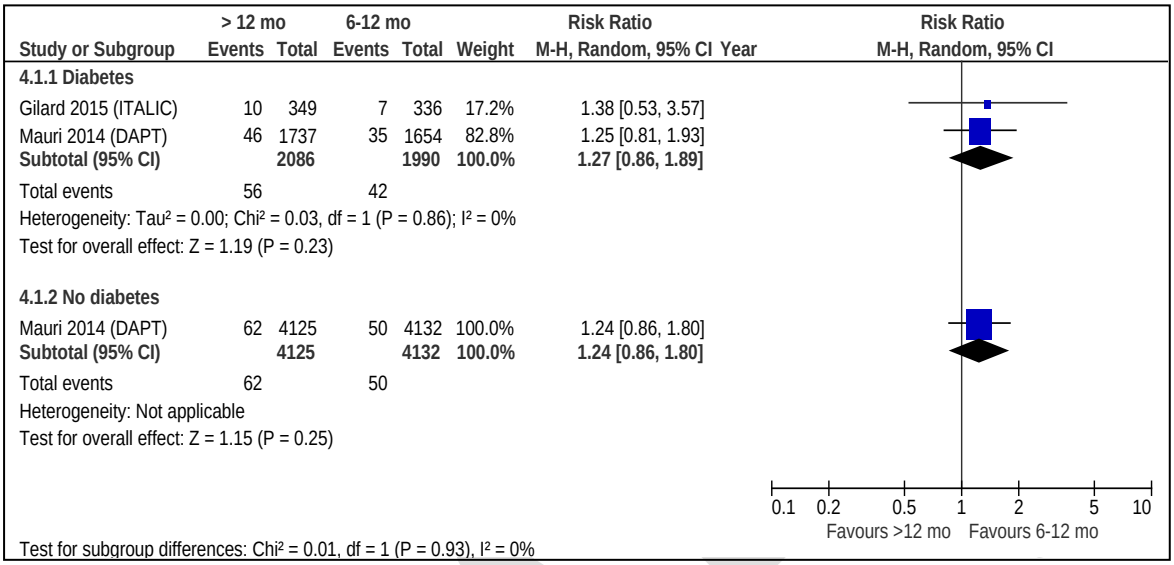
In total, two RCTs[24,31] reported outcome data among participants with diabetes. Both enrolled participants with either implanted DES or BMS. Neither study differentiated between Type 1 and Type 2 diabetes.

5.1.1.1.51 All-cause death

Two RCTs[24,31] reported all-cause death among 4,076 participants with diabetes, with no significant difference in the risk between DAPT for six to 12 months or >12 months (RR 1.27, 95%CI 0.86 to 1.89) (Figure 53).

One RCT[24] involving 8,257 participants without diabetes found no significant difference in the risk of all-cause death between DAPT durations (RR 1.24, 95%CI 0.86 to 1.80) (Figure 53).

Figure 53: Relative risk of all-cause death among participants with or without diabetes

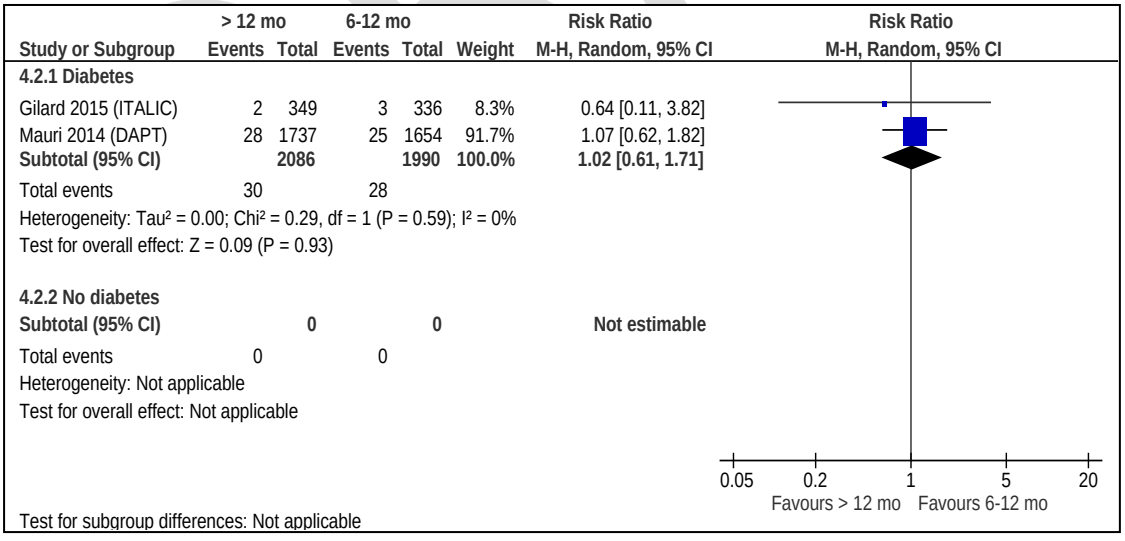


No studies assessed all-cause death among participants with or without diabetes by stent type (BMS or DES).

5.1.1.1.52 Cardiovascular death

Two RCTs[24,31] reported cardiovascular death among 4,076 participants with diabetes, with no significant difference in the risk between DAPT durations (RR 1.02, 95%CI 0.61 to 1.71) (Figure 54). No studies reported cardiovascular death among participants without diabetes.

Figure 54: Relative risk of cardiovascular death among participants with or without diabetes

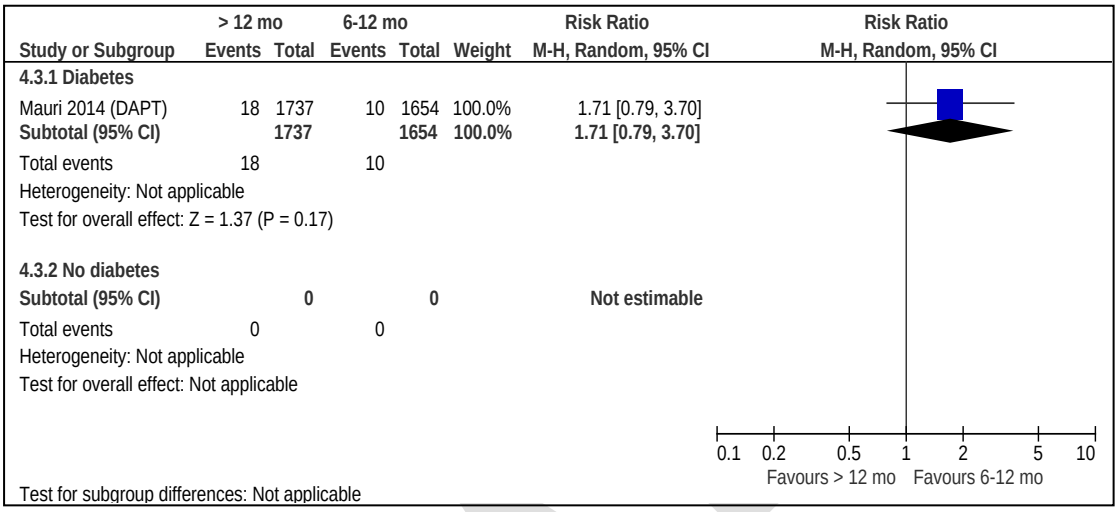


No studies assessed cardiovascular death among participants with or without diabetes by stent type (BMS or DES).

5.1.1.1.53 Non-cardiovascular death

One RCT[24] reported non-cardiovascular death among 3,391 participants with diabetes, with no significant difference in the risk between DAPT for six to 12 months or >12 months (RR 1.71, 95%CI 0.79 to 3.70) (Figure 55). No studies reported non-cardiovascular death among participants without diabetes.

Figure 55: Relative risk of non-cardiovascular death among participants with or without diabetes



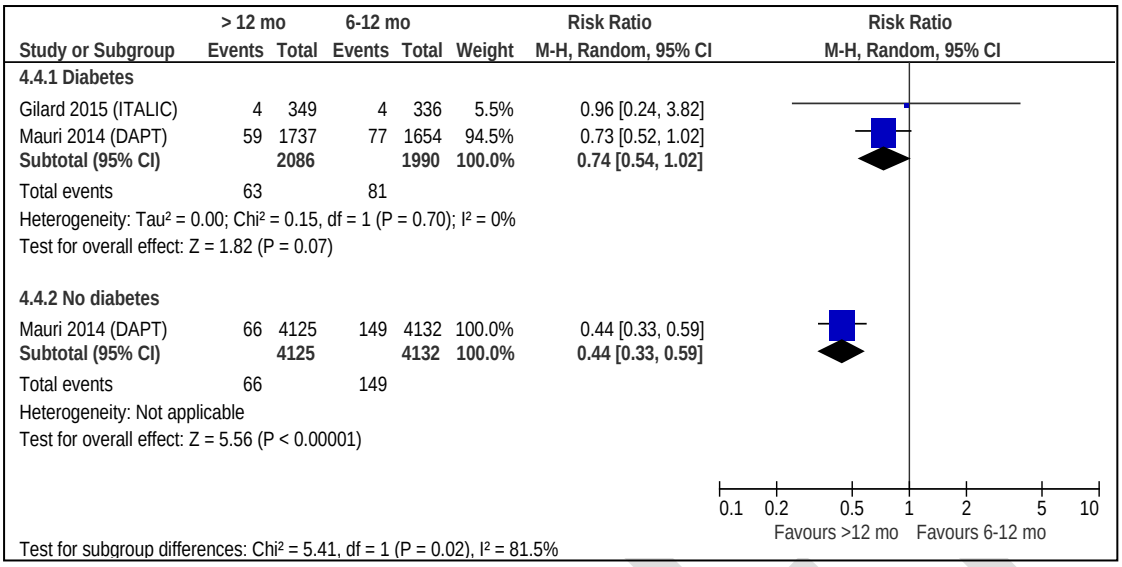
No studies assessed non-cardiovascular death among participants with or without diabetes by stent type (BMS or DES).

5.1.1.1.54 Myocardial infarction

Two RCTs[24,31] reported MI among 4076 participants with diabetes, with no significant difference in the risk between DAPT for 6–12 months or >12 months (RR 0.74, 95%CI 0.54 to 1.02) (Figure 56). Results from the DAPT trial suggest that extended DAPT may be protective against MI; however, these results were not statistically significant.

One RCT[24] involving 8257 participants without diabetes reported a significantly lower risk of MI among participants who received DAPT for >12 months compared with DAPT for six to 12 months (RR 0.44, 95%CI 0.33 to 0.59) (Figure 56).

Figure 56: Relative risk of myocardial infarction among participants with or without diabetes

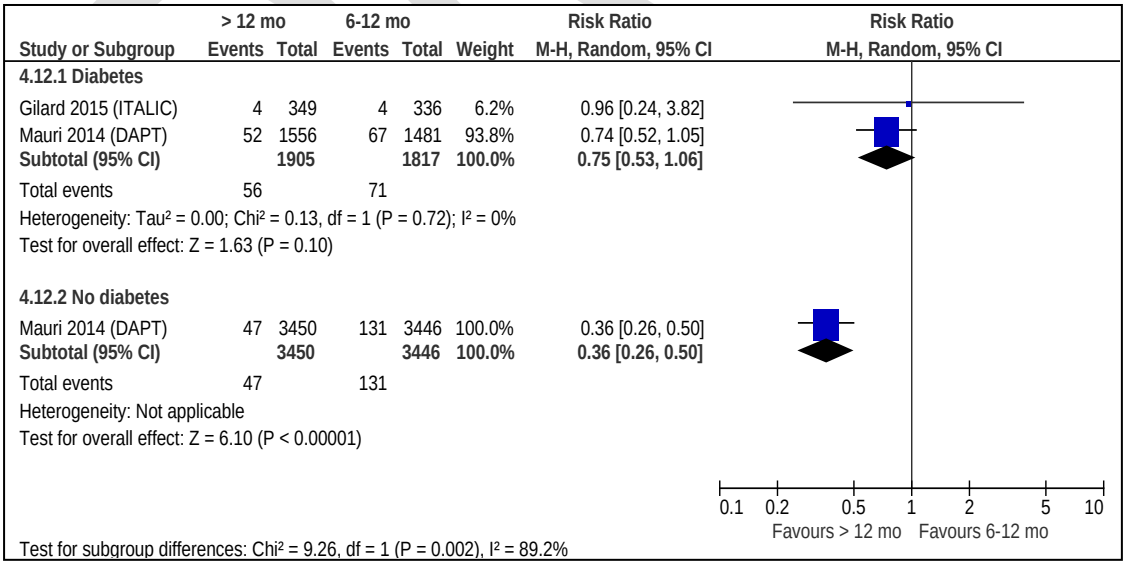


Drug-eluting stents

Two RCTs[24,31] assessed MI among participants with or without diabetes with an implanted DES. Among participants with diabetes, there was no significant difference in the risk between DAPT for six to 12 months or >12 months (RR 0.75, 95%CI 0.53 to 1.06) (Figure 57). Results from the DAPT trial suggest that extended DAPT may be protective against MI in this population; however, these results were not statistically significant.

Among participants without diabetes, the risk of MI was significantly lower among those who received DAPT for >12 months compared with 6–12 months (RR 0.36, 95%CI 0.26 to 0.50) (Figure 57).

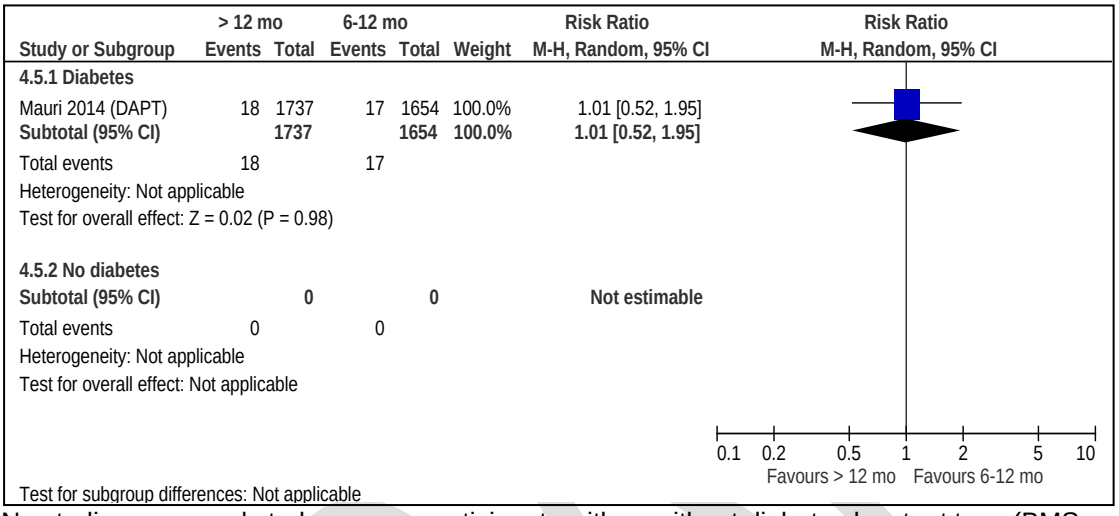
Figure 57: Relative risk of myocardial infarction among participants with an implanted DES, with or without diabetes



Bare-metal stents
No studies assessed myocardial infarction among participants with or without diabetes with an implanted BMS.

5.1.1.1.55 Stroke
One RCT[24] reported stroke among 3391 participants with diabetes, with no significant difference in the risk of stroke between DAPT for 6–12 months or >12 months (RR 1.01, 95%CI 0.52 to 1.95) (Figure 58). No studies reported stroke among participants without diabetes.

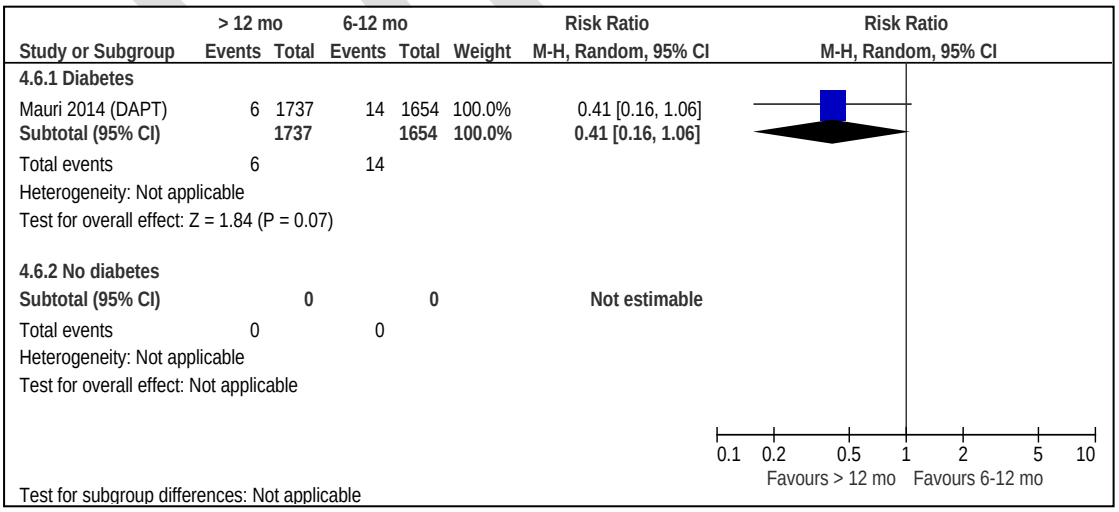
Figure 58: Relative risk of stroke among participants with or without diabetes



No studies assessed stroke among participants with or without diabetes by stent type (BMS or DES).

5.1.1.1.56 Stent thrombosis
Definite stent thrombosis
One RCT[24] reported definite stent thrombosis among 3,391 participants with diabetes, with no significant difference in the risk of definite stent thrombosis between DAPT for six to 12 months or >12 months (RR 0.41, 95%CI 0.16 to 1.06) (Figure 59). No studies reported definite stent thrombosis among participants without diabetes.

Figure 59: Relative risk of definite stent thrombosis among participants with or without diabetes



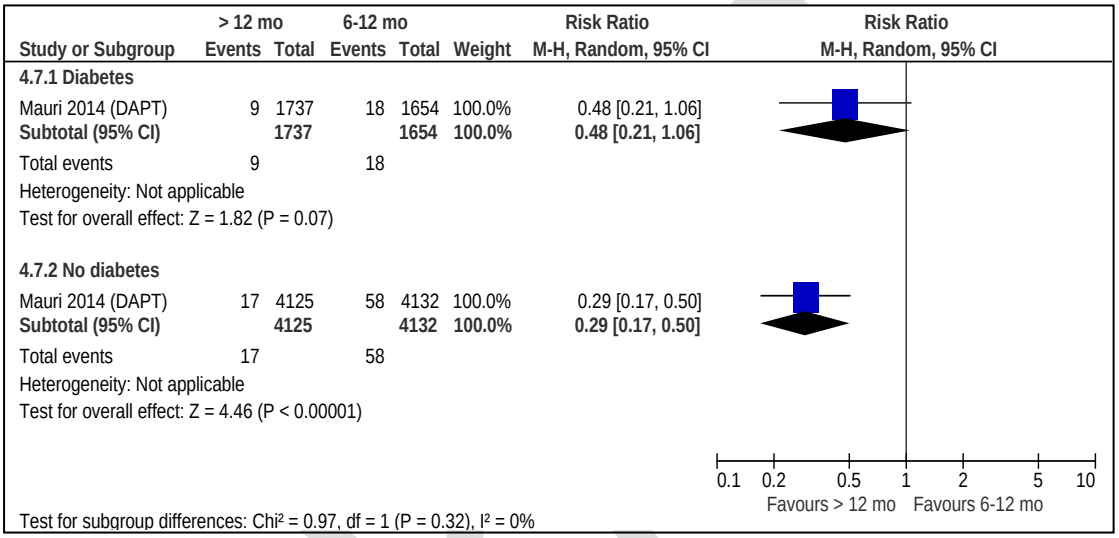
No studies assessed definite stent thrombosis among participants with or without diabetes by stent type (BMS or DES).

Definite or probable stent thrombosis

One RCT[24] reported no significant difference in the risk of definite or probable stent thrombosis among participants with diabetes (RR 0.48, 95%CI 0.21 to 1.06) (Figure 60).

Among participants without diabetes, one RCT[24] reported a significantly lower risk of definite or probable stent thrombosis among participants who received DAPT for >12 months compared with DAPT for six to 12 months (RR 0.29, 95%CI 0.17 to 0.50) (Figure 60).

Figure 60: Relative risk of definite or probable stent thrombosis among participants with or without diabetes

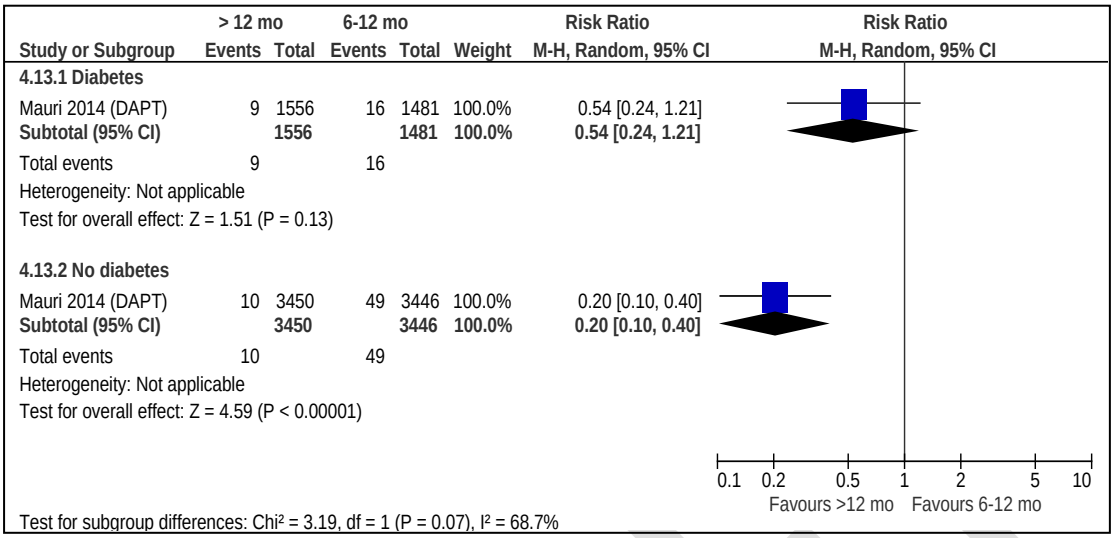


Drug-eluting stents

Among those with diabetes, there was no significant difference in the risk of definite or probable stent thrombosis with DAPT beyond 12 months compared with 6–12 months (RR 0.54, 95%CI 0.24 to 1.21) (Figure 61).

Among participants without diabetes, there was a significantly lower risk of definite or probable stent thrombosis among those who received DAPT for >12 months compared with 6–12 months (RR 0.20, 95%CI 0.10 to 0.40) (Figure 61).

Figure 61: Relative risk of definite or probable stent thrombosis among participants with an implanted DES, with or without diabetes



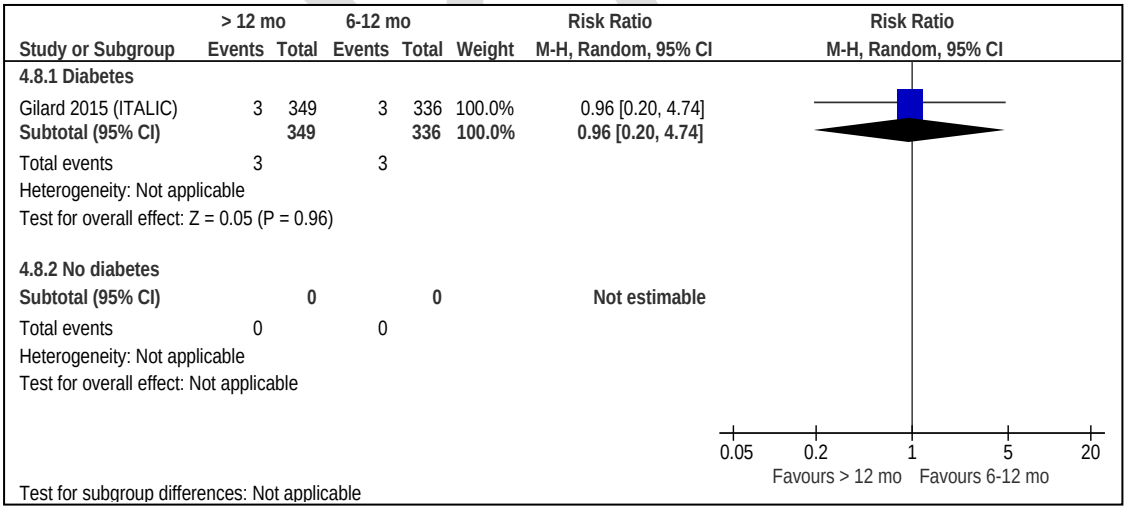
Bare-metal stents

No studies assessed definite or probable stent thrombosis among participants with or without diabetes with an implanted BMS.

5.1.1.1.57 Urgent revascularization

One RCT[31] involving 685 participants with diabetes reported no significant difference in the risk of urgent revascularization between 6–12 months and > 12 months of DAPT (RR 0.96, 95%CI 0.20 to 4.74) (Figure 62). No RCTs assessed urgent revascularization among participants without diabetes.

Figure 62: Relative risk of urgent revascularization among participants with or without diabetes



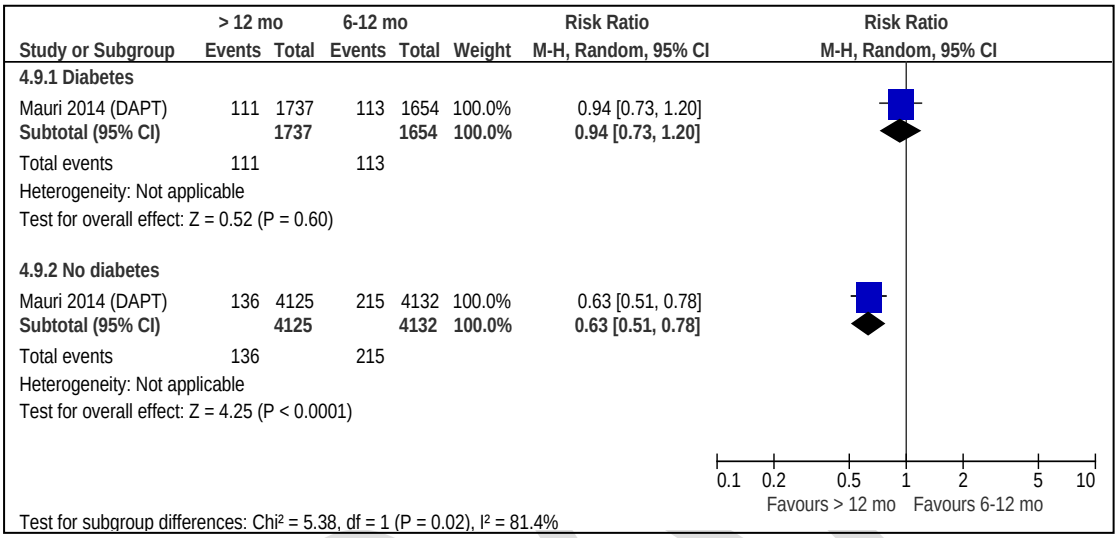
No studies assessed urgent revascularization among participants with or without diabetes by stent type (BMS or DES).

5.1.1.1.58 MACCE

Two RCTs[24,25] reported MACCE using a consistent definition (all-cause death, MI, stroke) and are described below. Valgimigli and colleagues (PRODIGY)[25] reported that there was no significant difference

in the hazard ratio for MACCE between DAPT for six or 24 months for participants with (HR 0.85, 95%CI 0.53 to 1.38) or without (HR 1.06, 95%CI 0.76 to 1.50) diabetes. Event counts were not reported, precluding pooling. Similarly, Mauri and colleagues (DAPT)[24] reported that there was no significant difference in the risk of MACCE between DAPT durations among those with diabetes (RR 0.94, 95%CI 0.73, 1.20) (Figure 63). However, among those without diabetes, Mauri and colleagues[24] found a significantly lower risk of MACCE with participants who received >12 months of DAPT compared with 6-12 months of DAPT (RR 0.63, 95%CI 0.51, 0.78) (Figure 63).

Figure 63: Relative risk of MACCE among participants with or without diabetes



An additional three RCTs[23,31,34] reported MACCE using alternative definitions. The outcome definitions and data are summarized in Table 12. Despite differences in definitions across trials, each of the RCTs reported no significant difference in the risk of MACCE between DAPT durations in either participants with or without diabetes (Table 12).

Table 12: MACCE reported by use of alternative definitions, by diabetes status

		Diabetes		No diabetes	
Trial	MACCE definition	No. events/ no. participants	RR (95%CI)	No. events/ no. participants	RR (95%CI)
Nakamura 2017 (NIPPON)	All-cause death, Q-wave or non–Q-wave MI, cerebrovascular events, major bleeding	6 mo: 17/619 18 mo: 10/635	0.57 (0.26, 1.24)	6 mo: 17/1035 18 mo: 14/1018	0.84 (0.41, 1.69)
Gilard 2015 (ITALIC)	All-cause mortality, MI, stroke, urgent revascularization, major bleeding	6 mo: 13/336 24 mo: 19/349	1.41 (0.71, 2.80)	NR	–
Collet 2014 (ARCTIC-INT)	All-cause death, myocardial infarction, stent thrombosis, stroke, urgent revascularisation	12 mo: 10/222 18-30 mo: 11/198	1.23 (0.54, 2.84)	12 mo: 17/402 18-30 mo: 13/437	0.70 (0.35, 1.43)

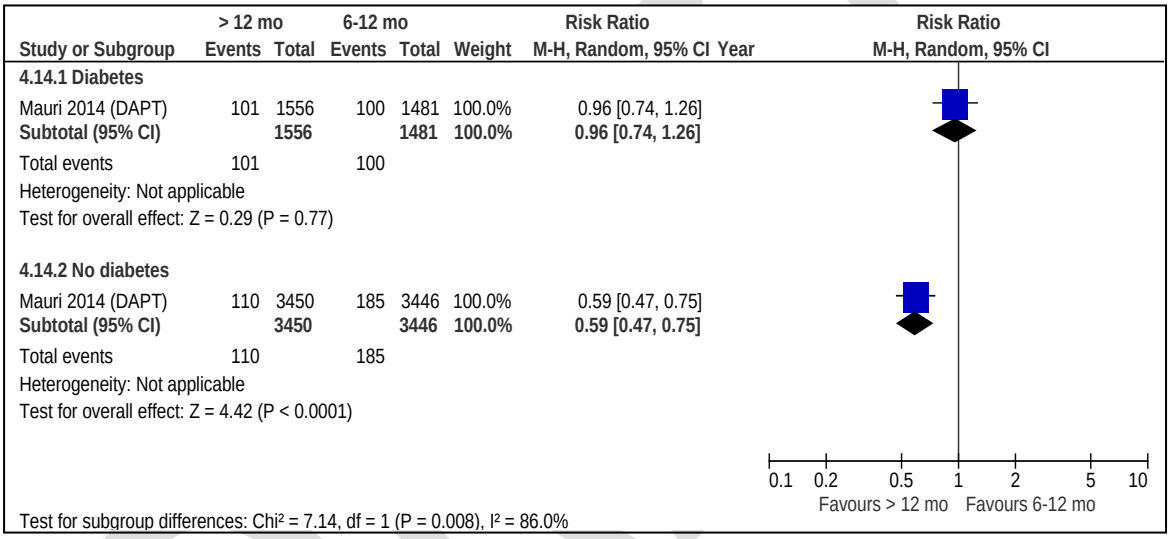
Note: CI = confidence interval, MACCE = major adverse cardiac and cerebrovascular events, MI = myocardial infarction, mo = months, NR = not reported, RR = relative risk..

Drug-eluting stents
One RCT[24] reported MACCE (all-cause death, MI, stroke) among participants with or without diabetes.

Among those with diabetes, there was no significant difference in the risk of MACCE between DAPT durations (RR 0.96, 95%CI 0.74, 1.26) (Figure 64). As reported in Table 12, three additional RCTs involving participants with diabetes found no significant difference in the risk of MACCE assessed by use of alternative definitions.

Among those without diabetes, the risk of MACCE was significantly lower among participants who received >12 months of DAPT compared with six to 12 months of DAPT (RR 0.59, 95%CI 0.47, 0.75) (Figure 64). As noted in Table 12, two additional RCTs involving participants without diabetes reported no significant difference in the risk of MACCE assessed by use of alternative definitions.

Figure 64: Relative risk of MACCE among participants with an implanted DES, with or without diabetes



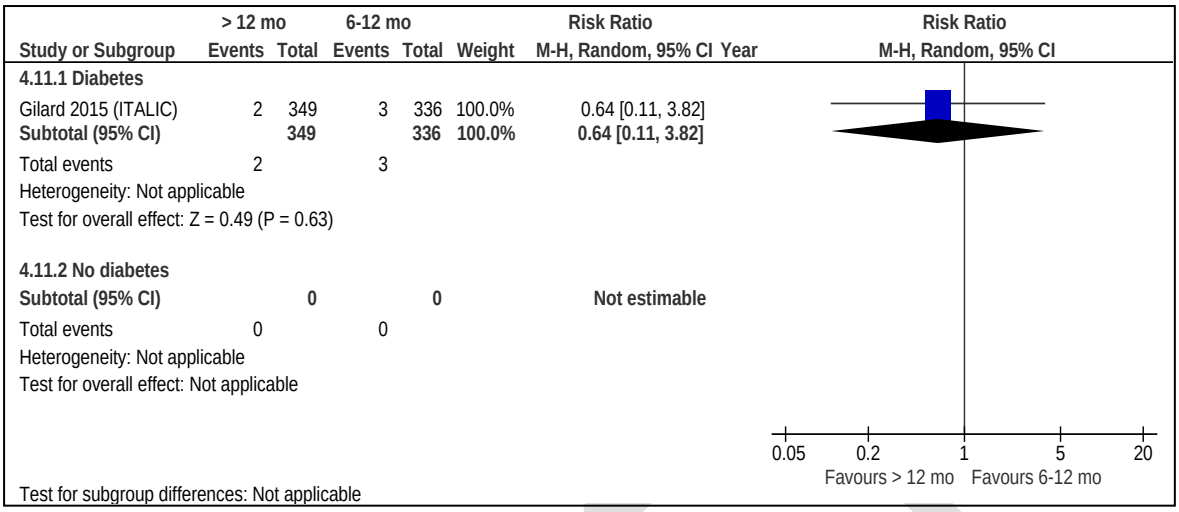
Bare-metal stents
No studies assessed MACCE among participants with or without diabetes with an implanted BMS.

5.1.1.1.59 Gastrointestinal bleeding
No studies reported gastrointestinal bleeding among participants with or without a history of diabetes.

5.1.1.1.60 Major and minor bleeding
TIMI Major Bleeding
No studies reported TIMI major bleeding among participants with or without diabetes.

TIMI Minor Bleeding
One RCT[31] reported no significant difference in the risk of TIMI minor bleeding among participants with diabetes (RR 0.64, 95% CI 0.11 to 3.82) (Figure 65). No data were reported for participants without diabetes.

Figure 65: Relative risk of TIMI minor bleeding among participants with or without diabetes



No studies assessed TIMI bleeding among participants with or without diabetes by stent type (BMS or DES).

Alternative bleeding classification systems

Among participants with diabetes, extended DAPT was associated with a significantly higher risk of BARC Type 2,3,or 5 bleeding (RR 1.59, 95%CI 1.15 to 2.19) as well as BARC Type 3 bleeding (RR 1.75, 95%CI 1.07 to 2.86) (Table 13).

Among those with no diabetes, there was a significant increase in the risk of GUSTO moderate or severe bleeding (RR 1.71, 95%CI 1.24 to 2.36) associated with extended DAPT.

Among participants with an implanted DES, there was a significantly higher risk of GUSTO moderate or severe bleeding among those without diabetes (RR 1.63, 95%CI 1.15 to 2.32) but not among those with diabetes (RR 1.55, 95%CI 0.93 to 2.56) (Table 13).

Table 13: Bleeding reported by use of alternative classification systems, among participants with or without diabetes

		Diabetes		No diabetes	
Trial	**Bleeding classification system***	**No. events/ no. participants**	**RR (95%CI)**	**No. events/ no. participants**	**RR (95%CI)**
Mauri 2014 (DAPT)†	GUSTO moderate or severe	12 mo: 26/1654 30 mo: 41/1737	1.50 (0.92, 2.44)	12 mo: 58/4132 30 mo: 99/4125	**1.71** **(1.24, 2.36)**
	GUSTO moderate	12 mo: 20/1654 30 mo: 32/1737	1.52 (0.87, 2.65)	NR	—
	GUSTO severe	12 mo: 6/1654 30 mo: 9/1737	1.43 (0.51, 4.00)	NR	—
	BARC 2,3,5	12 mo: 57/1654 30 mo: 95/1737	**1.59** **(1.15, 2.19)**	NR	—
	BARC 3	12 mo: 24/1654 30 mo: 44/1737	**1.75** **(1.07, 2.86)**	NR	—
	BARC 5	12 mo: 2/1654 30 mo: 1/1737	0.48 (0.04, 5.25)	NR	—

Mauri 2014 (DAPT)‡	GUSTO moderate or severe	12 mo: 24/1481 30 mo: 39/1556	1.55 (0.93, 2.56)	12 mo: 49/3446 30 mo: 80/3450	**1.63** **(1.15, 2.32)**

Note: CI = confidence interval, MI = myocardial infarction, mo = months, NR = not reported, RR = relative risk.
*Definitions for each bleeding classification system are available in Appendix 10.
†Participants with either an implanted DES or BMS.
‡Participants with an implanted DES.

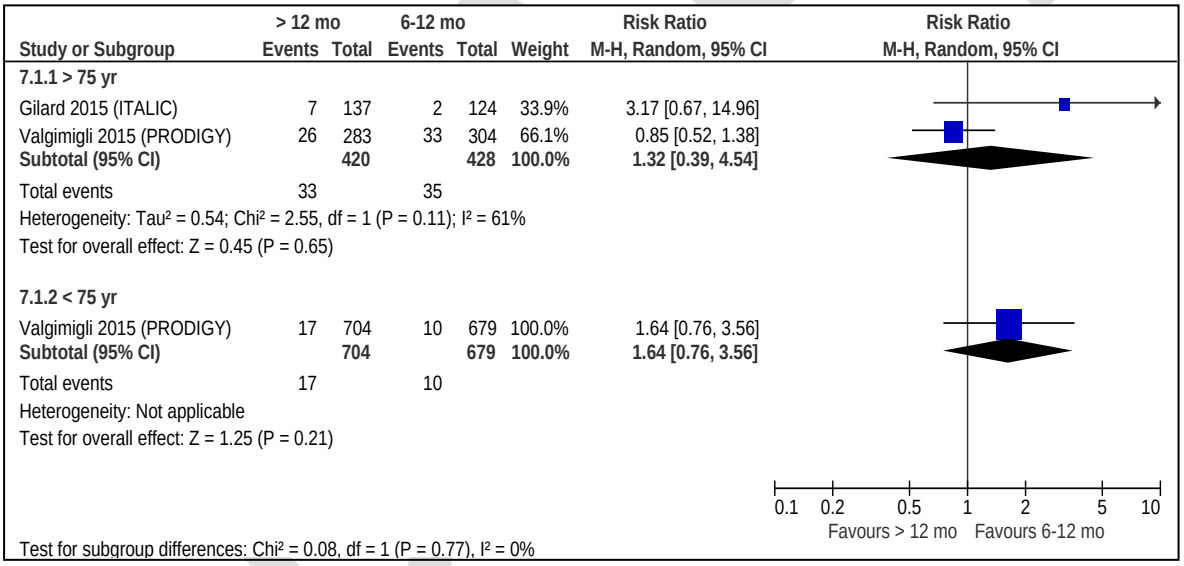
5.4.7 Age

In total, six RCTs[23-25,31,34] reported outcome data among participants aged more or less than 75 years. One additional RCT[27] provided risk outcome data among those aged more or less than 65 years. Outcome data were available for all-cause death, cardiovascular death, MI, stroke, stent thrombosis, urgent revascularization, MACCE, and bleeding.

5.1.1.1.61 All-cause death

Two RCTs[25,31] assessed all-cause death among 848 participants aged more than 75 years. There was no significant difference in the risk of all-cause death between DAPT for more than 12 months and six to 12 months (RR 1.32, 95%CI 0.39 to 4.54), with moderate heterogeneity between trials (I^2 = 61%) (Figure 66). One RCT[25] involving 1383 participants aged less than 75 years reported no significant difference in the risk of all-cause death between DAPT durations (RR 1.64, 95%CI 0.76 to 3.56) (Figure 66).

Figure 66: Relative risk of all-cause death, by age group



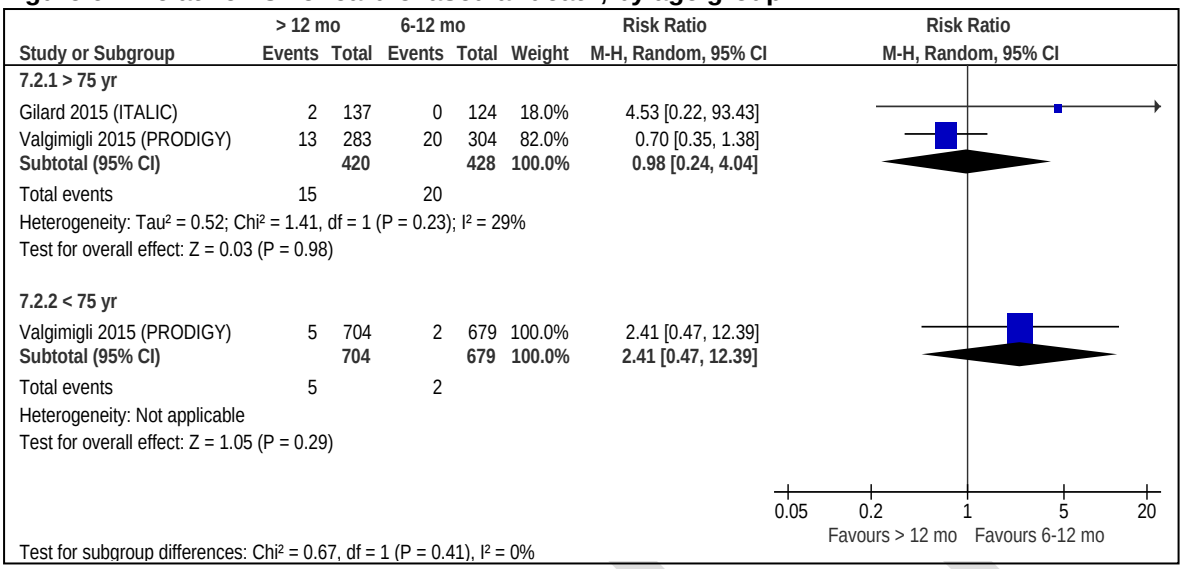
No studies assessed all-cause death among participants aged more or less than 75 years by stent type (BMS or DES).

5.1.1.1.62 Cardiovascular death

Two RCTs[25,31] assessed cardiovascular death among 848 participants aged more than 75 years. There was no significant difference in the risk of cardiovascular death between DAPT for more than 12 months and 6–12 months (RR 0.98, 95%CI 0.24 to 4.04), with moderate heterogeneity between trials (I^2 = 29%) (Figure 67).

One RCT[25] involving 1383 participants aged less than 75 years reported no significant difference in the risk of cardiovascular death between DAPT durations (RR 2.41, 95%CI 0.47 to 12.39) (Figure 67).

Figure 67: Relative risk of cardiovascular death, by age group



No studies assessed all-cause death among participants aged more or less than 75 years by stent type (BMS or DES).

5.1.1.1.63 Non-cardiovascular death

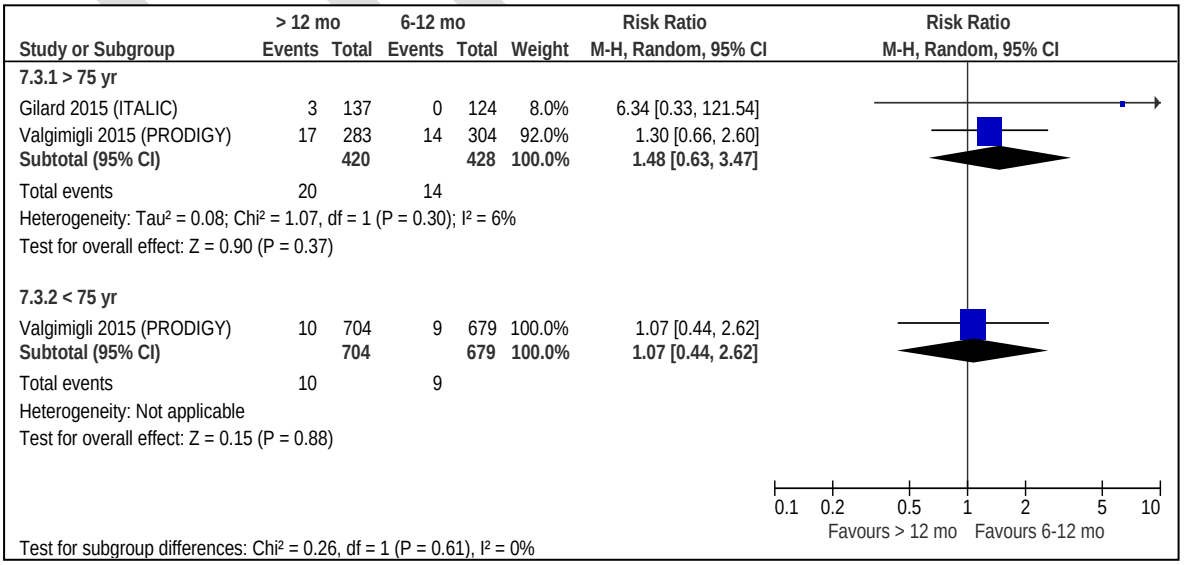
No studies assessed non-cardiovascular death among participants aged more or less than 75 years.

5.1.1.1.64 Myocardial infarction

Two RCTs[25,31] assessed MI among 848 participants aged more than 75 years. There was no significant difference in the risk of MI between DAPT for more than 12 months and 6–12 months (RR 1.48, 95%CI 0.63 to 3.47) (Figure 68).

One RCT[25] involving 1383 participants aged less than 75 years reported no significant difference in the risk of MI between DAPT durations (RR 1.07, 95%CI 0.44 to 2.62) (Figure 68).

Figure 68: Relative risk of myocardial infarction, by age group



One additional RCT (DAPT[24]) reported that there was a significantly lower risk of MI among participants aged less than 75 years (HR 0.46, 95%CI 0.36 to 0.60) but not among those aged more than 75 years (HR 0.76, 95%CI 0.38 to 1.54) (Table 14); the number of participants in each group was not reported, precluding pooling.

Table 14: Risk of myocardial infarction, by age group

		≥ 75 yr		< 75 yr	
Trial	**DAPT duration**	**%**	**Reported HR (95%CI)**	**%**	**Reported HR (95%CI)**
Mauri 2014 (DAPT)*	12 mo	3.6%	0.76 (0.38, 1.54)	4.2%	**0.46 (0.36, 0.60)**
	30 mo	2.7%		2.0%	

Note: CI = confidence interval, DAPT = dual anti-platelet therapy, DES = drug-eluting stent, HR = hazard ratio, mo = months, yr = year.
*Participants with a DES.

Drug-eluting stents
Two RCTs[24,31] assessed the risk of MI among participants with a DES aged more than 75 years. As shown in Figure 68, in the ITALIC trial,[31] there was no significant difference in the risk of MI between extended DAPT and DAPT for 6-12 months among participants aged more than 75 years.

Mauri et al. 2014 (DAPT[24]) reported that there was a significantly lower risk of MI among participants aged less than 75 years (HR 0.46, 95%CI 0.36 to 0.60) but not more than 75 years (HR 0.76, 95%CI 0.38 to 1.54).

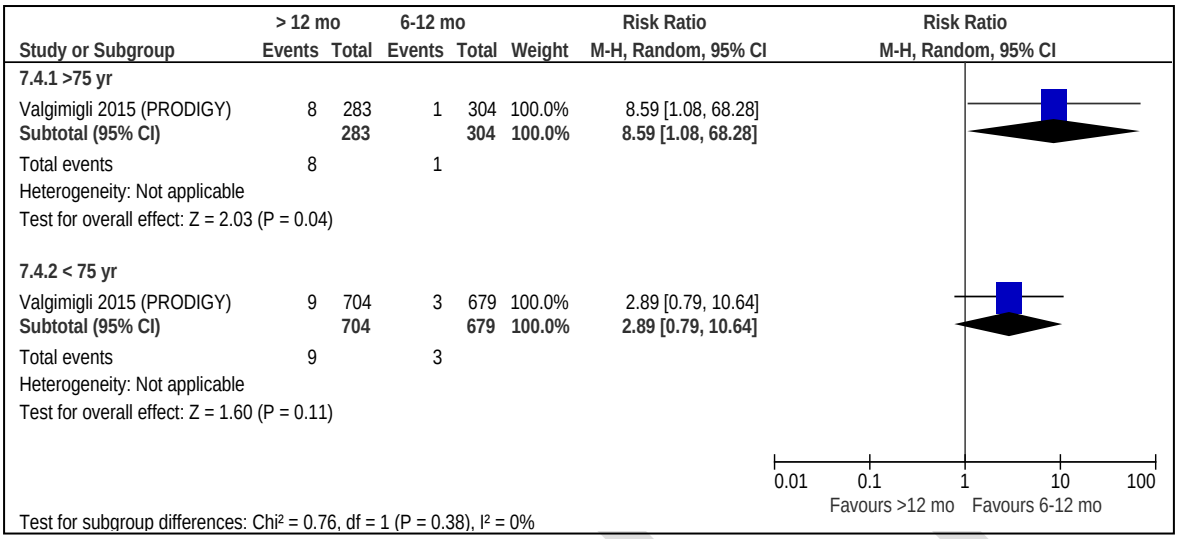
Bare-metal stents
No studies assessed myocardial infarction by age group among participants with an implanted BMS.

5.1.1.1.65 Stroke
One RCT[25] assessed the risk of stroke among 587 participants aged more than 75 years and 1383 participants aged less than 75 years.

Among participants aged more than 75 years, the risk of stroke was significantly higher in those who received DAPT for more than 12 months compared with 6–12 months (RR 8.59, 95%CI 1.08 to 68.28) (Figure 69).

Among those aged less than 75 years, there was no significant difference in risk between DAPT for more than 12 months and 6–12 months (RR 2.89, 95%CI 0.79 to 10.64) (Figure 69).

Figure 69: Relative risk of stroke, by age group



No studies assessed the risk of stroke among participants aged more or less than 75 years by stent type (BMS or DES).

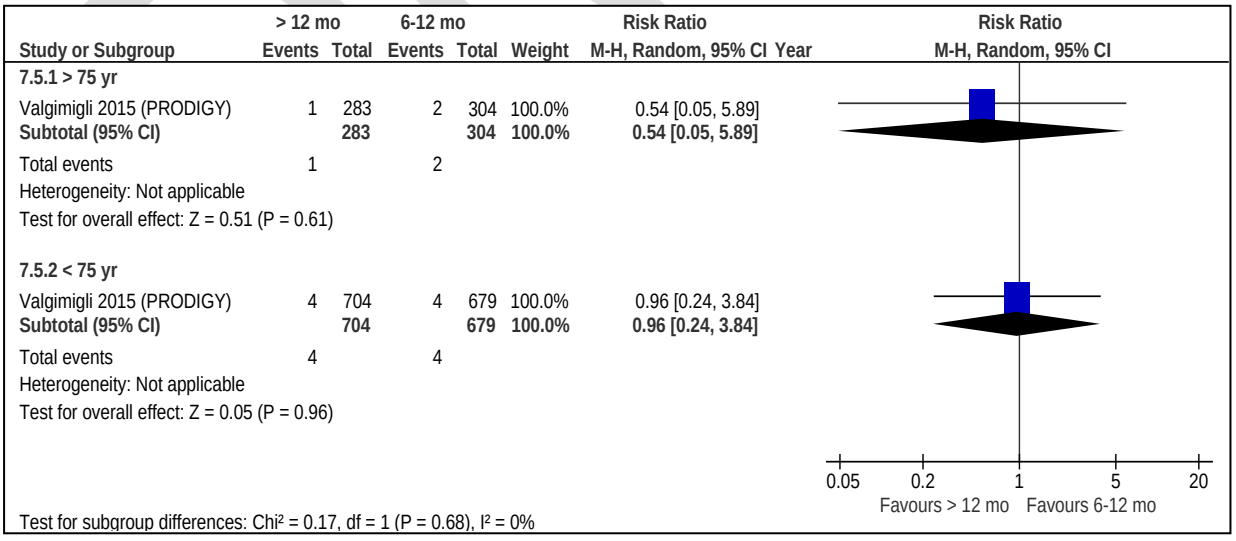
5.1.1.1.66 Stent thrombosis

Definite stent thrombosis

One RCT[25] assessed the risk of definite stent thrombosis among 587 participants aged more than 75 years and 1383 participants aged less than 75 years.

There was no significant difference in the risk of definite stent thrombosis between DAPT for more than 12 months or six to 12 months in either those aged more than 75 years (RR 0.54, 95%CI 0.05 to 5.89) or less than 75 years (RR 0.96, 95%CI 0.24 to 3.84) (Figure 70).

Figure 70: Relative risk of definite stent thrombosis, by age group

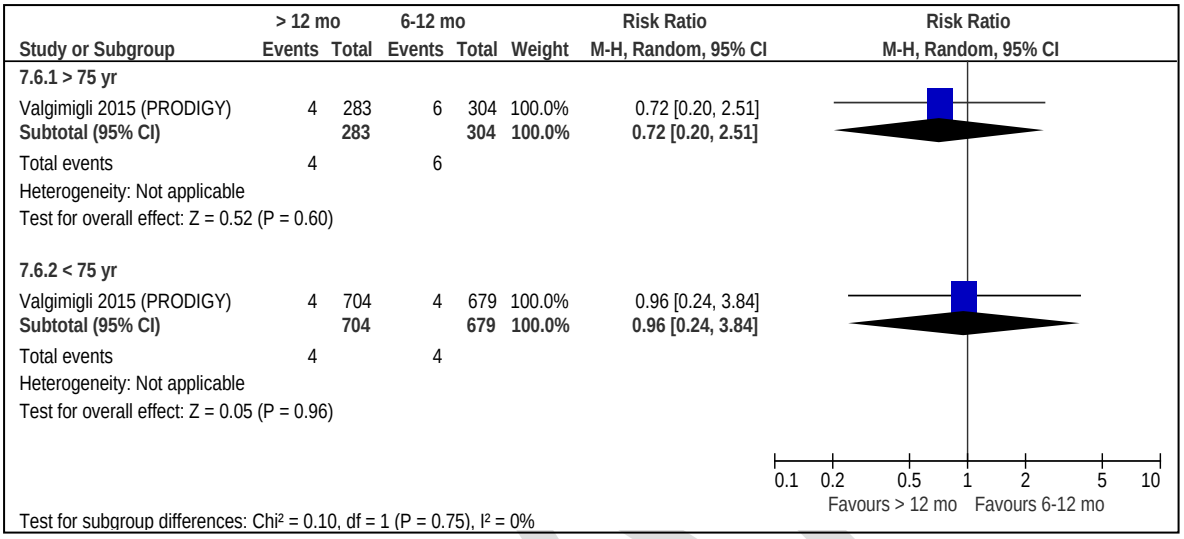


No studies assessed definite stent thrombosis among participants aged more or less than 75 years by stent type (BMS or DES).

Definite or probable stent thrombosis

One RCT[25] assessed the risk of definite or probable stent thrombosis among 587 participants aged more than 75 years and 1383 participants aged less than 75 years. There was no significant difference in the risk of definite stent thrombosis between DAPT for more than 12 months or 6–12 months in either those aged more than 75 years (RR 0.72, 95%CI 0.20 to 2.51) or less than 75 years (RR 0.96, 95%CI 0.24 to 3.84) (Figure 71).

Figure 71: Relative risk of definite or probable stent thrombosis, by age group



One additional RCT (DAPT[24]) reported that there was a significantly lower risk of definite or probable stent thrombosis among participants aged less than 75 years (HR 0.29, 95%CI 0.17 to 0.49) but not among those aged more than 75 years (HR 0.23, 95%CI 0.03 to 2.06) (Table 15); the number of participants in each group was not reported, precluding pooling.

Table 15: Risk definite or probable stent thrombosis, by age group

		≥ 75 yr		< 75 yr	
Trial	**DAPT duration**	**%**	**Reported HR (95%CI)**	**%**	**Reported HR (95%CI)**
Mauri 2014 (DAPT)*	12 mo	0.8%	0.23 (0.03, 2.06)	1.4%	0.29 (0.17, 0.49)
	30 mo	0.2%		0.4%	

Note: CI = confidence interval, DAPT = dual anti-platelet therapy, DES = drug-eluting stent, HR = hazard ratio, mo = months, yr = year.
*Participants with a DES.

Drug-eluting stents

Mauri et al. 2014[24] reported that there was a significantly lower risk of definite or probable stent thrombosis among participants aged less than 75 years (HR 0.29, 95%CI 0.17 to 0.49) but not more than 75 years (HR 0.23, 95%CI 0.03 to 2.06) (Table 15).

Bare-metal stents

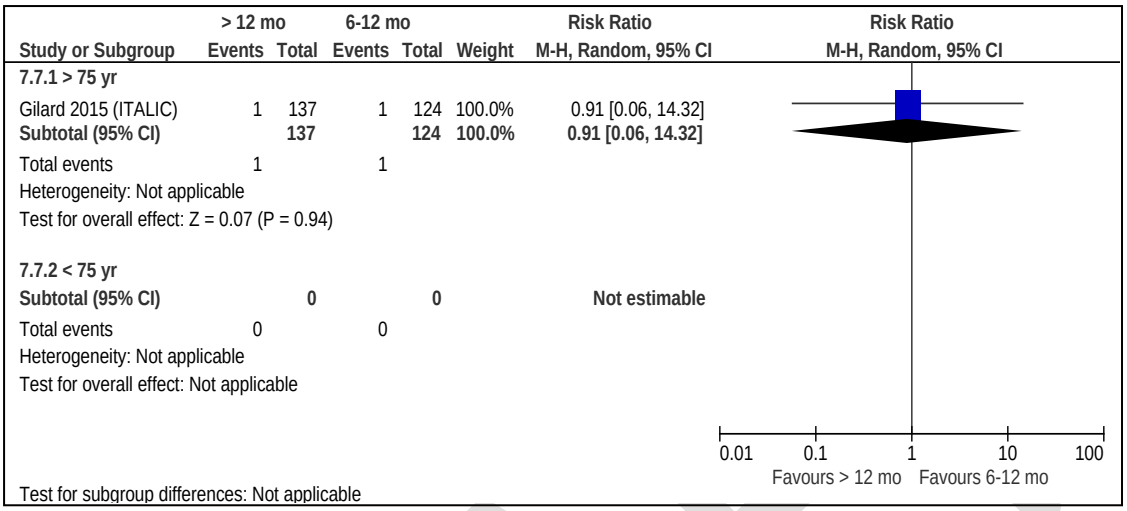
No studies assessed definite or probable stent thrombosis by age group among participants with an implanted BMS.

5.1.1.1.67 Urgent revascularization

One RCT[31] involving 261 participants aged more than 75 years assessed urgent revascularization. No data were reported for participants aged less than 75 years.

Among those aged more than 75 years, there was no significant difference in the risk of urgent revascularization between DAPT for more than 12 months or 6-12 months (RR 0.91, 95%CI 0.06 to 14.32) (Figure 72).

Figure 72: Relative risk of urgent revascularization, by age group

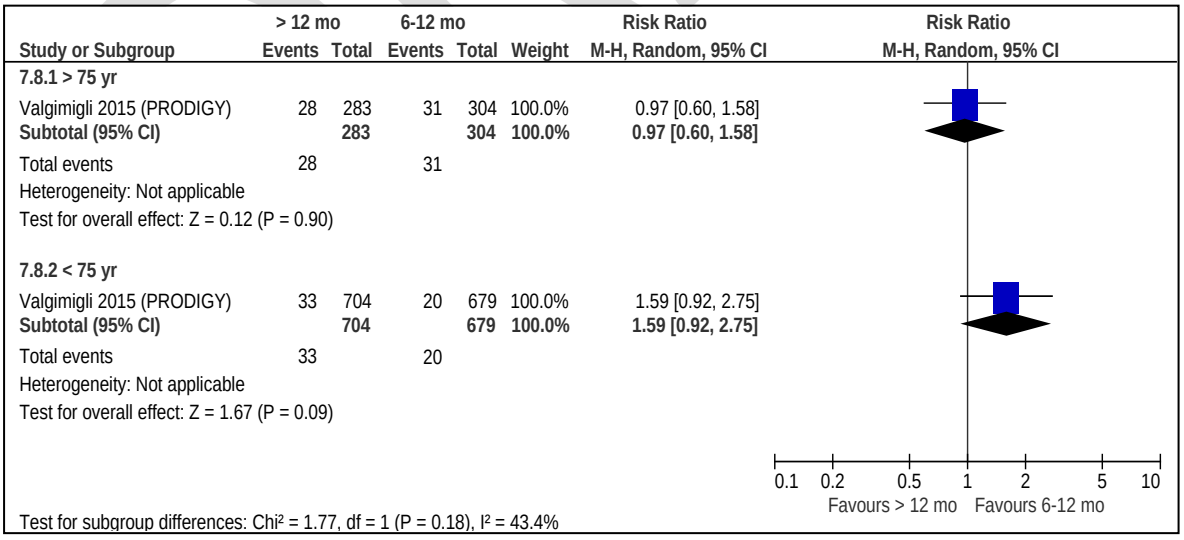


No studies assessed urgent revascularization among participants aged more or less than 75 years by stent type (BMS or DES).

5.1.1.1.68 MACCE

Two RCTs[24,25] reported MACCE using a consistent definition (all-cause death, MI, stroke) by age group. However, the number of randomized participants in each age group was not reported for the DAPT trial,[24] precluding pooling of study data. In the PRODIGY trial,[25] there was no significant difference in the risk of MACCE between DAPT for more than 12 months or 6–12 months in either those aged more than 75 years (RR 0.97, 95%CI 0.60 to 1.58) or less than 75 years (RR 1.59, 95%CI 0.92 to 2.75) (Figure 73).

Figure 73: Relative risk of MACCE, by age group



Mauri and colleagues (DAPT)[24] reported that there was no significant difference in the risk of MACCE between DAPT durations among those aged more than 75 years (HR 0.95, 95%CI 0.59, 1.52).

Among those aged less than 75 years, Mauri and colleagues[24] reported significantly lower risk of MACCE among participants who received >12 months of DAPT compared with 6–12 months of DAPT (HR 0.69, 95%CI 0.57, 0.83).

An additional four RCTs[23,27,31,34] reported MACCE using alternative definitions. The outcome definitions and data are summarized in Table 16. Despite differences in definitions across trials, each of the RCTs reported no significant difference in risk of MACCE between DAPT durations in participants aged more or less than 75 years (Table 16).

Table 16: MACCE reported by use of alternative definitions, by age group

		> 75 yr		< 75 yr	
Trial	MACCE definition	No. events/ no. participants	RR (95%CI)*	No. events/ no. participants	RR (95%CI)*
Nakamura 2017 (NIPPON)†	All-cause death, Q-wave or non–Q-wave MI, cerebrovascular events, major bleeding	6 mo: 13/341 18 mo: 5/348	0.38 (0.14, 1.05)	6 mo: 20/1300 18 mo: 19/1296	0.95 (0.51, 1.78)
Gilard 2015 (ITALIC)†	All-cause mortality, MI, stroke, urgent revascularization, major bleeding	6 mo: 4/124 24 mo: 12/137	2.72 (0.90, 8.20)	NR	—
Collet 2014 (ARCTIC-INT)†	All-cause death, myocardial infarction, stent thrombosis, stroke, urgent revascularisation	12 mo: 9/103 18–30 mo: 7/117	0.68 (0.26, 1.77)	6 mo: 18/521 24 mo: 17/518	0.95 (0.50, 1.82)
		> 65 yr		< 65 yr	
Lee 2014 (DES-LATE)†	Cardiac death, myocardial infarction, or stroke	12 mo: 2.9%‡ 36 mo: 3.7%‡	HR 0.81 (0.51, 1.30)	12 mo: 2.0%‡ 36 mo: 1.7%‡	HR 1.18 (0.67, 2.08)

Note: CI = confidence interval, HR = hazard ratio, MACCE = major adverse cardiac and cerebrovascular events, MI = myocardial infarction, mo = months, NR = not reported, RR = relative risk, yr = year.
*Unless reported otherwise.
†Involved participants with an implanted drug-eluting stent.
‡Percentage of participants with an event; denominator not reported.

No studies assessed MACCE among participants with an implanted BMS by age group.

5.1.1.1.69 Gastrointestinal bleeding

No studies assessed gastrointestinal bleeding by age group.

5.1.1.1.70 Major and minor bleeding

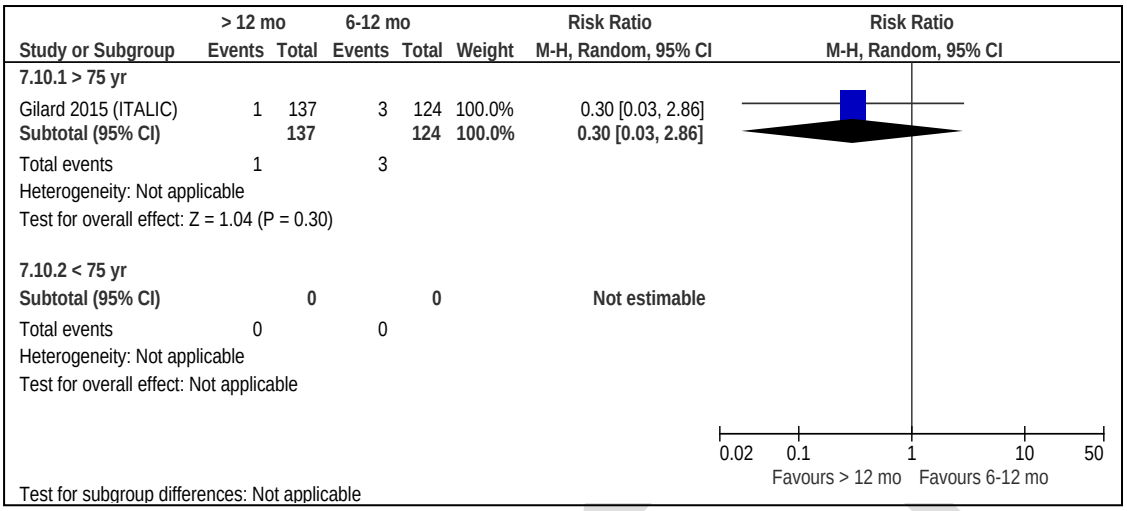
TIMI major bleeding

No studies assessed TIMI major bleeding by age group.

TIMI minor bleeding

One RCT[31] reported no significant difference in the risk of TIMI minor bleeding between DAPT for more than 12 months compared with six to 12 months among participants aged more than 75 years (RR 0.30, 95% CI 0.03 to 2.86) (Figure 74). This study involved participants with an implanted DES. No data were reported for participants aged less than 75 years.

Figure 74: Relative risk of TIMI minor bleeding, by age group



No studies assessed TIMI bleeding among participants aged more or less than 75 years among participants with a BMS.

Alternative bleeding classification systems

Among participants aged more than 75 years, extended DAPT was associated with a significantly higher risk of BARC Type 2,3,5 bleeding, BARC Type 3,5 bleeding, and GUSTO moderate/severe bleeding (Table 17). Among those aged less than 75 years, there was a significant increase in the risk of BARC type 2,3, or 5 bleeding (RR 2.63, 95%CI 1.33 to 5.21).

Drug-eluting stent

Among participants with an implanted DES, there was a significantly higher risk of GUSTO moderate or severe bleeding among those aged less than 75 years (RR 1.78, 95%CI 1.29 to 2.47) but not among those aged more than 75 years (RR 1.03, 95%CI 0.54 to 1.98) (Table 17).

Bare-metal stent

No studies assessed bleeding by use of an alternative classification system in participants with a bare metal-stent by age group.

Table 17: Bleeding reported by use of alternative classification systems, by age group

		> 75 yr		< 75 yr	
Trial	**Bleeding classification system***	**No. events/ no. participants**	**RR (95%CI)¶**	**No. events/ no. participants**	**RR (95%CI)¶**
Valgimigli 2012 (PRODIGY)†	BARC 2,3,5	6 mo: 9/304 24 mo: 23/283	**2.75 (1.29, 5.83)**	6 mo: 11/679 24 mo: 30/704	**2.63 (1.33, 5.21)**
	BARC 3, 5	6 mo: 5/304 24 mo: 14/283	**3.01 (1.10, 8.24)**	6 mo: 5/679 24 mo: 10/704	1.93 (0.66, 5.61)
	BARC 3	6 mo: 4/304 24 mo: 9/283	2.42 (0.75, 7.76)	6 mo: 5/679 24 mo: 9/704	1.74 (0.58, 5.15)
	GUSTO moderate/severe	6 mo: 3/304 24 mo: 14/283	**5.01 (1.46, 17.26)**	6 mo: 5/679 24 mo: 8/704	1.54 (0.51, 4.69)
Mauri 2014 (DAPT)‡	GUSTO moderate or severe	12 mo: 3.6% 30 mo: 3.7%	HR 1.03 (0.54, 1.98)	12 mo: 1.3% 30 mo: 2.3%	**HR 1.78 (1.29, 2.47)**

Note: BMS = bare-metal stent, CI = confidence interval, DES = drug-eluting stent, HR = hazard ratio, mo = months, RR = relative risk, yr = year.
*Definitions for each bleeding classification system are available in Appendix 10.
†Participants with an implanted DES or BMS.
‡Participants with an implanted DES.
¶Unless otherwise stated.

5.4.8 Participants who smoke

In total, three RCTs[24,25,34] reported outcome data by smoking status. One RCT[25] categorized participants as "smokers" or "non-smokers", one RCT[24] categorized smoking status as "current tobacco use" and "no current tobacco use," and one RCT[34] categorized smoking as "current smoking" and "no smoking." For the purpose of this analysis, we considered "smoking," "current tobacco use," and "current smoking" to include participants who smoke. Data from the DAPT trial[24] by smoking status were provided only for participants with an implanted DES.

5.1.1.1.71 All-cause death

One RCT[25] reported all-cause death among participants categorized as "smokers" (n = 469) or "non-smokers" (n = 1493). There was no significant difference in the hazard ratio for all-cause death between DAPT for 6 or 24 months for smokers (HR 0.90, 95%CI 0.42 to 1.92) or non-smokers (HR 0.99, 95%CI 0.67 to 1.47). Data were not available separately by stent type (BMS or DES).

5.1.1.1.72 Cardiovascular death

No studies reported cardiovascular death among smokers or non-smokers.

5.1.1.1.73 Non-cardiovascular death

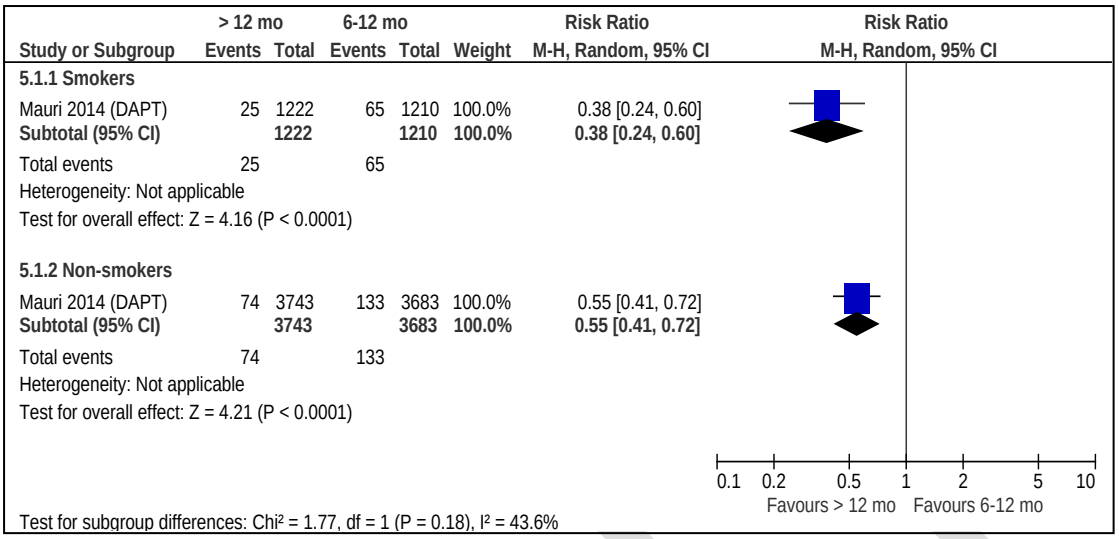
No studies reported non-cardiovascular death among smokers or non-smokers.

5.1.1.1.74 Myocardial infarction

One RCT[24] reported a significantly lower risk of MI with DAPT for > 12 months compared with DAPT for six to 12 months among both smokers (RR 0.38, 95%CI 0.24 to 0.60) and non-smokers (RR 0.55, 95%CI 0.41 to 0.72) (Figure 75).

Although the DAPT trial[24] included participants with either a DES or BMS, these data are specific to participants with an implanted DES. No data were available for participants with an implanted BMS.

Figure 75: Relative risk of myocardial infarction, by smoking status



5.1.1.1.75 Stroke

No studies reported stroke among smokers or non-smokers.

5.1.1.1.76 Stent thrombosis

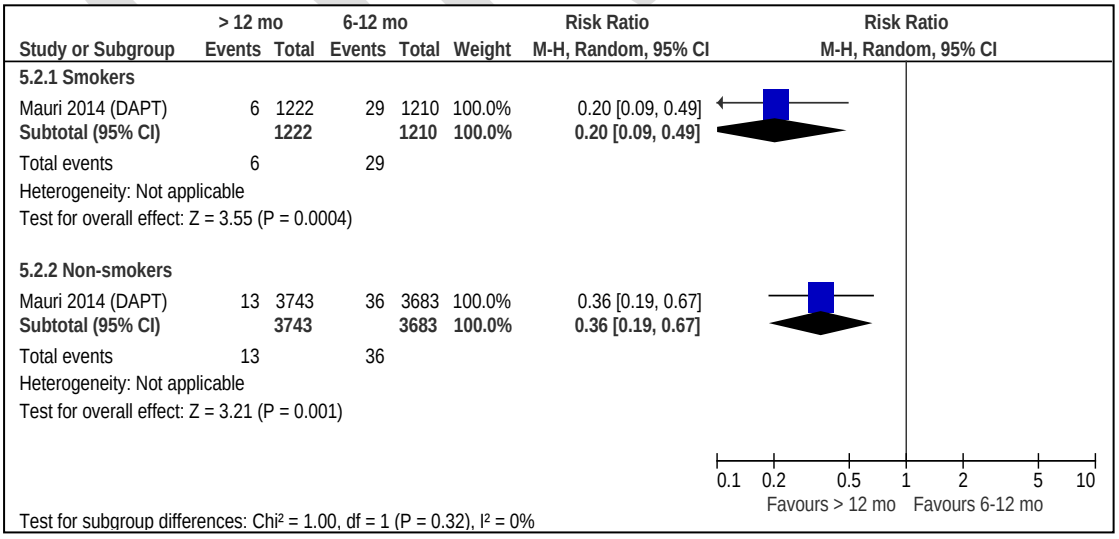
Definite stent thrombosis

No studies reported definite stent thrombosis among smokers or non-smokers.

Definite or probable stent thrombosis

One RCT[24] reported a significantly lower risk of definite or probable stent thrombosis with DAPT for > 12 months compared with DAPT for six to 12 months among both smokers (RR 0.20, 95%CI 0.09 to 0.49) and non-smokers (RR 0.36, 95%CI 0.19 to 0.67) (Figure 76). Although the DAPT trial[24] included participants with either a DES or BMS, these data are specific to participants with an implanted DES. No data were available for participants with an implanted BMS.

Figure 76: Relative risk of definite or probable stent thrombosis, by smoking status



5.1.1.1.77 Urgent revascularization

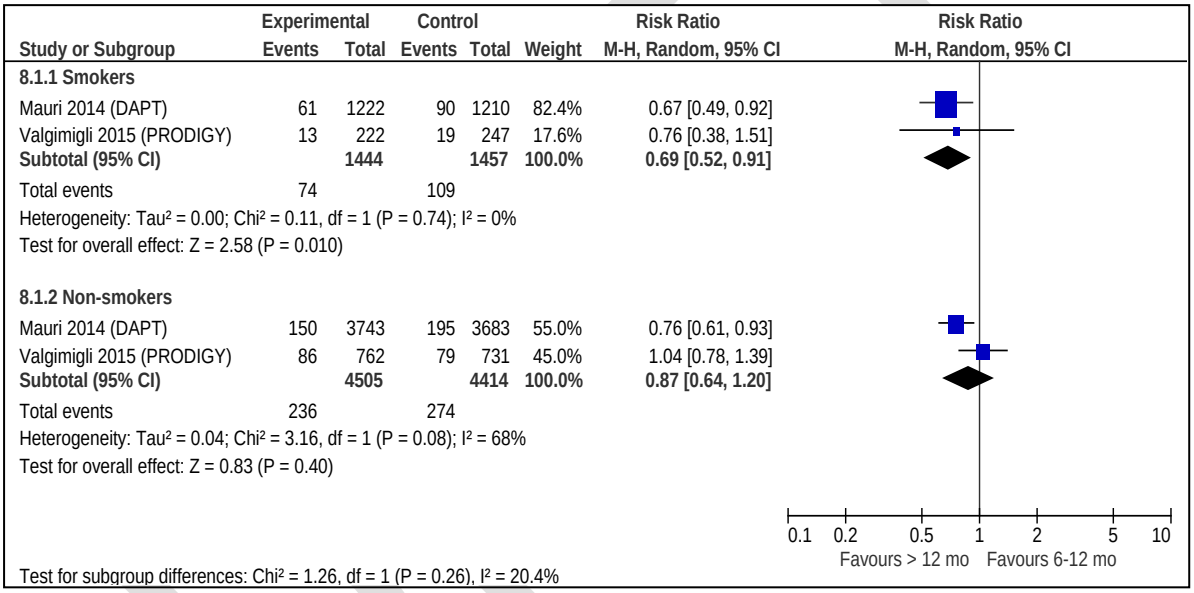
No studies reported urgent revascularization among smokers or non-smokers.

5.1.1.1.78 MACCE

In total, three RCTs[24,25,34] reported MACCE among smokers and non-smokers, with variation in definition of the composite outcome.

Two RCTs[24,25] reported MACCE using a consistent definition (all-cause death, MI, stroke). Among smokers, DAPT for > 12 months was associated with a lower risk of MACCE (RR 0.69, 95%CI 0.52 to 0.91) compared with DAPT for 6-12 months (Figure 77). Among non-smokers, there was no significant difference in the risk of MACCE between DAPT durations (RR 0.87, 95%CI 0.64 to 1.20). One additional RCT[34] assessed MACCE among smokers and non-smokers by use of an alternative definition (all-cause death, MI, stent thrombosis, stroke, urgent revascularization), finding a non-significant difference in risk between DAPT durations for both smokers (RR 0.86, 95%CI 0.27 to 2.76) and non-smokers (RR 0.88, 0.48 to 1.61).

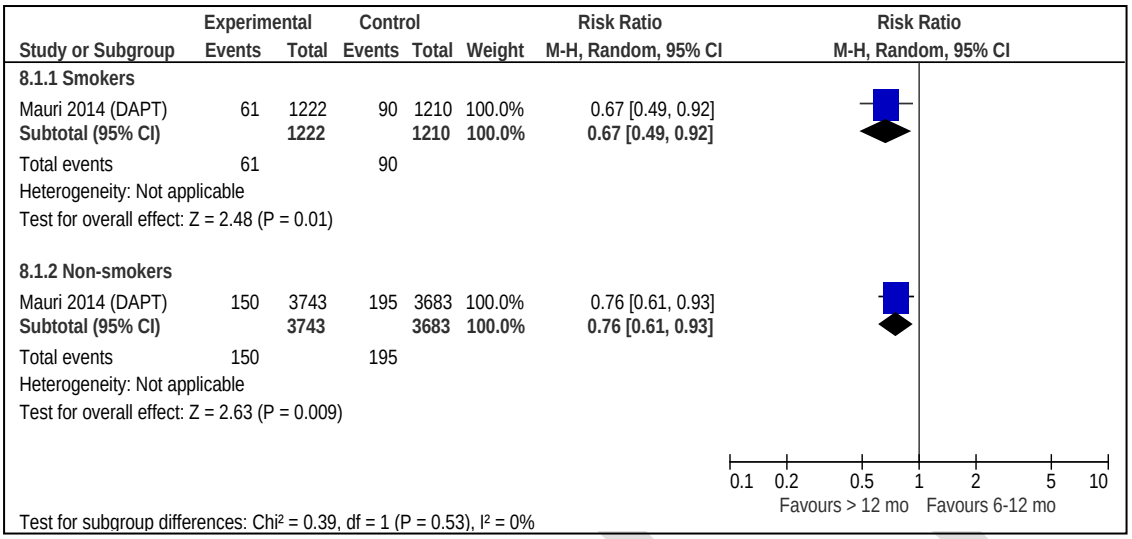
Figure 77: Relative risk of MACCE, by smoking status



Drug-eluting stents

One RCT[24] reported the risk of MACCE (all-cause death, MI, stroke) among participants with an implanted DES by smoking status. Among both smokers and non-smokers with a DES, the risk of MACCE was significantly lower among participants who received DAPT for more than 12 months compared with for 6-12 months (Figure 78).

Figure 78: Relative risk of MACCE among participants with a DES, by smoking status



Bare-metal stents

No data were available for participants with an implanted DES by smoking status.

5.1.1.1.79 Gastrointestinal bleeding

No studies reported gastrointestinal bleeding among smokers or non-smokers.

5.1.1.1.80 Major and minor bleeding

No studies reported major or minor bleeding by use of the TIMI classification criteria among smokers or non-smokers. Two RCTs[24,25] assessed bleeding by use of an alternative classification system (Table 18). By use of either the GUSTO (moderate or severe) or BARC (Type 2, 3, 5), the risk of bleeding was increased among non-smokers who received DAPT for >12 months compared with DAPT for six to 12 months. Among smokers, there was no significant difference in the risk of bleeding between DAPT durations by use of either classification system (Table 18).

Table 18: Bleeding reported by use of alternative classification systems, by smoking status

		Smoking		No smoking	
Trial	**Bleeding classification system***	**No. events/ no. participants**	**RR (95%CI)**	**No. events/ no. participants**	**RR (95%CI)**
Valgimigli 2012 (PRODIGY)†	BARC Type 2,3,5	6 mo: 10/247 24 mo: 12/222	1.34 (0.59 to 3.03)	6 mo: 24/731 24 mo: 61/762	**2.44** **(1.54 to 3.87)**
Mauri 2014 (DAPT)‡	GUSTO moderate or severe	12 mo: 17/1210 30 mo: 15/1222	0.87 (0.44 to 1.74)	12 mo: 56/3683 30 mo: 104/3743	**1.83** **(1.32 to 2.52)**

Note: BMS = bare-metal stent, CI = confidence interval, DES = drug-eluting stent, mo = months, RR = relative risk.
*Definitions for each bleeding classification system are available in Appendix 10.
†Participants with an implanted DES or BMS.
‡Participants with an implanted DES.

Research Question 3: *Compared with shorter treatment duration (6 to 12 months), what is the comparative clinical efficacy and safety of ASA plus clopidogrel, prasugrel, or ticagrelor, when used for longer (i.e. > 12 months) duration of DAPT following PCI with BMS or DES insertion in the following groups: all post-PCI patients; those with a prior myocardial infarction; those presenting with ACS; those with diabetes; those in different age subgroups; and those who smoke?*

As with Research Question 1, the evidence-base for this research question included data from seven RCTs,[23-25,27,30,31,34] representing the treatment period starting six months after PCI.

Clopidogrel was the most commonly used P2Y12 inhibitor in the included RCTs (Table 3). Three RCTs (OPTIDUAL,[30] DES-LATE,[27] PRODIGY[25]) involved only clopidogrel, while the remaining RCTs included more than one P2Y12 inhibitor. Of the RCTs that involved more than one P2Y12 inhibitor, clopidogrel was the predominate P2Y12 inhibitor used, administered to between 89.6% and 99.6% of participants.

Because of the limited data available for prasugrel and ticagrelor, NMA was not feasible. The available data are summarized below for each P2Y12 inhibitor.

5.4.9 Clopidogrel

The RCTs that were used to address Research Question 1 primarily involved use of clopidogrel, with between 90% and 100% of participants receiving this antiplatelet. Because the findings of the base case were driven primarily by clopidogrel, we did not perform additional analyses to address research question 3. The results of the base case were presented earlier in section 5.4 of this report.

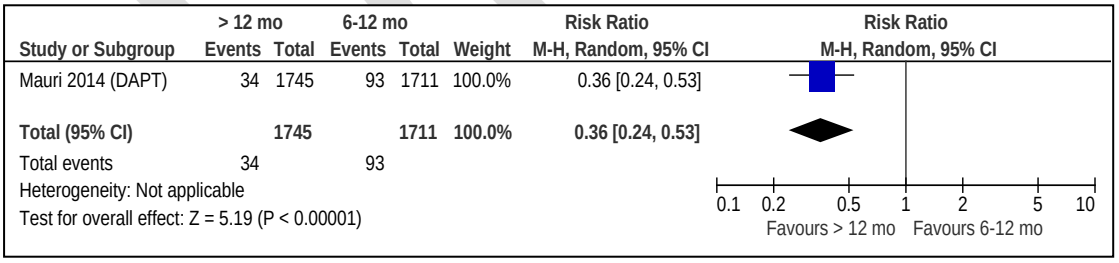
5.4.10 Prasugrel

Four of the included RCTs involved use of prasugrel (ITALIC,[31] DAPT,[24] ARCTIC-INTERRUPTION,[34] NIPPON[23]), with use by 0.1% to 35% of participants. Of these, one RCT (DAPT[24]) provided subgroup data for participants who received prasugrel. Data from the DAPT trial were available for the following outcomes: MI, stent thrombosis, MACCE, and GUSTO moderate/severe bleeding and are summarized below. No data were reported for all-cause death, cardiovascular death, non-cardiovascular death, stroke, urgent revascularization, or TIMI bleeding.

5.1.1.1.81 Myocardial infarction

Among participants who received prasugrel, DAPT for > 12 months was associated with a lower risk of MI compared with those who received DAPT for six to 12 months (RR 0.36, 95%CI 0.24 to 0.53) (Figure 79).

Figure 79: Relative risk of myocardial infarction among participants who received prasugrel



5.1.1.1.82 Stent thrombosis

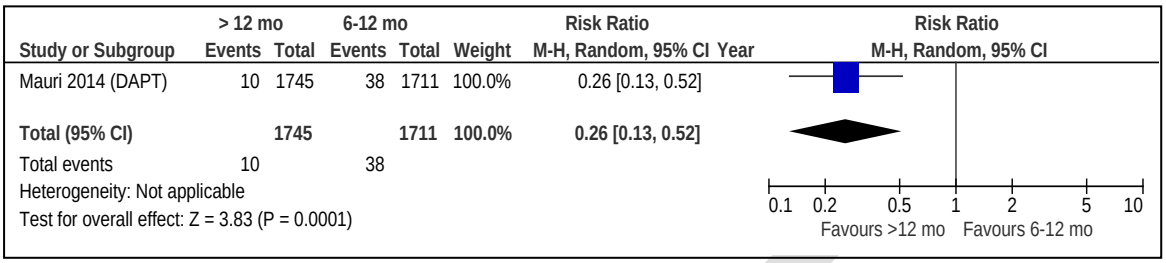
Definite thrombosis

No data were reported for definite stent thrombosis among participants taking prasugrel.

Definite or probable stent thrombosis

Among participants who received prasugrel, DAPT for > 12 months was associated with a lower risk of definite or probable stent thrombosis compared with those who received DAPT for six to 12 months (RR 0.26, 95%CI 0.13 to 0.52) (Figure 80).

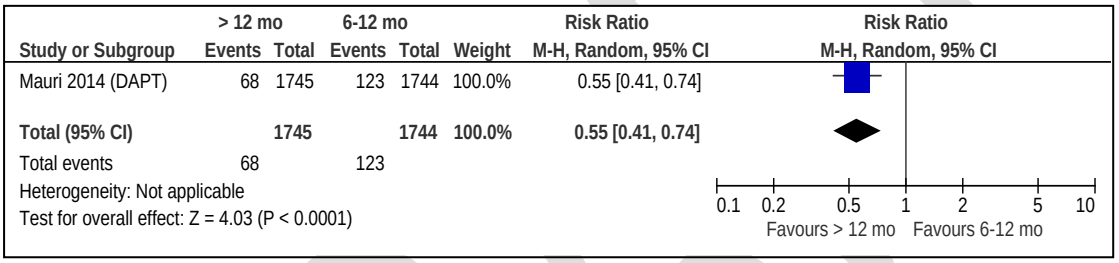
Figure 80: Relative risk of definite or probable stent thrombosis among participants who received prasugrel



5.1.1.1.83 MACCE

Among participants who received prasugrel, DAPT for > 12 months was associated with a lower risk of MACCE compared with those who received DAPT for six to 12 months (RR 0.55, 95%CI 0.41 to 0.74) (Figure 81).

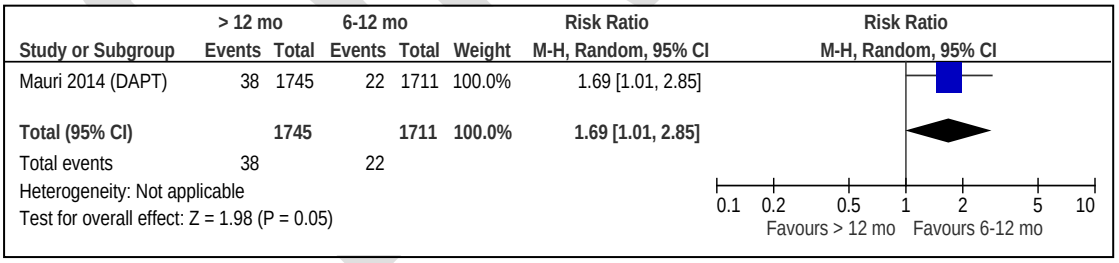
Figure 81: Relative risk of MACCE among participants who received prasugrel



5.1.1.1.84 GUSTO moderate or severe bleeding

Among participants who received prasugrel, DAPT for > 12 months was associated with a higher risk of GUSTO moderate or severe bleeding compared with those who received DAPT for six to 12 months (RR 1.69, 95%CI 1.01 to 2.85) (Figure 82).

Figure 82: Relative risk of GUSTO moderate or severe bleeding among participants who received prasugrel



5.4.11 Ticagrelor

Of the included RCTs, ticagrelor was an eligible P2Y12 inhibitor in one RCT (ITALIC[31]); however, no participants in the 24 month DAPT group and 0.1% of participants in the 6 month DAPT group received ticagrelor (Table 3). As such, there was insufficient data available to assess the benefits and harms of extended DAPT involving ticagrelor.

One large RCT (PEGASUS-TIMI 54[35]) involving participants with a prior MI was identified during the review but not included. Participants were randomized to ticagrelor 60 or 90 mg twice daily or placebo one to three years after a MI (median 1.7, interquartile range 1.2 to 2.3 years) which did not meet our

eligibility criterion. Given the paucity of evidence for ticagrelor in this review, results from this RCT may be of interest. In the PEGASUS-TIMI 54[35] trial, about 83% of participants had undergone stenting, with 39% receiving a DES and 41% receiving a BMS. After PCI, participants received a P2Y12 inhibitor at the discretion of their treating physician, and the percentage of participants who received a P2Y12 inhibitor was not reported.

Because of uncertainty about whether all participants received a P2Y12 inhibitor, and because the duration of potential DAPT before randomization was longer than the eligibility criteria for the current review (6-12 months following PCI), this RCT was not eligible for inclusion; as well, less than 85% of patients had undergone PCI with stenting. Because this trial represents the only identified RCT to assess the benefits and harms of long-term ticagrelor use, we have provided a summary of the PEGASUS-TIMI 54[35] in Appendix 12.

Overall, given the predominance of published trials that compared longer DAPT regimens with shorter ones that enrolled patients who received clopidogrel as the P2Y12 inhibitor part of DAPT, it was not possible to determine whether the choice of P2Y12 inhibitor impacts the effect of extending DAPT beyond 12 months.

6 METHODS - ECONOMICS

The economic evaluation was developed to address the following two research questions:

Research Question 2. What is the comparative cost-effectiveness of a shorter duration (six months to 12 months) versus a longer duration (more than 12 months) of DAPT following PCI with BMS or DES insertion in:

- *all post-PCI patients*
- *those with a prior MI*
- *those presenting with ACS*
- *those with diabetes*
- *different age groups*
- *those who smoke.*

Research Question4. Compared with a shorter treatment duration (six months to 12 months), what is the comparative cost-effectiveness of ASA plus clopidogrel, prasugrel, or ticagrelor when used for a longer duration (more than 12 months) of DAPT following PCI with BMS or DES insertion in:

- *all post-PCI patients*
- *those with a prior MI*
- *those presenting with ACS*
- *those with diabetes*
- *different age groups*
- *those who smoke.*

In view the limited amount of data available, economic analyses to answer Research Question 4 could not be performed. More details are given in section 6.2.7.3. The economic evaluation therefore focused on Research Question 2.

6.1 Review of Published Economic Evaluations

A literature search was conducted to identify previously published economic evaluations comparing antiplatelet regimens following PCI, to determine whether research had been conducted to address the research question.

Nineteen (19) publications were found.[36-54] Of these, only 3 compared DAPT of different durations – aligning with the research questions of interest.[36,39,43]One of these was an exploratory analysis of the effect size needed for 30 months of DAPT to be cost-effective.[39] Of the other two publications, one was conducted in the US setting and compared DAPT 12 months to DAPT 18 months post-PCI with a DES.[43] The findings from this analysis indicated that DAPT 18 months was dominant (i.e., more effective and less expensive) than DAPT 12 months. The other publication was an economic evaluation conducted in Canada which compared DAPT 3 to 6 months to DAPT 6 to 12 months, and DAPT 30 to 36 months, post-PCI. This analysis found that DAPT 3 to 6 months was dominant over the two other strategies where DAPT was used over a longer period.[36] Both the analyses by Jiang et al and by Arbel et al reported little differences in terms of clinical benefit between the various strategies. In the case of the Canadian analysis, the uncertainty was high, with the DAPT 3 to 6 months being the preferred option in only 55% of the iterations.[36] The US analysis was very sensitive to the risk of non-fatal stroke and cardio-vascular death. Further description of the identified analyses can be found in Appendix 13, Table 35.

Since the publication of these analyses, the results of two additional RCTs became available and were included in the meta-analysis, adding approximately 4,800 patients to previous meta-analyses.[23,55] Therefore, it was felt necessary to perform an economic analysis reflecting the new clinical evidence base. Published economic models were used to develop the model structure and identify some of the data inputs.

6.2 Economic Evaluation

To address the research questions, CADTH built an economic model assessing the costs and health outcomes associated with the administration of DAPT for more than 12 months (extended DAPT group) versus use of ASA alone (6 to 12 month-DAPT group) after an initial six to 12 months treatment period with DAPT. The analysis was in the form of a cost-utility analysis. The results of the clinical evaluation and meta-analysis were used to inform the clinical efficacy and safety outcomes in the model. The medical literature was used to supplement the meta-analysis, in particular for long-term outcomes, utilities and, costs (when costs could not be found directly from Canadian sources).

6.2.1 Type of Economic Evaluation

A cost-utility analysis was conducted to address the research questions.

6.2.2 Target Population

Patients who had a PCI with a BMS or DES and were well after an initial 6 to 12 month treatment phase with DAPT (i.e., the costs and clinical events occurring during the initial 6 to 12 month DAPT treatment phase were not included in the analysis).

6.2.3 Treatments

Treatments considered in the analysis included:

- continuing DAPT beyond 6 to 12 months followed by ASA 62.5 mg to 125 mg per day for the rest of the time horizon (extended DAPT group)
- ASA 62.5 mg to 125 mg per day only beyond the initial 6 to 12 months DAPT (6 to 12 month-DAPT group)

P2Y12 inhibitor specific analyses were originally planned to address RQ4. However, too few data was available and thus these agent specific analyses could not be performed.

6.2.4 Perspective

The perspective was that of the Canadian public health care payer.

6.2.5 Time Horizon

A lifetime time horizon was taken to capture long-term consequences. Costs, life-years (LYs) and quality-adjusted life-years (QALYs) were discounted at 1.5% per annum (0% and 3% in sensitivity analyses).

6.2.6 Model Structure

To replicate the results from the clinical studies and forecast the clinical effects over a longer time horizon, a Markov cohort model was built in two phases (Figure 83 and Figure 84).

The first phase (extended DAPT phase, Figure 83) was built to reflect the results of the meta-analysis and the endpoints from the studies, i.e., all-cause mortality, non-fatal MI, non-fatal stroke, probable or definite stent thrombosis, urgent revascularization, and bleeding. The cohort receives ASA or extended DAPT for a number of monthly cycles reflective of the treatment duration of the various studies included in our meta-analysis (i.e., 12 to 36 months beyond the initial 6 to 12 months of DAPT).

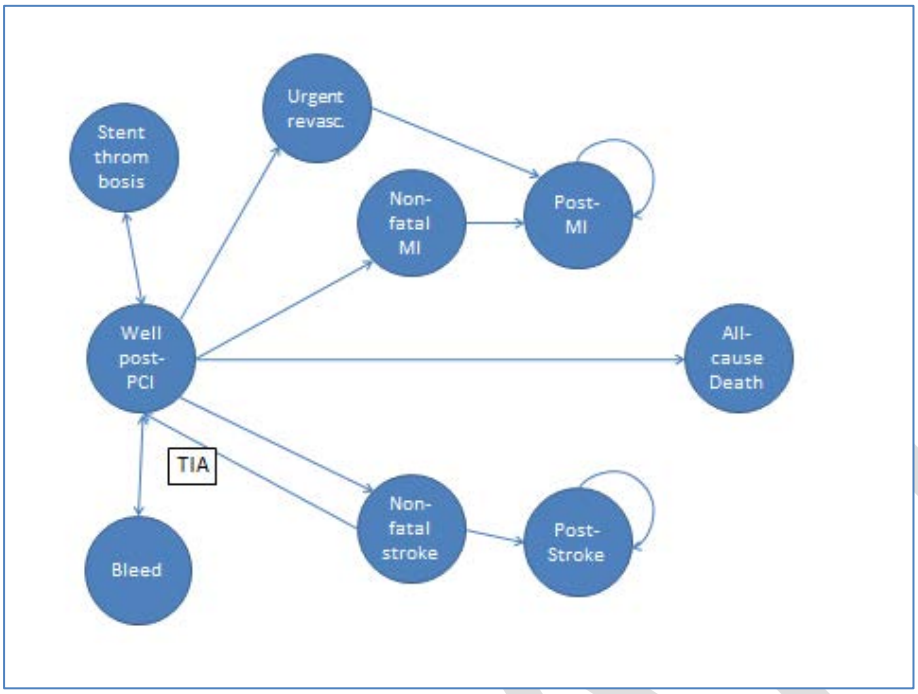
Once the cohort completes the extended DAPT phase, it moves into the second phase of the model (post-extended DAPT phase) which reflects the rest of their life, i.e., up until 100 years of age. In the post-extended DAPT phase, additional health states were included to reflect the possibility of having subsequent cardio-vascular events (e.g., stroke or second MI in an MI patient, MI or second stroke in stroke patients). These transitions are highlighted in red in Figure 84. Published literature supplemented results from the meta-analysis for the post-extended DAPT phase of the model.

In both phases of the model, patients who had a bleeding event, a stent thrombosis, or a transient ischemic attack (TIA) were assumed to fully recover and moved back into the “well post-PCI” state, while patients who had an urgent revascularization were treated similarly to patients who had an MI and moved to the “post-MI” state.

While fatal MI, stroke and bleeding events were included in the all-cause death state of the extended DAPT phase of the model (due to how data was reported in the studies included in the meta-analysis), they were computed separately in the post-extended DAPT phase of the model.

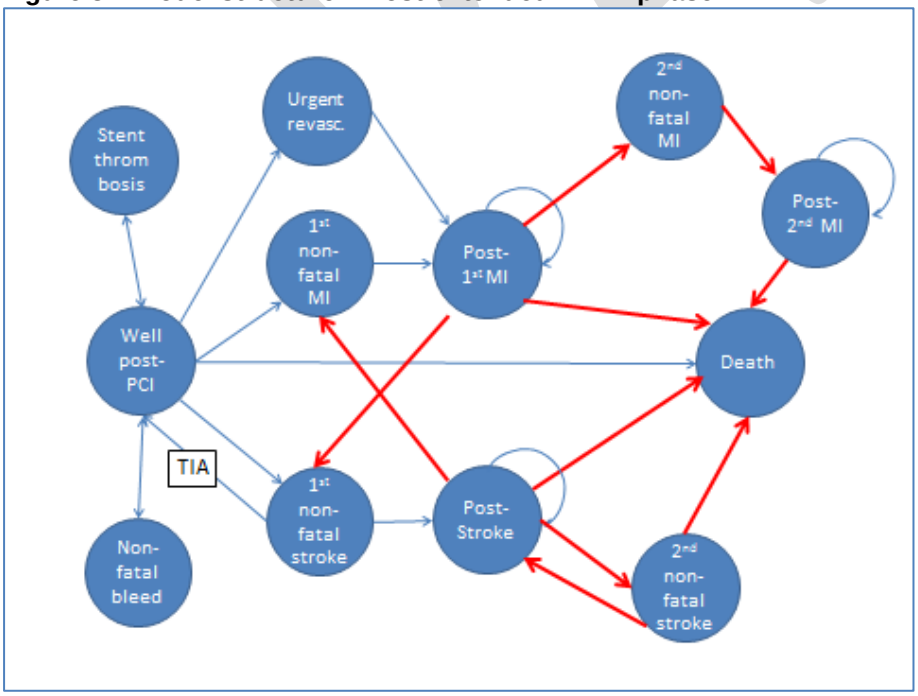
Outcomes of interest were costs, LYs and QALYs derived from the presence/absence of clinical events such as all-cause death, non-fatal MI, non-fatal stroke, definite or probable stent thrombosis, urgent revascularization, and bleeds. It was originally planned to model strokes with major disabilities versus those with minor disabilities separately, however this proved to be difficult to implement. Most studies included in the CADTH meta-analysis reported either stroke as one entity or if categories were reported those were ischemic and hemorrhagic. Furthermore, several assumptions would have needed to be made on costs, utilities and survival post-major or minor strokes as the data was often not reported by the extent of disability remaining after the acute phase. As such, combined approach was thus adopted and thus preferred.

Figure 83: Model structure – extended DAPT phase



TIA: transient ischemic attack; Urgent revasc.: urgent revascularization; MI: myocardial infarction; PCI: percutaneous coronary intervention.

Figure 84: Model structure – Post-extended DAPT phase



TIA: transient ischemic attack; Urgent revasc.: urgent revascularization; MI: myocardial infarction; PCI: percutaneous coronary intervention.

6.2.7 Data Inputs

The results of our meta-analysis were used for the extended DAPT phase of the model, and supplemented by the medical literature for the probability of events in the post-extended DAPT phase.

6.2.7.1 Cohort demographics and treatment duration

The results from the meta-analysis were used to define the cohort age and gender. As studies of different duration were pooled in the meta-analysis, the number of monthly cycles in the extended DAPT phase of the model was randomly varied according to the study duration of the trials included in our meta-analysis (i.e., from 12 to 36 months following the initial 6-12 month DAPT treatment). Values for the cohort demographics and treatment duration can be seen in Table 19. Further information on patient demographics from each trial included in the meta-analysis can be found in Appendix 5.

Table 19: Cohort demographics and treatment duration

Parameter	Value	SE	Alpha	Beta	95%CI LL	95%CI UL	Distribution
Age at start (years)	63.6	1.0220					Normal
Gender (% men)	74.98		20579	6897			Beta
Extended DAPT phase duration (months)	19.0				12.0	36.0	Normal

SE: standard error; 95%CI LL: 95% confidence interval lower limit; 95%CI UL : 95% confidence interval upper limit; DAPT : dual anti-platelet therapy

6.2.7.2 Treatment efficacy and safety (extended DAPT phase)

The results of our meta-analysis were used to estimate the probability of events (i.e., all-cause death: Figure 3; non-fatal MI: Figure 6; non-fatal stroke: Figure 7; probable or definite stent thrombosis: Figure 9; urgent revascularization: Figure 10; bleeding: Figure 13 and Figure 14) in the extended DAPT phase of the model. More specifically, the risk of events (number of events/number of patients) from each study was divided by the study duration beyond the initial DAPT treatment to give a monthly rate of events. A weighted average of monthly rates for the studies included in the meta-analysis was computed and then transformed into a probability to be used in the Markov model using Equation 1.

Equation 1: calculating a probability from a rate

$$p = 1 - e^{-r}$$

Where p is the monthly probability, e is the natural exponential function and r is the monthly rate.

An example of the calculations for non-fatal MI for the extended DAPT arm is shown in Table 20.

Table 20 Calculations for non-fatal MI/extended DAPT arm

Trial	(a) Number of events	(b) Sample size	(c) Study duration beyond initial phase (months)	(a/b/c) Monthly rate (deterministic)
NIPPON	1	1653	12	0.000050
OPTIDUAL	11	701	36	0.000436
ITALIC	9	924	18	0.000541
ARCTIC	9	645	17	0.000821
DAPT	121	5862	18	0.001147
DES-LATE	19	2514	24	0.000313
Weighted average				0.000725

These calculations were performed for the 6 to 12 month-DAPT and the extended DAPT arms separately and for all outcomes (i.e., all-cause death, non-fatal MI, non-fatal stroke, probably or definite stent thrombosis, urgent revascularization, bleeding).

From reviewing the studies included in CADTH meta-analysis, some inconsistency in the reporting of bleeds was identified. Some studies reported only major bleeding rather than all bleeding events.[27,31] This was complicated by the fact that the categorization of bleeds was different among studies. For the base case of the economic analysis, major and minor TIMI bleeding events were used as per our meta-analysis base case. However, as this was likely to underestimate bleeding events, other approaches were considered in sensitivity analyses. These are described in section 6.4. An overview of the rates used in the extended DAPT phase of the model is provided in Table 21. Detailed data inputs can be found in Appendix 13, Table 36.

Table 21: Monthly rates used in the extended DAPT phase of the model

Parameter	6 to 12 month-DAPT	Extended DAPT	Source
All-cause death	0.000831	0.000930	Weighted average from the studies included in the meta-analysis
Non-fatal MI	0.001268	0.000725	
Non-fatal stroke	0.000400	0.000377	
Probable or definite stent thrombosis	0.000496	0.000165	
Urgent revascularization	0.000657	0.000396	
Bleed	0.000712	0.000826	

DAPT: dual anti-platelet therapy; MI: myocardial infarction

6.2.7.3 Post-extended DAPT phase

In the post-extended DAPT phase of the model, the transition probabilities for non-fatal MI, non-fatal stroke, probable or definite stent thrombosis, urgent revascularization and bleeding of the six to 12 month-DAPT arm in the extended DAPT phase of the model were applied to both the six to 12 month-DAPT and the extended DAPT arms. It was recognized that this might underestimate the rates of events, in particular for stent thrombosis as a rebound effect once long-DAPT is stopped has been observed in some studies.[24]The impact of this rebound effect was tested in sensitivity analyses. Targeted literature searches were performed to identify missing probabilities of events (i.e., secondary cardiovascular events, death post cardio-vascular events). Preference was given to studies performed in Canada.

Probability of subsequent cardio-vascular events

A retrospective cohort study in individuals admitted for an MI (International Classification of Diseases, 10th Revision (ICD-10) I21) between April 1st 2006 and March 31st 2010 in the province of Manitoba and followed until November 30th 2014 was used to populate the probability of a subsequent MI as well as the probability of stroke in MI patients.[56] The cohort had an average age of 67.7 years and was constituted of 65.7% of men, which was relatively consistent with the age and gender of the individuals from the meta-analysis (63.6 years old and 75% men). Proportions at year 1, 2 and 4 were used to generate an average monthly rate (later transformed into a probability) for the first 4 years post event, which was assumed to remain the same throughout the rest-of-life model.

The probability of subsequent events in stroke patients was derived from a retrospective case-control study in patients who had no early complications after stroke or TIA.[57] Cases were identified from the Ontario regional stroke centers while controls were identified from the community between 2003 and 2013. This study had a larger proportion of women than our meta-analysis cohort (46.9% vs 25%) and patients were also older (72 vs 63.6 years old). Furthermore, the analysis was limited to those patients who did not experience any adverse complication within 90 days of discharge (69.5% of the 38,241 patients discharged after a stroke). Although the sample was not entirely representative of the meta-analysis population and the study underestimated the number of events for the purpose of our model (it excluded those patients who had early complications), as it had been performed in Canada in the last decade, it was felt to represent the best evidence available. The study reported the proportion of patients with a 2nd stroke or an MI at year 1, year 3 and year 5. Monthly rates were averaged and used to derive probabilities for the model. Rates of secondary events were assumed to be the same in both the 6 to 12 month-DAPT and the extended DAPT arms of the model.

An overview of the rates of subsequent cardio-vascular events (later transformed into probabilities) used in the post-extended DAPT phase model is shown in Table 22, while more details can be found in Appendix 13 Table 37.

Table 22: Overview of monthly rates of subsequent cardio-vascular events

Parameter	6 to 12 month-DAPT	Extended DAPT	Source
Second MI in an MI patient	0.004416	0.004416	Tangri et al[56]
Stroke in an MI patient	0.000912	0.000912	Tangri et al [56]
Second stroke in stroke patient	0.001638	0.001638	Edward et al[57]
MI in a stroke patient	0.000626	0.000626	Edward et al [57]

DAPT: dual anti-platelet therapy; MI: myocardial infarction

Probability of death

There is a lack of long term mortality data post-PCI. Most studies on coronary stents or anti-platelet therapy lasted only a few years. A 15-year US study in 1,211 post-PCI patients suggests that survival post-PCI might be slightly lower (with the difference growing larger in particular in the 6 to 12 years post-PCI range) when compared with an age- and gender-matched US population, however no statistical analysis was performed and the number of individual at risk was less than 50% of the original cohort at 6 years and beyond.[58] Furthermore, the patients in this long-term study had had their PCI in the years 1999 to 2004, i.e., in the pre-DES and pre-DAPT era. Therefore, it was decided to model survival in two steps similar to what others have considered.[36] The proportion of the cohort in the "well post-PCI state" was assumed to have a probability of death similar to the Canadian population of the same age and gender and hazard ratios of death post cardio-vascular events (identified from the literature) were applied to this background mortality to calculate mortality post-MI and post-stroke.

Using Canadian life tables for the "well post-PCI" state might represent an underestimation of the risk of death in these individuals as this would imply that the insertion of a coronary stent is halting the

progression of the underlying coronary artery disease. On the other hand, Canada life tables include a certain proportion (varying with age and gender) of patients dying from cardio-vascular diseases and hence using a hazard ratio of death post cardio-vascular events might overestimate death from cardio-vascular events, unless the hazard ratio is calculated over the general population. In view of the lack of ideal data, alternative scenarios were tested in sensitivity analyses.

Mortality in the "Well post-PCI" state

The probability of death for the "well post-PCI" state was computed from a weighted average of the Canadian lifetables for men and women using the men to women ratio (i.e., 75:25) from the meta-analysis.

Mortality in post-MI

Although the probability of death up to 4 years post-MI was available from the retrospective study in Manitoba mentioned earlier, no comparison to the general population was done in this study and hence this data could not be used for the analysis.[56] No other Canadian sources of data were identified from the medical literature. A Danish study was identified reporting hazard ratios for cardio-vascular death in incident MI patients diagnosed between 1997 and 2006.[59] In the late period (2000-2006) cohort, 11,923 of the 43,769 MI patients died from cardiovascular disease over a 5-year period, giving an overall annual risk of death of 5.45%%. In comparison, the study in Manitoba reported a rate of 2.74% (annualized over 4 years) and an international study comparing ASA to clopidogrel in patients at risk of ischemic events reported a rate of 3.11% (annualized over 3 years). [56,60] The Danish data was used in the base case, but the difference with Canadian data was further explored in sensitivity analyses.

Mortality post-stroke

The case-control study in stroke from Ontario (previously described) provided the estimated hazard ratio of death at year 1, year 3 and year 5 for stroke patients over a control cohort.[57] These hazard ratios were averaged into a single hazard ratio which was used to adjust mortality from the Canadian lifetables.[61] This likely underestimated the risk of death from stroke, for the same reasons as cited before.

An overview of the values used for death post cardio-vascular events is shown in Table 23, while detailed inputs can be found in Appendix 13 Table 37.

Table 23: Overview of hazards ratios (HR) for death post cardio-vascular events

Parameter	6 to 12 month-DAPT	Extended DAPT	Source
Post-MI (HR)	2.3014	2.3014	Average of late period (2000 to 2006) years 1 to 3 and years 3 to 5 for men and women weighted for proportion of men and women in CADTH meta-analysis[59]
Post-stroke (HR)	1.6560	1.6560	Average of years 1, 3 and 5 from Edward et al[57]

HR: hazard ratio; DAPT: dual anti-platelet therapy

Fatal bleeding events

In the extended DAPT phase of the model, fatal bleeding events were assumed to have been reported in the all-cause mortality of each respective trial included in the meta-analysis. However, as the method for estimating mortality was different in the post-extended DAPT phase, it was necessary to introduce the proportion of bleeding events that were fatal. The proportion of fatal bleeding events was extracted from each study where it was reported and a weighted average (i.e., 5.4%) was computed and used to calculate the proportion of the cohort that would die from a bleeding event.

6.2.7.4 Comparative effects of anti-platelet agents

P2Y12 inhibitor specific analyses were planned to address RQ4. However, as noted in section 5.1.7, the studies included in the base case of our meta-analysis consisted of participants receiving mainly (90% to 100%) clopidogrel and no additional analysis specific to clopidogrel were felt to be needed. Similarly, no clopidogrel-specific economic analysis was performed. Four studies were included in the prasugrel-specific analysis of the meta-analysis (section 5.1.8). However, the available endpoints (i.e., MI, stent thrombosis, MACCE, bleeding) were too limited to conduct the economic analysis. Only one study included patients on ticagrelor, but the number of participants was too small for CADTH to conduct an analysis (see section 5.1.9).

6.2.7.4 Costs

Costs were obtained from official Canadian sources when possible or from Canadian publications. All costs were inflated to 2018 costs using the Canadian consumer price index.[62]

Medication costs

The costs of medications (i.e., ASA, clopidogrel, prasugrel) were obtained from the Ontario Drug Benefit (ODB) Program formulary.[63] A ratio 81:19 clopidogrel:prasugrel as per usage in the studies included in the meta-analysis was used to computed a weighted average cost for P2Y12 agents. As per the Ontario Benefit Drug Program requirements for chronic conditions medications shall be dispensed every 3 months.[64] In the model, medication costs and dispensing fees were distributed over 3 months rather than being applied every 3 months.

Acute event costs

The Ontario Case Costing Initiative (OCCI) was used to obtain the costs for MI, stroke and bleeding acute events.[65] This was supplemented with two Canadian publications estimating physician costs.[66,67] Both studies had a population that was older and including more women than the studies in the the meta-analysis (72 years old, 52.5% men in Ewara et al publication and 79.7 years old and 51.9% men in Cohen et al). The publication by Ewara et al provided regression parameters showing that each year of age was associated with a 0.53% decrease of overall stroke costs in the first 30 days.[66] Similarly, in the paper by Cohen et al, each year of age was associated with a 0.7% decrease in acute MI overall health care costs.[67] On the other hand, costs were 3.87% lower in men than women in Ewara et al and 11.1% higher in men than women in Cohen et al.[66,67] These regression factors were used to adjust physician costs for acute MI and stroke. However, as an average age and the proportion of men were not available for OCCI costs, no adjustment, other than inflation, was applied to OCCI costs. Over or underestimation of acute MI costs is expected to be minimal as the meta-analysis patient cohort is likely representative of MI patients. However, in general, stroke patients are older than the meta-analysis cohort and hence, using unadjusted values from OCCI might overestimate the costs of an acute stroke event.

Costs for bleeding events were extracted from the OCCI database using appropriate ICD-10 codes. In order to identify these appropriate ICD-10 codes, the medical literature was surveyed for studies identifying bleeding events from administrative databases. Seven studies (3 from Canada, 2 from Denmark, 1 from Finland, 1 from New Zealand) were identified.[68-74] Only one of these seven studies had validated its method by performing a medical chart review.[68] This chart review showed that the selected set of ICD-10 codes was accurate (positive predictive value) in identifying major bleeding events (defined as imaging consistent with bleeding or confirming bleeding source or documentation of direct visualization of blood by staff) in 88% of the cases. However, it was felt that this study was missing important codes, e.g., hemoptysis, hematuria. Therefore, codes used by the majority of studies (i.e., >4 out of 7) were used for extracting the cost of bleeding events from the OCCI database. These included codes for gastrointestinal, hematology, intracranial (other than hemorrhagic stroke), respiratory and urogenital bleedings. Hemorrhagic stroke codes were not included as these events were already taken into account in the acute stroke events. The costs for major bleeding events were taken from the inpatient database while those for the minor bleeding events were taken from emergency visits in the ambulatory database. A full list of ICD-10 codes used can be found in Table 38 of Appendix 13. The proportion of minor (TIMI)

bleed as reported in our meta-analysis (i.e., 84.62%) was used to calculate a weighted average for the cost of bleeding events.

Urgent revascularization was assumed to have costs equivalent to an MI, while stent thrombosis costs were limited to those of a PCI. The Ontario Health Insurance Plan (OHIP) schedule of benefit was used for stent thrombosis.[75]

Monthly costs

Targeted literature searches were performed to identify monthly costs post cardio-vascular events. Healthcare costs (initial and subsequent hospitalizations, emergency room visits, rehabilitation services, long-term care, home care, medications, etc) for the management of a stroke patient following the acute event was derived from Ewara et al described earlier.[66] The two-year costs ($49,203) minus the hospitalization, emergency room and physician costs during the first 30 days ($8,424, $709, and $1,384 respectively), were divided by 24 months to obtain a monthly cost. This monthly cost was adjusted for age and gender following the same methodology used for the physician costs for the acute event.

Cohen et al reported a cost per patient-day of $6.32 (SD: $14.39) for the care of patients in the post-MI period (physician fees, medications, hospitalization, etc).[67] This cost was multiplied by 30 to obtain a monthly cost and adjusted for age and gender as per the physician costs for the acute event.

An overview of the cost inputs used in the model is given in Table 24. More details can be found in Appendix 13 Table 39.

Table 24: Overview of cost inputs (adjusted for age and gender when applicable; all in 2018 Canadian dollars)

Parameter	Value	Standard Error	Source & details
Medications			
ASA (per month)	$9.25	Not applicable	ODB; 325 mg divided by 2[63]
Clopidogrel (per month)	$16.72	Not applicable	ODB[63]
Prasugrel (per month)	$16.72	Not applicable	ODB[63]
Pharmacist dispensing fee (per month)	$2.94	Not applicable	ODB; 1 prescription per 3 months[63]
Acute events (one time per event)			
Stroke	$12,890		Aggregate of hospital and physician costs
Hospitalization	$11,420	$248	OCCI CMG groupers 025, 026, 027, 028 and 029[65]
Physician	$1,927	Not applicable	Ewara et al; physician costs during the first 30 days adjusted for age and gender[66]
MI	$10,763		Aggregate of hospital and physician costs
Hospitalization	$8,731	$87	OCCI IC-10 I21 and I22[65]
Physician	$2,890	Not applicable	Cohen et al; physician costs during acute event adjusted for age and gender[67]
Bleeding event	$1,195	Not applicable	Weighted average of minor (84.62%) and major (15.38%) bleed
Major bleed	$6,441	$124	OCCI inpatient costs for bleeding events (see Appendix 13, Table 36 for full list of ICD-10 codes)[65]
Minor bleed	$223	$1	OCCI emergency costs from ambulatory care for bleeding events (see Appendix

Parameter	Value	Standard Error	Source & details
			13, Table 36 for full list of ICD-10 codes)[65]
PCI	$550.55	Not applicable	OHIP schedule of benefit for Z434 (transluminal coronary angioplasty; 1 major vessel=$471.60) and G298 (coronary angioplasty stent, per stent=$78.95)[75]
Monthly costs			
Post-stroke	$2,246	Aggregate value. PSA performed on each component of cost	Ewara et al; 2-year costs minus hospital, emergency room and physician costs during the first 30 days; adjusted for age and gender.[66]
Post-MI	$308	Aggregate value. PSA performed on each component of cost	Cohen et al; physician costs during acute event adjusted for age and gender[67]

ASA: acetyl-salicylic acid; ODB: Ontario Drug Benefit; OCCI: Ontario Case Costing Initiative; CMG Case Mix Group; MI: myocardial infarction; ICD-10: International Classification of Diseases 10th Revision; PCI: percutaneous coronary intervention; PSA: probabilistic sensitivity analysis

6.2.7.5 Utilities

Targeted literature searches were performed to identify utility or disutility values for the various health states of the model. Preference was given to EQ-5D values and Canadian sources. All utilities and disutilities used in the model are shown in Table 25.

Table 25: Overview of utility and disutility inputs

Health state	Average	Standard Error	Applied for	Source & details
Disutility				
Stroke (acute event)	-0.0524	0.0001	1 monthly cycle	Sullivan et al; Acute cerebrovascular disease[76]
MI (acute event)	-0.0409	0.0002	1 monthly cycle	Sullivan et al; Acute MI[76]
Bleed – major (event)	-0.0290	0.0077	1 monthly cycle	Wang et al; average of major gastrointestinal and major non-gastrointestinal disutility.[77]
Bleed – minor (event)	-0.0160	0.0041	1 monthly cycle	Wang et al; relevant non-major bleeding.[77]
Post-MI	-0.0120	0.0002	Until death	Sullivan et al; myocardial infarction[78]
Post-stroke	-0.0400	0.0002	Until death	Sullivan et al; stroke [78]
Utility (per monthly cycle)				
Baseline	0.7930	0.0100	Until death	Szende A. EQ-5D norms for Alberta 65 to 74 years old.[79]

MI: myocardial infarction

Acute event disutilities

Disutilities were applied to the proportion of the cohort entering the acute event health state, i.e., MI, stroke, bleeding, urgent revascularization. As the cohort was staying in this health state for only one monthly cycle, the disutility for the acute event was applied for one month only.

Stroke, MI and urgent revascularization

No source of EQ-5D for Canadians with an acute MI or stroke was identified in the literature. However a US source was found and felt to be the best evidence available. The source is a catalogue of EQ-5D values generated from years 2000 to 2003 data from the US-based Medical Expenditure Panel Survey and the US EQ-5D tariffs. [76] Although this data is now getting older and would probably need to be refreshed, this source is still nowadays used in several health technology assessments, likely due to the lack of more recent data.[80,81]The EQ-5D disutility value for MI (i.e., -0.0409) had been generated in 62 years old individuals (no information on gender), while that for stroke (acute cerebrovascular disease; -0.0524) came for individuals of 68 years old on average (no information on gender). No correction for age or gender was applied. The disutility for MI (i.e., -0.0409) was also used for urgent revascularization.

A similar catalogue exists for the UK and was used in sensitivity analyses.[82]

Bleeding events

Data from the ENGAGE AF-TIMI 48 trial was used for the disutility of bleeding events.[77] The ENGAGE AF-TIMI 48 study is an international study in 10,706 patients needing anticoagulation with Factor Xa for atrial fibrillation thrombolysis in MI. This study was conducted from 2008 to 2010. EQ-5D was collected every 3 months for up to 4 years in approximately 80% of the patient population. A post-hoc analysis of the impact of bleeding on EQ-5D was performed. Major gastrointestinal and non-gastrointestinal bleeding events had the same point estimate (i.e., -0.0290) but slightly different 95% CI. These values were averaged and used for major bleeding while the disutility for clinically relevant non-major bleeding (i.e., -0.0160) was used for minor bleeding. In this study, patients were older with a slightly lower proportion of men (i.e., 70 to 74 years old; 60 to 62% men), but no regression parameters were available to adjust values. Therefore, no correction for age or gender was performed.

Baseline utility and post-event disutilities

The baseline EQ-5D value applied to the "well post-PCI state" was taken from population norms for Canada.[79] These norms are available for various age groups and age-specific norm values were applied as the cohort aged. Values for each age group are displayed in Table 26.

Table 26: Baseline utility values per age group

Age group (years)	Average	Standard Error	Source
18 to 24	0.8730	0.0090	Szende et al.[79]
25 to 34	0.8640	0.0070	
35 to 44	0.8430	0.0070	
45 to 54	0.7980	0.0080	
55 to 64	0.8050	0.0080	
65 to 74	0.7930	0.0100	
75 +	0.7560	0.0120	

Post-MI and post-stroke utilities were obtained from an analysis of the US-based Medical Expenditure Survey mentioned earlier but from which chronic conditions (presence for > 1 year) were extracted.[78] The disutilities for post-MI (-0.0120) and post-stroke (-0.0400) were subtracted from the baseline utility and applied to the proportion of the cohort in the post-MI and post-stroke health states at each cycle. As the

cohort remained in the post-event health state until death, these utilities were applied until death or 100 years.

6.3 Assumptions within the Economic Model

Several assumptions needed to be made, either to supplement missing information or to simplify the model. These assumptions are listed in Table 27.

Table 27: Model assumptions

Parameter	Assumption	Comment
Death from MI, stroke, bleeding during the extended DAPT phase of the model	Death from acute events are taken into account in the all-cause death rate	Studies included in the meta-analysis reported non-fatal events. It was impossible to deduct how many MI, stroke or bleeding resulted in death. These fatal events were likely reported in the all-cause deaths.
Subsequent events during the extended DAPT phase of the model	Subsequent events are accounted for in the number of events reported in the studies included in the meta-analysis	As study patients were followed until the end of the follow-up period, subsequent events were likely recorded and reported in the total number of events
Event rates in the post-extended DAPT phase of the model	Event rates observed in the control group during the trials included in the meta-analysis and used in the extended DAPT phase of the model are representative of event rates occurring later in life	This may be an underestimation of event rates as the cohort is ageing and event rates might increase with age. Furthermore, the DAPT study showed a slight rebound of stent thrombosis in the 30 to 33 month period.[24] A sensitivity analysis was done using this data.
Number of subsequent MIs and strokes	Subsequent MIs and strokes are limited to two in a lifetime	Although possible, it is unlikely that an individual may have more than 2 MIs or strokes in his/her lifetime.
Mortality in post-PCI patients free from cardio-vascular events	Mortality assumed to be similar to that of the Canadian population of the same age and gender	This may be an underestimation of mortality as this would imply that stent placement is halting the underlying coronary artery disease. Alternative scenarios were tested in sensitivity analyses.
Mortality post cardio-vascular event	Using a hazard ratio over general population mortality rates is an adequate representation of mortality post cardio-vascular events	The mortality in the general population is already including a certain proportion of individuals dying from cardio-vascular disease which may result in an overestimation of cardio-vascular death. However, as the hazard ratio had been calculated over a general population, this is likely adequate. Nonetheless, alternative scenarios were tested in sensitivity analyses.
Weighted HR of death	A weighted average of HR values at 1 to 5 years is	This may be an overestimation as it is possible that the increased risk of

Parameter	Assumption	Comment
post-MI and post-stroke	representative of the increased risk of death post-MI or post-stroke and this, for the entire modelling period	death observed within 5 years post-event returns to normal with time. The data source used for the post-MI HR showed a large overlap in the 95%CI of the various estimate.[59] For the HR of death post-stroke, there was overlap between the 3- and 5-years value 95% CI (indicating not statistical difference), but the 1-year value was statistically lower (i.e., 1.4 vs 1.7 and 1.8) than the 3- and 5-year values.[57]Alternative scenarios were tested in the sensitivity analyses.
Minor bleed costs	Minor bleed events are managed as outpatient in the emergency room	As per TIMI bleeding definition, a minor bleed requires medical attention to stop bleeding, including hospitalization and unscheduled visit to a healthcare professional. It is difficult to know if using ER costs for ambulatory care might be an under- or overestimation of bleeding costs. Sensitivity analyses on this parameter have been performed.
Rate of subsequent strokes or MI in stroke patients	The rates observed in the first 36 months post-stroke are representative of the rates post 36 months	It is unknown if this is likely to be an under or overestimation
Rate of subsequent MI or stroke in MI patients	The rate observed in the first 48 months post-MI are representative of rates post 48 months	It is unknown if this is likely to be an under or overestimation
Secondary event rates in the post-extended DAPT phase of the model	Rates of secondary events in the post-extended DAPT phase of the model are assumed to be the same in the 6 to 12 month-DAPT and the extended DAPT arms of the model	There is no reason to believe that event rates would be different in the two treatment arms once extended DAPT is stopped, apart from the possible rebound effect in stent thrombosis as noted before.
Stent thrombosis	Stent thrombosis is assumed to be diagnosed at routine visit and is managed via a scheduled PCI	As per discussion with the clinical expert involved in this review (Expert, personal communication, XX/XX/2018)
Urgent revascularization	Urgent revascularization is an emergency situation equivalent to having an MI	As per discussion with the clinical expert involved in this review Expert, personal communication, XX/XX/2018)

MI: myocardial infarction; DAPT: dual anti-platelet therapy; PCI: percutaneous coronary intervention; HR: hazard ratio

6.4 Scenario and sensitivity analyses

All calculations were performed in a probabilistic fashion (5,000 iterations) to account for parameter uncertainty. In addition to the primary analysis performed in all patients, secondary analyses were performed for the following subgroups of patients:

- prior MI
  - Patients with a prior MI
  - Patients with no prior MI
- ACS
  - Patients with ACS
- Diabetes
  - Patients with diabetes
  - Patients with no diabetes
- Age
  - Patients ≥ 75 years old
  - Patients < 75 years old

Analyses planned for patients with no ACS, smokers and non-smokers could not be conducted due to too few data available.

For all subgroup analyses conducted, the rates of events in the extended DAPT phase of the model were taken from our meta-analyses. However, due to lack of data, no modification was made to the risk of death or subsequent events in the post-extended DAPT part of the model. Because of this and because the amount of data from the meta-analysis in these patients subgroups was often very limited (requiring additional assumptions to be made), these subgroup analyses should be considered as exploratory only. Detailed inputs for these secondary analyses and additional assumptions made can be found in Appendix 13 Table 40 to Table 47.

Additional sensitivity and scenario analyses were undertaken to address structural uncertainty or parameter uncertainty.

For example, when reviewing the studies included in our meta-analysis, it was clear that bleeding events were not reported is a similar manner in all studies. In addition to using different bleeding categorization systems, several studies reported major bleeding only. Hence, to align with the primary analysis of the meta-analysis, bleeding events reported with the TIMI classification only were used for the base case economic analysis. This was likely underestimating the total number of bleeding events. As this is the most important adverse event related to DAPT, it was important to estimate the extent of this underestimation on the model results. Two alternative methods for estimating the number of bleeding events and the impact of therapy were thus used in scenario analyses:

a) Rather than limiting the analysis to bleeding using the TIMI classification, an alternative bleeding classification was allowed. More specifically, for studies not reporting bleeding with the TIMI classification, i.e., DAPT and NIPPON, bleeding events reported with the BARC classification were pooled to the TIMI classification events. For this, it was assumed that BARC 2 bleeding events were equivalent to TIMI minor and that BARC 3 and 5 bleeding events were equivalent to TIMI major. All events were summed up together and the ratio of major:minor observed in the studies reporting major and minor events was applied for costs.

b) As several studies only reported major bleeding, minor bleeding events were likely underestimated in the model. Therefore, an alternative method was to use only the major bleeding events reported in the studies included in the meta-analysis and estimate the number of minor events if all studies had recorded minor bleeding events. The ratio major:minor observed in the studies reporting minor and major events was used for this estimate. For example, if this ratio of major:minor was 20:80 and if 100 major events were

observed in the studies, then, it was assumed that 400 minor events would have been seen in the studies if all studies had recorded minor bleeding events. This scenario was felt to give an estimate closer to the reality by the clinical expert involved in this review.

Another example is the assumption taken on events rates in the post-extended DAPT phase of the model, i.e., rates are similar to what was observed in the 6 to 12 month-DAPT arm during the extended DAPT phase. However, a rebound effect on stent thrombosis, MACCEs and in particular MI has been observed in one large study (DAPT) once extended DAPT is stopped.[24] Over three months, the hazard ratios (extended DAPT over 6 to 12 month-DAPT) increased by 7% in the case of strokes, 30% in the case of MI and 55% in the case of stent thrombosis.[17] It is therefore unknown if the maximal rebound effect had been observed at three months or if this rebound effect would have continued further had the patients been followed for more than three months. To account for this, 2 scenarios were tested:

a) The rates of stroke, MI and stent thrombosis in the post-extended DAPT phase were multiplied by a calibration during the first 3 months of the post-extended DAPT phase to give a difference in the number of events similar to what was observed at the end of the 3-month period after discontinuation of extended DAPT
b) A similar approach was taken to bring the rates of events in post-extended DAPT phase for the extended DAPT arm equal to those of the 6 to 12 month-DAPT arm after six monthly cycles..

Scenario and sensitivity analyses are described in Table 28 and detailed data inputs can be found in Appendix 13 Table 47.

Table 28: Description of scenario & sensitivity analyses

Scenario/sensitivity analysis description	Justification
Discounting at 0% and 3%	As per CADTH economic guidelines[83]
Using the risk ratio from the meta-analysis rather than rates in each group	There are small variations between the risk ratios estimated by the meta-analysis and the rate ratios used in the economic base case analysis.
Alternative calculation for bleeding events	The TIMI classification selected for the main analysis was not used in all studies. Some studies did not report minor bleeding events.
Minor bleed costs	It is possible that not all minor bleed are managed at the emergency room and that some might be managed at the physician office. This alternative scenario uses the cost of a medical visit (i.e., $77.20) as the cost for a minor bleeding event.[75]
Alternative proportions of anti-platelet agent	Extreme value scenarios using 100% clopidogrel, 100% prasugrel and 100% ticagrelor monthly costs.
Dispensing fees	Applied monthly rather than spread over 3 months
Alternative utility values (using UK tariff) for MI and stroke	Populations vary in their preference to various health states. As no Canadian EQ-5D values could be found, using a different set of utilities for the two most important cardio-vascular complications helps understand the importance of these utility values on the results of the analysis
Shorter time horizon (19 months)	There is a uncertainty coming from lifetime calculations in the post-extended DAPT phase of the model. It is unknown if the benefits of extended DAPT will remain once treatment is stopped. Furthermore, as long-term

Scenario/sensitivity analysis description	Justification
	follow-up of post-PCI patients is limited to 3 to 5 years, the data to inform lifetime events was taken from several different studies in different populations (e.g., MI, ACS, stroke patients, Danish population). Removing the post extended DAPT phase and analysing the extended DAPT phase only will remove this uncertainty.
Impact of duration of DAPT treatment in the control group	DAPT duration in the control group was 6 months in 3 studies and 12 months in four studies. It is possible that the DAPT treatment duration in the control group has an impact of the safety and efficacy of extended DAPT.
Impact of duration of extended DAPT duration	Extended DAPT duration varied from 18 months to 48 months, again it is possible that extended DAPT duration has an impact on efficacy and safety.
Alternative values for survival in the post-extended DAPT phase	Patients in the well post-PCI state were assumed to have a survival similar to the Canadian population. Death post-MI was estimated by multiplying this survival in the Canadian population by an HR from the Danish population. Death post-stroke was estimated by multiplying the survival in the Canadian population by an HR estimated at 3 and 5 years post stroke in a Canadian population. It is unknown how close these are from the reality. Alternative values will help understand the importance of the uncertainty in these parameters on the model results
No secondary MI or stroke	The rates of secondary MI or stroke were taken from Canadian retrospective studies in patients that did not necessarily have a PCI and received DAPT. Furthermore, these rates were available for only up to 4 or 5 years post the initial MI or stroke. Removing the rate of secondary MI or stroke allows to estimate the impact of these on the conclusions.

TIMI: thrombolysis in myocardial infarction; UK: United Kingdom; DAPT: dual anti-platelet therapy; MI: myocardial infarction; EQ-5D: EuroQol 5 Dimensions; PCI: percutaneous coronary intervention; MACCE: major adverse cardiovascular and cerebrovascular event; HR: harzard ratio

6.5 Model Validation

Face validity of the model was achieved through consultation with a Canadian clinical expert in interventional cardiology throughout the research phase to ensure that the model was consistent with current medical knowledge and Canadian practice. Internal validity was ensured by testing extreme parameter values and comparing the results of the first phase of the model with the results of the meta-analysis. The model results were compared with the results of similar economic evaluations for external validity.

7 RESULTS OF ECONOMIC EVALUATION

7.1 Primary analysis

Clinical outcomes

The results of the model showed only marginal differences (i.e., ± 1% or 2%) in clinical outcomes between the 6 to 12 month-DAPT and the extended DAPT arms (Table 29). The largest difference was a 1.38% reduction in MI which translated into a 0.79% reduction in death post-MI.

Table 29: Model results: clinical outcomes

	6 to 12 month-DAPT			Extended DAPT			
Clinical outcome	Extended DAPT phase	Post-extended DAPT phase	Total	Extended DAPT phase	Post-extended DAPT phase	Total	Difference (extended DAPT – 6 to 12 month-DAPT)
MI	2.34%	41.63%	43.97%	1.35%	41.24%	42.59%	-1.38%
Stroke	0.74%	18.67%	19.41%	0.70%	18.36%	19.07%	-0.35%
Urgent revascularization	1.21%	11.77%	12.98%	0.74%	11.93%	12.66%	-0.32%
Stent thrombosis	0.92%	8.93%	9.85%	0.31%	9.04%	9.35%	-0.50%
Bleeding events	1.31%	12.08%	13.40%	1.54%	12.23%	13.77%	+0.38%
All-cause death	1.57%			1.75%			+0.19%
Death post-MI		33.72%			32.93%		-0.79%
Death post-stroke		9.90%			9.74%		-0.17%
Fatal bleeding events		0.69%			0.70%		0.01%

DAPT: dual anti-platelet therapy; MI: myocardial infarction

These modest differences in clinical outcomes resulted in small LY and QALY gains for extended DAPT (Table 30). The QALY differences came from more patients in the 'well post-PCI' state rather than post-MI or post-stroke (Figure 85) and less QALY loss due to MI (Figure 86). This offset any QALY loss due to more frequent bleeding events.

Table 30: Model results: LY and QALY (1.5% discounted)

	6 to 12 month-DAPT			Extended DAPT			
	Extended DAPT phase	Post-extended DAPT phase	Total	Extended DAPT phase	Post-extended DAPT phase	Total	Difference (extended DAPT – 6 to 12 month-DAPT)
LY	1.55	16.15	17.70	1.55	15.16	17.71	0.0089
QALY	1.24	12.39	13.63	1.24	12.41	13.65	0.0154

LY: life-year; QALY: quality adjusted life-year; DAPT: dual anti-platelet therapy

Figure 85: Drivers of accumulated QALY

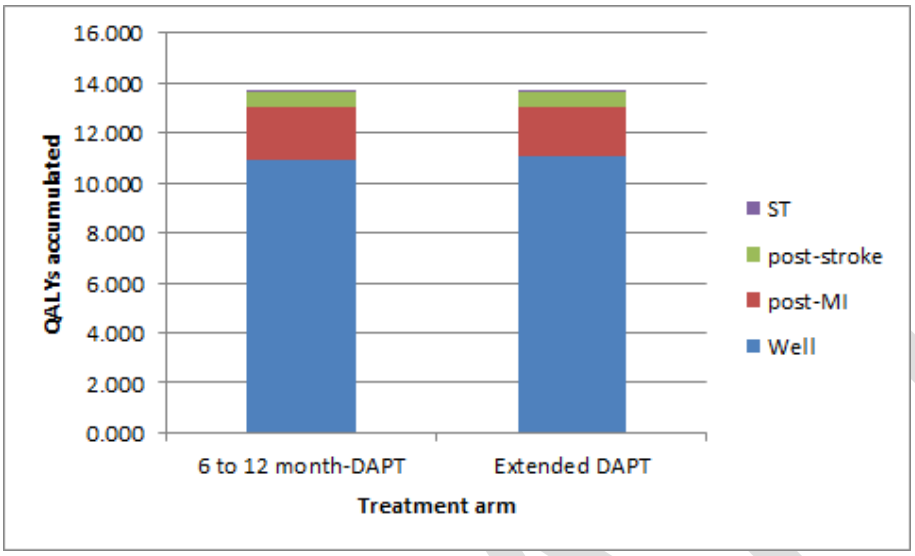
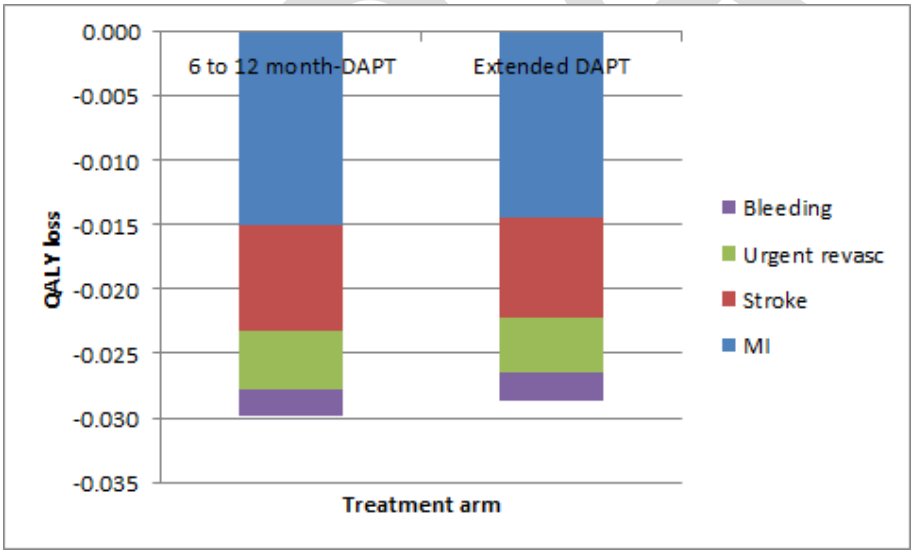


Figure 86: Drivers of QALY loss



Costs

The management of post-stroke patients was the largest (57%) contributor to lifetime costs in these patients, followed by post-MI patient management (24%) and acute MI events (9%).

Costs were slightly higher (+$161) with extended DAPT during the extended DAPT phase of the model, but slightly lower (-$1,865) in the post-extended DAPT phase of the model, resulting in overall savings of $908 versus the 6 to 12 month-DAPT (Table 31). Medication costs were higher (+$380) in the extended

DAPT arm, but these were entirely offset by lower costs secondary to acute MI and post-MI state and to a lesser extent acute stroke and post-stroke state. Bleeding events had little impact on the overall cost difference.

Table 31: Model results: costs (1.5% discounted)

	6 to 12 month-DAPT			Extended DAPT			
	Extended DAPT phase	Post-extended DAPT phase	Total	Extended DAPT phase	Post-extended DAPT phase	Total	Difference (extended DAPT – 6 to 12 month-DAPT)
Average total costs	$796	$41,417	$42,213	$957	$40,349	$41,306	-$908
Medication	$61	$503	$564	$434	$510	$944	+$380
MI	$249	$3,685	$3,934	$144	$3,644	$3,788	-$146
Post-MI	$102	$10,215	$10,317	$60	$9,704	$9,764	-$553
Stroke	$94	$1,938	$2,032	$89	$1,904	$1,994	-$38
Post-stroke	$140	$23,856	$23,996	$132	$23,325	$23,457	-$539
Bleeding	$15	$120	$136	$18	$122	$140	+$4
Stent thrombosis	$5	$42	$47	$2	$43	$45	-$3
Urgent revascularization	$129	$1,058	$1,187	$78	$1,073	$1,151	-$36

DAPT: dual anti-platelet therapy; MI: myocardial infarction

This resulted in the extended DAPT strategy being dominant (i.e., more effective and less costly) over the 6 to 12 month-DAPT strategy (Table 32). This dominance was observed in 73.3% of the 5,000 iterations while extended DAPT was dominated (i.e., less effective and more expensive than the 6 to 12 month-DAPT) in only 0.6% of the iterations. However, 15.7% of the iterations resulted in an ICUR above $50,000 per QALY.

Table 32: Results from the base case

Analysis	6 to 12 month-DAPT		ExtendedDAPT		Incremental		
	Costs	QALY	Costs	QALY	ΔCosts	ΔQALY	ICUR
All patients (base case)	$42,213	13.63	$41,306	13.65	-$908	0.0154	Extended DAPT dominant

QALY: quality adjusted life-year; ΔCosts: incremental costs; ΔQALY: incremental QALY; ICUR: incremental cost-utility ratio

7.2 Exploratory analyses

Exploratory analyses were performed in the following patient subgroups:

- prior MI
  - Patients with a prior MI
  - Patients with no prior MI
- ACS
  - Patients with ACS
- Diabetes
  - Patients with diabetes
  - Patients with no diabetes

- Age
  - Patients ≥ 75 years old
  - Patients < 75 years old

However, the number of studies was often limited to one or two for most subgroup analyses and results must be interpreted with a lot of caution.

Patients with or without a prior MI

Only two studies contributed to the data for the analysis in patients with a prior MI, i.e., the DAPT trial and the ITALIC trial.[24,31] For some of the endpoints (e.g., stroke, urgent revascularization, stent thrombosis), only one of these two studies contributed to the data. For the no prior MI subgroup, the only study contributing to the analysis was DAPT.[24] Furthermore, the urgent revascularization endpoint could not be populated for this subgroup. Therefore, the probability of this event was assumed to be the same as in the base case (all patient analysis) as only 16% of the full cohort had a prior MI.

While prior MI patients seem to benefit from extended DAPT, this is not the case for patients with no prior MI as the exploratory analysis indicates that extended DAPT is dominated (i.e., less effective, more costly) by the 6- to 12-month DAPT duration (Table 33).

Patients with ACS

The inputs for this analysis came from two studies, ITALIC and DAPT, although for some endpoints, only one of them had data.[24,31] Exploratory results in ACS patients seem to indicate that extended DAPT is a valid economic option for these patients.

Patients with or without diabetes

The same ITALIC and DAPT studies provided input for the analysis in DM patients.[24,31] For the non-DM patients, only one study (DAPT), contributed to the analysis.[24] Extended DAPT does not seem to be a valid economic option in patients with diabetes, as results indicate that extended DAPT is dominated (i.e., less effective and more costly than the 6 to 12 month-DAPT arm). The exploratory analysis in patients without diabetes seems to indicate that extended DAPT is dominant (i.e., more effective and less costly) over the 6 to 12 month-DAPT arm.

Patients above and below 75 years old

The ITALIC and PRODIGY studies contributed to the analyses in patients above 75 years.[25,31] Similar to the other subgroups analyses, some of the endpoints were populated by data from only one or the other study. For the below 75 years old patient population, only the PRODIGY study provided data.[25] These exploratory analyses seem to indicate that extended DAPT may not be a valid economic option in patients above 75 years old as extended DAPT is more expensive and less effective than the 6 to 12 month-DAPT arm. Extended DAPT seems to be cost-effective in patients less than 75 years old.

Table 33: Model results: subgroup analyses

Subgroup	6 to 12 month-DAPT		Extended DAPT		Incremental		
	Costs	QALY	Costs	QALY	ΔCosts	ΔQALY	ICUR
All patients (base case)	$42,213	13.63	$41,306	13.65	-$908	0.0154	Extended DAPT dominant
Prior MI	$60,090	12.93	$57,597	12.99	-$2,494	0.0577	Extended DAPT dominant
No prior MI	$49,232	13.48	$47,926	13.42	-$1,307	-0.0578	6 to 12 month-DAPT dominant
ACS	$52,803	13.19	$50,737	13.25	-$2,066	0.0683	Extended DAPT dominant
Diabetes	$54,445	13.14	$54,274	13.08	-$171	-0.0631	6 to 12 month-DAPT dominant
No diabetes	$48,552	13.42	$46,959	13.44	-$1,594	0.0167	Extended DAPT dominant
Above 75 years old	$10,199	6.50	$15,056	6.46	$4,858	-0.0391	6 to 12 month-DAPT dominant
Below 75 years old	$34,292	14.00	$38,300	14.11	$4,008	0.1075	$37,269

QALY: quality adjusted life-year; ΔCosts: incremental costs; ΔQALY: incremental QALY; ICUR: incremental cost-utility ratio; MI: myocardial infarction; ACS: acute coronary syndrome

7.3 Sensitivity analyses

The results of the sensitivity analyses are shown in Table 34. In most sensitivity analyses, extended DAPT remained dominant, i.e., more effective and less expensive. However, four sensitivity analyses stand out as having an ICUR above $25,000 per QALY. These are when ticagrelor is assumed to be the sole P2Y12 inhibitor used in the DAPT regimen, when the analysis is performed on a shorter time horizon (i.e., 19 months) and when using studies with an extended DAPT duration of 24 to 30 months and of 36 to 48 months only. In the short time horizon analysis, the ICUR is rather high at $545,805 per QALY. As mentioned earlier, P2Y12 inhibitor-specific analyses could not be performed due to too few data available. The sensitivity analysis with ticagrelor as the sole P2Y12 agent in the DAPT regimen therefore assumed that the clinical impact of ticagrelor is the same as that of clopidogrel and prasugrel in the studies included in CADTH meta-analysis.

Using an alternative method to estimate bleeding events did not significantly impact the results. The same could be said for using alternative utility values.

In an attempt to estimate the impact of the variability in the duration of DAPT treatment in the control arm (i.e., either 6 or 12 months depending on the study) and the variability in extended DAPT duration (i.e., 18 to 48 months depending on the study), several analyses were done by grouping studies of similar duration. For example, when analysing studies where the control arm had a 6-month versus a12-month

DAPT duration, it can be seen that the incremental benefit is greater in studies where the control arm had 6-month duration. Savings are seen in the studies where the control arm is 12-month duration, but not where it is of 6-month duration. Therefore, extended DAPT appears cost-effective compared to 6-month duration in the control arm and dominant (i.e., more effective and less expensive) compared to 12-month duration in the control arm. However, this is not a perfect comparison as the extended DAPT duration varies among studies in each of these two subsets. Then, grouping studies with similar extended DAPT duration showed that the benefit decreases with increasing extended DAPT treatment duration, with the 18-month extended DAPT duration showing the largest incremental benefit of all sensitivity analyses (i.e., 0.1067). It is important to note that the 18-month extended DAPT duration analysis is based on only one study (NIPPON, 1,600 patients in each group). These sensitivity analyses also show that 24 month of more of extended DAPT duration might not be a cost-effective option with an ICUR well above $50,000 per QALY.

Alternative values for some probabilities of death in the post-extended DAPT phase of the model were tested in two scenarios to assess the impact of these parameters on the results. The first of these scenarios involved the calibration of deaths post-MI by adding a calibration factor to the HR of death post-MI (coming from a Danish study) in order to reproduce the proportion of death post-MI observed in the study from Manitoba (i.e., 7.4% at 4 years).[56,59] The second scenario used a similar calibration factor, this time applied to both the hazard ratio of death post-MI and the hazard ratio of death post-stroke in order to give an all-cause death proportion at 6 years similar to that reported by the US long-term post-PCI study described earlier, i.e., 11.8%.[58] Calibrating the death post-MI had little impact on the accumulated benefit in each arm, but resulted in a slightly larger incremental benefit than in the base case. The second calibration produced a larger reduction of the benefit in both groups and also a larger increase in the incremental benefit. For both scenarios, the conclusion was the same, i.e., extended DAPT was dominant.

Removing the probability of secondary events had little impact on the results. Adding a rebound effect at discontinuation of extended DAPT reduced the benefit and even produces a QALY loss when the rates of MI, stroke and stent thrombosis reach those of the control group 6 months after the discontinuation of extended DAPT.

In scenarios where extended DAPT was dominant, costs varied only minimally. The smallest saving ($62) was seen with the calibration of death post-MI, while the largest saving ($1,540) was seen with the 12-month DAPT duration in the control arm. QALY gains varied a little more with the smallest QALY gain (0.0086) seen with the 3% discounting and the largest QALY gain (0.1049) noted with the 18-months extended DAPT duration.

Table 34: Model results: scenario analyses

Scenario	6 to 12 month-DAPT		Extended DAPT		Incremental		
	Costs	QALY	Costs	QALY	ΔCosts	ΔQALY	ICUR
Base case	$42,213	13.63	$41,306	13.65	-$908	0.0154	Extended DAPT dominant
Discounting: 0%	$53,292	16.23	$53,199	16.25	-$1,093	0.0255	Extended DAPT dominant
Discounting: 3%	$33,996	11.64	$33,249	11.65	-$748	0.0086	Extended DAPT dominant
Risk ratios vs rates	$42,214	13.64	$41,388	13.66	-$826	0.0222	Extended DAPT dominant
Alternative bleeding count							Extended DAPT dominant
a)	$42,119	13.60	$41,237	13.61	-$882	0.0130	Extended DAPT dominant

Scenario	6 to 12 month-DAPT		Extended DAPT		Incremental		
	Costs	QALY	Costs	QALY	ΔCosts	ΔQALY	ICUR
b)	$42,234	13.42	$41,354	13.43	-$879	0.0092	Extended DAPT dominant
Minor bleed costs	$42,199	13.63	$41,297	13.64	-$902	0.0144	Extended DAPT dominant
Alternative proportion for anti-platelet agents							
d) 100% clopidogrel	$42,173	13.64	$41,099	13.65	-$1,074	0.0151	Extended DAPT dominant
e) 100% prasugrel	$42,126	13.63	$41,955	13.65	-$171	0.0151	Extended DAPT dominant
f) 100% ticagrelor	$42,263	13.65	$42,745	13.66	$481	0.0150	$32,092
Dispensing fee (monthly)	$43,085	13.65	$42,319	13.66	-$766	0.0146	Extended DAPT dominant
Alternative utility values	$42,252	13.62	$41,340	13.64	-$912	0.0160	Extended DAPT dominant
Shorter time horizon (19 months)	$796	1.24	$957	1.24	$161	0.0003	$545,805
DAPT duration in control: 6 months	$30,229	14.05	$30,241	14.08	$254	0.0257	$448
DAPT duration in control: 12 months	$46,104	13.50	$44,564	13.52	-$1,540	0.0161	Extended DAPT dominant
Extended DAPT duration: 18 months	$29,221	14.12	$29,058	14.22	-$162	0.1049	Extended DAPT dominant
Extended DAPT duration: 24 to 30 months	$48,533	13.43	$47,376	13.43	-$1,157	-0.0046	$253,873
Extended DAPT duration: 36 to 48 months	$31,866	14.00	$31,280	14.00	-$586	-0.0077	$75,641
Alternative values for survival in the post-extended DAPT phase							
a) Post-MI death calibration	$40,653	13.46	$39,823	13.48	-$830	0.0216	Extended DAPT dominant
b) All-cause death calibration	$14,328	11.58	$14,265	11.68	-$62	0.0982	Extended DAPT dominant
No secondary events	$34,153	13.61	$33,876	13.63	-$277	0.0159	Extended DAPT dominant
Rebound effect							
a) Maximal rebound at 3 months	$42,274	13.65	$41,701	13.65	-$573	0.0082	Extended DAPT dominant
b) Rates reaching control rates at 6 months	$42,248	13.64	$42,136	13.64	-$113	-0.0067	$16,846

QALY: quality adjusted life year; ΔCosts: incremental costs; ΔQALY: incremental QALY; DAPT: dual anti-platelet therapy

7.4 Validation

Results of the extended DAPT phase of the model compared to the results of the meta-analysis are shown in Table 35. In general, the model was able to reproduce the results of the meta-analysis, including relative risks, within a plus or minus 5% difference. There were two exceptions to this. The first one was the relative risk of stent thrombosis, while the events estimated in each arm were within 5% of the results of the meta-analysis; the resulting relative risk was approximately 12% lower than in the meta-analysis indicating that the model might overestimate the extended DAPT benefit on stent thrombosis. As stent thrombosis contributes only minimally to the QALY gain and patients are assumed to return to the 'well post-PCI' state afterward, this is expected to have a minimal impact on the results of the analysis. The other difference with the meta-analysis is on bleeding events. Although, at first sight it seems that the model is underestimating the number of bleeding events, this is due to the fact that not all studies contributed to the bleeding event calculations in the base case as only four studies (i.e., OPTIDUAL, ITALIC, ARCTIC, DES-LATE) reported bleeding events with the TIMI classification.[27,31,34,55] In two of these studies (OPTIDUAL, DES-LATE), extended DAPT was given for 24 to 36 months beyond the initial 6 to 12 months, while the other two studies were 18 and 17 months. So, the risks calculated in the meta-analysis are for an average extended DAPT duration of 23 months beyond the initial 6 to 12 months, compared to 19 months when all studies are combined. The model uses monthly rates that are applied for an extended DAPT phase of 19 months on average, and hence, while the model estimations are accurate for bleeding events, they cannot replicate the meta-analysis results which are reported for a longer extended DAPT duration.

Table 35: Comparison of the model results (extended DAPT phase) and CADTH meta-analysis

Clinical Outcome	Model results			CADTH meta-analysis results		
	6 to 12 month-DAPT	Extended DAPT	RR	6 to 12 month-DAPT	Extended DAPT	RR
MI	2.34%	1.35%	0.5776	2.38%	1.38%	0.5790
Stroke	0.74%	0.70%	0.9462	0.76%	0.71%	0.9370
Urgent revascularization	1.21%	0.74%	0.6075	1.15%	0.70%	0.6050
Stent thrombosis	0.92%	0.31%	0.3342	0.89%	0.31%	0.3800
Bleeding	1.31%	1.54%	1.1722	1.94%	2.17%	1.1162
Bleeding (major)				1.36%	1.29%	0.9510
Bleeding (minor)				0.59%	0.87%	1.4190
Death	1.57%	1.75%	1.1181	1.58%	1.79%	1.0680

Only two other analyses compared various DAPT durations and resulted in diverging conclusions for extended DAPT.[36,43] It is somewhat difficult to compare our results to theirs as they only report a few of the clinical outcomes. In comparison to Arbel et al, CADTH model estimates more MI and slightly less bleeding events while stent thromboses are in the same range.[36] However, both costs and QALY are higher in CADTH analysis, likely due to a lower risk of death in post-stroke patients who are the largest contributor of costs in CADTH analysis. Cost are slightly higher in the analysis by Jiang while QALY are lower.[43] This is likely due to higher unit costs.

8 DISCUSSION

8.1 Summary of Clinical Evidence

Among all participants, extending DAPT beyond 12 months may reduce the risk of myocardial infarction and stent thrombosis but may increase the risk of bleeding. There were no significant differences in the risk of death (all-cause, cardiovascular, non-cardiovascular), stroke, urgent target revascularization,

MACCE or gastrointestinal bleeding between extended DAPT (more than 12 months) and shorter-duration DAPT (6-12 months).

Most of the included studies enrolled participants with drug-eluting stents. As such, the findings for this subgroup were similar to the reference case involving all participants. Two RCTs (DAPT, PRODIGY) included a small proportion of participants with a bare-metal stent (15%–25%), and data were not reported for all the outcomes of interest. The available data for participants with a bare-metal stent suggest an increased risk of BARC Type 2 and 3 bleeding with DAPT for more than 12 months; however, no data were available for non-cardiovascular death or urgent revascularization. These findings were based on a small number of participants with a bare-metal stent (2,179) and should be interpreted with caution.

Data were limited for some subgroup analyses. We highlight the differences between groups below.

Prior Myocardial Infarction

- Participants with a previous myocardial infarction who receive DAPT for more than 12 months had a reduced risk of myocardial infarction, MACCE, and stent thrombosis, but an increased risk of moderate bleeding. No significant differences were found in the risk of death (all-cause death, cardiovascular), stroke, urgent revasularization, TIMI minor bleeding, GUSTO severe bleeding, or BARC Type 3 or 5 bleeding.
- Participants without a previous myocardial infarction had an increased risk of all-cause death and moderate bleeding with extended DAPT, but at lower risk of myocardial infarction and stent thrombosis. No significant differences were found in the risk of stroke, MACCE, GUSTO severe bleeding, or BARC Type 5 bleeding.

Acute Coronary Syndrome

- Participants with ACS at presentation who received more than 12 months of DAPT had a lower risk of myocardial infarction and stent thrombosis, but an increased risk of moderate bleeding. There were no significant differences between DAPT durations for all-cause or cardiovascular death, stroke, MACCE, TIMI minor bleeding or GUSTO severe bleeding.
- Limited data were available for participants without ACS. There were no significant differences in the risk of MACCE between DAPT durations among patients without ACS, with no data available for the other outcomes.

Diabetes

- Participants with diabetes on extended DAPT had an increased risk of BARC Type 3 bleeding, with no significant differences between DAPT durations for the risk of death (all-cause, cardiovascular, non-cardiovascular), myocardial infarction, stroke, stent thrombosis, urgent revascularization, MACCE, and TIMI minor bleeding.
- Participants without diabetes had a lower risk of myocardial infarction, stent thrombosis, and MACCE, but at higher risk of GUSTO moderate or severe bleeding. There were no significant differences between DAPT durations for all-cause death. No data were available for the remaining outcomes.

Age

- Participants aged more than 75 years had an increased risk of stroke with extended DAPT compared with DAPT for 6-12 months, as well as increased risk of GUSTO moderate or severe bleeding and BARC Type 2, 3 or 5 bleeding. There were no significant differences between DAPT durations for the risk of death (all-cause, cardiovascular), myocardial infarction, stroke, stent thrombosis, urgent revascularization, MACCE, and TIMI minor bleeding.
- Participants aged less than 75 years who received extended DAPT had a lower risk of myocardial infarction but at increased risk of GUSTO moderate or severe bleeding and BARC Type 2, 3 or 5 bleeding. There were no significant differences between DAPT durations for the risk of death (all-

cause, cardiovascular), stent thrombosis, MACCE, and TIMI minor bleeding. No data were available for the remaining outcomes.

Smoking

- Both smokers and non-smokers had a reduced risk of myocardial infarction and stent thrombosis with extended DAPT, with no significant difference in the risk of GUSTO moderate or severe bleeding or BARC Type 2,3 or 5 bleeding.
- Participants who smoked had a reduced risk of MACCE with extended DAPT; no difference in the risk of MACCE was observed among non-smokers.
- Data for the other outcomes were not available.

8.2 Interpretation of the Clinical Results

This systematic review builds on previously published reviews by considering the benefits and harms of extended DAPT for more than 12 months in clinically important patient subgroups following PCI with stenting in order to determine groups to best target long-term DAPT. The protocol for this review was registered *a prior* and followed rigorous systematic procedures throughout the review process.
Overall, extended DAPT beyond 12 months in patients after PCI was predominantly beneficial in the reduction of stent thrombosis and myocardial infarction; however, this benefit was accompanied by an increase of bleeding.

Patients with prior myocardial infarction, those with acute coronary syndrome at presentation, no diabetes, or aged less than 75 years may derive the most benefit from long-term DAPT; accordingly, individualized risk assessments should be made to determine optimal duration of therapy.
The findings of this review are generally consistent with our previous umbrella review (review of systematic reviews) of the optimal duration of DAPT,[18] which found some patient subgroups, such as those with prior myocardial infarction or aged less than 75 years may receive the most benefit from long-term DAPT. This is also consistent with the guideline-proposed concept of individualizing therapy based on risk factors. The identified subgroups with differences in ischemic and bleeding outcomes are also consistent with the components of previously proposed risk-scores such as the DAPT score.[17]

In 2015, the US Food and Drug administration issued a safety communication concerning the increased risk of death observed in the DAPT trial.[84] In the DAPT study, participants who received 30 months of DAPT were at higher risk of death compared to those who received 12 months of DAPT.[24] Specifically, the DAPT study showed an increase in the risk of all-cause death, primarily due to an increased number of non-cardiovascular deaths, among those who received extended DAPT. In their meta-analysis involving the DAPT trial and “other long-term clinical trials”, the FDA found no increased risk of all-cause death with extended DAPT (>12 months) compared with short-term (6 months or less) DAPT. In the present review, we compared extended DAPT to DAPT for 6-12 months, with a similar finding of no increased risk of all-cause death with extended DAPT. However, for non-cardiovascular death, the findings are inconsistent: although the DAPT trial reported an increased risk of non-cardiovascular death with extended DAPT, these findings were not replicated in two smaller RCTs.[23,30] Although we aimed to investigate the effect of patient characteristics on this risk, limited subgroup data were available for this outcome at the time of the review.

In the current review, we observed an increased risk of all-cause death among participants without prior myocardial infarction and the increased risk of stroke among those aged more than 75 years and older who received extended DAPT. Again, these findings highlight the importance of performing individualized assessment of risk and tailoring the duration of DAPT to both patients’ clinical characteristics as well as to their individual preferences and values related to the potential benefits and harms.

8.3 Strengths and Limitations of the Clinical Systematic Review

8.3.1 Strengths

We performed a comprehensive review of published RCTs that aimed to compare extended DAPT (> 12 months) with DAPT for six to 12 months. The review followed an a priori protocol and used standard approaches for the identification of evidence, data abstraction, quality assessment, and reporting. Our review further analyzed important subgroups who may derive benefits or suffer harm with prolonged DAPT; thus affording confirmation for clinicians to identify patient characteristics which may alter decision on DAPT duration.

8.3.2 Limitations

This review has several limitations that merit consideration. Although all of the included trials involved random allocation of participants to treatment arms, most were open-label. However, all of the included outcomes were objective, and unblinding should not affect the effect estimates.

Most of the included trials involved use of clopidogrel as the P2Y12 inhibitor associated with ASA, with limited subgroup data available for prasugrel and none for ticagrelor; thus, the findings of this review mainly apply to clopidogrel. Given that clopidogrel is still currently widely used post-PCI, these findings are nonetheless important for clinicians looking at optimizing the care of their patients who recently underwent a PCI. The findings are also relevant to the policy questions of this review. There is a need to understand whether reimbursement policies for thromboembolic prophylaxis with P2Y12 inhibitors (as part of DAPT regimens) initiated immediately post-PCI should accommodate renewal of the reimbursement of the P2Y12 inhibitor for a period extending beyond the first 12 months.

The lack of data for ticagrelor in the current review may require jurisdictions to consider findings from the PEGASUS-TIMI 54 trial,[35] which randomized participants to receive ticagrelor or placebo. This study did not meet the eligibility criteria for this review (as described in Appendix 12) but results may be informative to clinical and policy decisions in practice. Using ticagrelor 60 mg twice daily after the first 12 months of DAPT may be considered for candidates meeting the PEGASUS TIMI 54 trial inclusion criteria. More specifically, patients older than 50 years of age with a history of MI (one to three years before), with one of the following risk factors for atherothrombotic events:

- age of 65 years or greater;
- diabetes requiring medication;
- second prior spontaneous MI (> 1 year ago);
- angiographic evidence of multivessel coronary artery disease; or,
- chronic renal dysfunction (defined as creatinine clearance < 60 ml/min).

Also, reimbursement of ticagrelor at a dose of 60 mg twice daily (as opposed to the currently indicated 90 mg twice daily post-ACS prophylaxis) is a different, yet clinically-related, policy question than the ones being asked in this review. Importantly, the 60 mg dose of ticagrelor in the PEGASUS-TIMI 54 trial trends to a lowering of complications. This is reflected in the 2016 listing recommendation from the Canadian Expert Drug Committee which, among other criteria, involves meeting the inclusion criteria from the PEGASUS-TIMI 54 trial in order to obtain reimbursement for this secondary prevention regimen[85].

The included RCTs enrolled heterogeneous populations, with important differences in the inclusion criteria, particularly related to the baseline inclusion of high-risk participants. Because some high-risk patients may have been excluded based on the inclusion criteria, the findings may not be generalizable to all patients in clinical practice. As well, first-generation DESs were used in some of the participants in the DES-LATE,[27] ARCTIC-Interruption,[34] and DAPT[24] trials, which may limit generalizability to current clinical practice where these stents are no longer in use.

The timing of randomization of patients varied between trials. Four trials[23,25,31,32] randomized patients within the first 30 days after stenting. In contrast, in four trials (DAPT,[24] DES-LATE,[27] OPTIDUAL,[30]

ARCTIC-Interruption[34]), patients who had completed the first 12 months of DAPT after stenting without experiencing an adverse event were then randomized to continue or discontinue DAPT, which may have excluded some high-risk patients who may have obtained a larger benefit from extended DAPT.
The outcome definitions varied among the included RCTs. In particular, the definition of MACCE and major bleeding differed in important ways between trials. In order to increase homogeneity, we reported separately data that were assessed by use of different bleeding classification scales and did not pool data where they were not deemed to be clinically similar. For MACCE, we pooled only data from trials that used a comparable definition of the composite outcome.

Limited data were available for some patient subgroups, limiting the power of these analyses to detect differences between DAPT duration. Randomization may not hold in the subgroups, potentially leading to imbalances between the comparison groups. As well, the small number of participants in some subgroups may increase the probability of a false negative finding. It should be noted that a statistically non-significant finding does not preclude a potentially clinically important finding. Because of these limitations, the results of the subgroup analyses should be interpreted with caution.

8.4 Interpretation of the Economic Evaluation

The economic analyses showed that, when considering the estimated lifetime impacts, extending DAPT beyond the initial six to 12 months is a dominant option, i.e., generating a small incremental benefit (i.e., 0.0154 QALY) and small savings (i.e., $908). However, 98% of this benefit was accrued in the post extended DAPT phase of the model. In the extended DAPT phase of the model, the incremental benefit was only 0.0003 QALY; there were incremental costs ($957) and the ICUR was $545,805 per QALY.

In our economic analysis, it is unknown if the impact of extended DAPT will remain beyond the 3 to 5 years that lasted the studies included in our meta-analysis. Evidence of an increase in stent thromboses, strokes and MIs once extended DAPT is discontinued (rebound effect) has been observed in the DAPT study, but will need to be confirmed in additional studies.[24] Several assumptions needed to be made on the risk of events (e.g., death post-MI or stroke, second MI or stroke, etc), in particular in the post-extended DAPT phase of the model. As 98% of extended DAPT incremental benefit came from the post-extended DAPT phase of the model, it is possible that using other assumptions or inputs for this phase of the model could have led to different results. Several scenarios were designed to address this and resulted in conclusions similar to that of the base case except in four cases. These were when ticagrelor was the P2Y12 inhibitor in the DAPT regimen (assuming that clinical impact is the same across agents), when treatment duration was extended by 24 to 48 months beyond the initial 6 to 12 months and when the analysis was limited to the duration of the trials included in CADTH meta-analysis.

Analyses per patient subgroups should only be considered as exploratory as data to inform these analyses were coming from only one or two studies and required additional assumptions to be made. Exploratory subgroup analyses indicate that extended DAPT is more effective and less costly, hence the preferred option in patients who had a prior MI and those presenting with an ACS. However, extended DAPT is less effective and more costly, and hence not the preferred option for patients with diabetes and patients above 75 years old, but more evidence would be required in order to provide more robust conclusions.

9 CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Overall, extended DAPT beyond 12 months after PCI was predominantly beneficial in reducing MI and probable or definite stent thrombosis; however, this benefit was accompanied by increased risk of bleeding. Given most study participants received clopidogrel, these findings mainly apply to clopidogrel-

based DAPT regimens. Similar results were however found for participants using prasugrel. Indeed, among participants who received this P2Y12 inhibitor, DAPT for > 12 months was associated with a lower risk of MI, definite or probable stent thrombosis and MACCE, but higher risk of moderate or severe bleeding, compared with those who received DAPT for six to 12 months. We were unable to compare extended DAPT using ticagrelor versus standard ticagrelor-based DAPT in post-PCI patients due to lack of data. Of note, an increased risk of death was observed among participants without prior MI and the increased risk of stroke among those aged more than 75 years who received extended clopidogrel-based DAPT. In general, from a clinical perspective, patients with prior MI, those with ACS at presentation, no diabetes, or aged less than 75 years may derive the most benefit from extended DAPT, provided bleeding risks are also accounted for when deciding to extend DAPT duration.

From an economic perspective, extending DAPT beyond the initial six to 12 months was more effective and less costly than using ASA only. Exploratory analyses suggest that extended DAPT might be more effective and less costly, and hence preferred, in patients who had a prior MI and those presenting with an ACS. However, it may be less effective and more costly, and hence not preferred, in patients with diabetes and patients above 75 years old. As such, our economic findings are in line with our clinical findings and call for careful selection of patients that may benefit most from extended DAPT in order to ensure extending DAPT beyond 12 months leads to improved clinical and economic outcomes.

These findings have important implications for clinicians. They may also have implications for current reimbursement policies of P2Y12 inhibitors prescribed following PCI. In particular, as reported in this assessment, some patients at high risk of cardiovascular events may benefit from extended DAPT, while such an approach would be best avoided for patients at high-risk of bleeding or stroke complications. The pharmaco-economic benefit of extended DAPT may also be lost if patients most likely to benefit from such therapy are not carefully selected. The findings of this report support the ongoing need for surveillance studies to monitor outcomes based on the proposed criteria.

10 REFERENCES

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11 APPENDICES

Appendix 1: Literature search strategy

OVERVIEW	
Interface:	Ovid
Databases:	Embase <1974 to 2017 November 16> Ovid MEDLINE <1946 to Present> Ovid MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	November 17, 2017
Alerts:	Monthly search updates began December 1, 2017 and will run until project completion
Study Types:	Randomized controlled trials
Limits:	Adults-only

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading Word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)

.pt	Publication type
.rn	CAS registry number

Multi-database Strategy

1 exp Stents/
2 (stent or stents or stented or stenting).tw,kf.
3 (DES or DESs).tw,kf.
4 (Strecker* or Supremo* or WallFlex* or Wallstent*).tw,kf.
5 or/1-4
6 ((dual or double) adj (antiplatelet* or anti-platelet*)).tw,kf.
7 (DAPT or DAPTs).tw,kf.
8 6 or 7
9 Platelet Aggregation Inhibitors/
10 (antiplatelet* or anti-platelet*).tw,kf.
11 (platelet* adj2 inhibit*).tw,kf.
12 thrombocyte aggregation inhibit*.tw,kf.
13 Purinergic P2Y Receptor Antagonists/
14 ((P2Y or P2Y1 or P2Y12 or P2Y2) adj (receptor antagonist* or purinoceptor antagonist*)).tw,kf.
15 (ADP receptor adj (antagonist* or blocker*)).tw,kf.
16 (adenosine diphosphate receptor adj (antagonist* or blocker*)).tw,kf.
17 clopidogrel*.tw,kf.
18 (clopilet or grepid or iscover or PCR 4099 or PCR4099 or plavix or SC 25989C or SC 25990C or SR 25989 or zopya or zylagren or zyllt).tw,kf.
19 (duocover or duoplavin).tw,kf.
20 clopidogrel.rn.
21 Prasugrel Hydrochloride/
22 (prasugrel or CS 747 or CS747 or effient or efient or LY 640315 or LY640315).tw,kf.
23 prasugrel.rn.
24 ticagrelor.tw,kf.
25 (AZD 6140 or AZD6140 or brilinta or brilique or possia).tw,kf.
26 ticagrelor.rn.
27 Aspirin/
28 asa.tw,kf.
29 aspirin.tw,kf.
30 ("2-(Acetyloxy)benzoic Acid" or acetylsalicylic acid or acetysal or acylpyrin or aloxiprimum or colfarit or dispril or easprin or ecotrin or endosprin or magnecyl or micristin or polopirin or polopiryna or solprin or solupsan or zorprin).tw,kf.
31 ("2 acetoxybenzoate" or "8-hour bayer" or acenterine or acesal or acetan or acetard or aceticil or aceticyl or acetonyl or acetophen or acetosal or acetosalicylic acid or acetosalin or acetosalum or acetyl salicylate or acetyl salicylic acid or acetylic salicylic acid or acetylin or acetylo or acetylon or acetylosalicylic acid or acetylsal or acetylsalicyclic acid or acetylsalicyl or

acetylsalicylate or acetylsalicylic acid or acetylsalycic acid or acetylsalycylic acid or acetysal or acidulatum or acidum acetyl salicylicum or acidum acetylosalicylicum or acidum acetylsalicylicum).tw,kf.
32 (actorin or acylpyrine or acytosal or adiro or alabukun or alasil or albyl-e or alka seltzer or alkaspirin or anasprin or andol or anopyrin or ansin or anthrom or aptor or arthralgyl or asaflow or asaphen or asapor or asatard or asawin or aspec or aspent or aspex or aspilets or aspirem or aspirgran or aspirina or aspirine or aspirinine or aspirisucre or aspisol or aspo cid or aspro or asrina or asrivo or asta or asteric or astrix).tw,kf.
33 (bebesan or biprin or bokey or boxazin or breoprin or bufferin or cafenol or caprin or cardioaspirina or caspirin or catalgine or catalgix or cemerit or cemirit or claradin or claragine or comoprin or contrheuma).tw,kf.
34 (darosal or dispirin or dolean or dolean or dusil or ecasil or ecosprin or egalgic or emocin or empirin or encaprin or encine or endosprin or entaprin or entericin or enteroprin or enterosarine or enterospirine or entrophen or eskotrin or euthermine or extren).tw,kf.
35 (genasprin or globentyl or godamed or gotosan or helicon or idotyl or infatabs or istopirin or istopyrine or ivepirine or juvepirine or keypo or kilios or "mcn r 358" or measurin or mejoral or melabon or micropyrin or mikristin or miniasal or mycristin).tw,kf.
36 (naspro or novasen or nu seal or nu seals or nuseal? or ortho acetoxybenzoate or ortho acetoxybenzoic or ostoprin or pancemol or paracin or paynocil or pengo or platet 300 cleartab or plewin or polopiryna or premaspin or primaspan or proprin or pyronoval).tw,kf.
37 (reumyl or rhodine or rhonal or ronal or salacetin or salacetogen or saletin or salisalido or sargepirine or soldral or solpyron or solucetyl or solupsa or spren).tw,kf.
38 (tapal or temagin or tevapirin or "th 2152" or thrombo-aspilets or treupahlin or treuphalin or tromalyt or tromcor or turivital or verin or vitalink or xaxa or zero-order release).tw,kf.
39 aspirin.rn.
40 or/9-39
41 Drug Combinations/
42 Drug Therapy, Combination/
43 Combined Modality Therapy/
44 ((combination* or combine* or combining) adj2 (agent or agents or drug or drugs)).tw,kf.
45 ((combination* or combine* or combining) adj2 (therap* or treatment*)).tw,kf.
46 ((dual or double) adj2 (therap* or treatment*)).tw,kf.
47 or/41-46
48 40 and 47
49 8 or 48
50 5 and 49
51 exp Percutaneous Coronary Intervention/ (134063)
52 (percutaneous coronary adj3 (intervention? or revascular* or re-vascular*)).tw,kf.
53 (PCI or PCIs or PPCI or PPCIs).tw,kf.
54 (coronary adj2 balloon adj (dilation* or dilatation*)).tw,kf.
55 (coronary angioplast* adj2 balloon).tw,kf.
56 PTCA.tw,kf.
57 Angioplasty, Balloon, Laser-Assisted/
58 (laser-assisted adj2 angioplast*).tw,kf.
59 (laser balloon* adj2 angioplast*).tw,kf.
60 percutaneous transluminal laser angioplast*.tw,kf.

61 PTLA.tw,kf.
62 or/51-61
63 49 and 62
64 50 or 63
65 (controlled clinical trial or randomized controlled trial or pragmatic clinical trial).pt.
66 clinical trials as topic.sh.
67 exp Randomized Controlled Trials as Topic/
68 (randomi#ed or randomly or RCT$1 or placebo*).tw,kf.
69 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kf.
70 trial.ti.
71 or/65-70
72 64 and 71
73 Adolescent/ not (exp Adult/ and Adolescent/)
74 exp Child/ not (exp Adult/ and exp Child/)
75 exp Infant/ not (exp Adult/ and exp Infant/)
76 or/73-75
77 72 not 76
78 exp Animals/ not (exp Animals/ and Humans/)
79 77 not 78
80 (comment or editorial or interview or news or newspaper article).pt.
81 (letter not (letter and randomized controlled trial)).pt.
82 79 not (80 or 81)
83 82 use ppez
84 exp stent/
85 (stent or stents or stented or stenting).tw,kw.
86 (DES or DESs).tw,kw.
87 (Strecker* or Supremo* or WallFlex* or Wallstent*).tw,kw.
88 or/84-87
89 ((dual or double) adj (antiplatelet* or anti-platelet*)).tw,kw.
90 (DAPT or DAPTs).tw,kw.
91 acetylsalicylic acid plus clopidogrel/
92 (duocover or duoplavin).tw,kw.
93 or/89-92
94 antithrombocytic agent/
95 (antiplatelet* or anti-platelet*).tw,kw.
96 (platelet* adj2 inhibit*).tw,kw.
97 thrombocyte aggregation inhibit*.tw,kw.
98 purinergic P2Y receptor antagonist/
99 ((P2Y or P2Y1 or P2Y12 or P2Y2) adj (receptor antagonist* or purinoceptor antagonist*)).tw,kw.
100 (ADP receptor adj (antagonist* or blocker*)).tw,kw.
101 (adenosine diphosphate receptor adj (antagonist* or blocker*)).tw,kw.
102 clopidogrel/
103 (clopidogrel or clopilet or grepid or iscover or PCR 4099 or PCR4099 or plavix or SC 25989C or SC 25990C or SR 25989 or zopya or zylagren or zyllt).tw,kw.
104 clopidogrel.rn.

105 prasugrel/
106 (prasugrel or CS 747 or CS747 or effient or efient or LY 640315 or LY640315).tw,kw.
107 prasugrel.rn.
108 ticagrelor/
109 ticagrelor.tw,kw.
110 (AZD 6140 or AZD6140 or brilinta or brilique or possia).tw,kw.
111 ticagrelor.rn.
112 acetylsalicylic acid/
113 asa.tw,kw.
114 aspirin.tw,kw.
115 ("2-(Acetyloxy)benzoic Acid" or acetylsalicylic acid or acetysal or acylpyrin or aloxiprimum or colfarit or dispril or easprin or ecotrin or endosprin or magnecyl or micristin or polopirin or polopiryna or solprin or solupsan or zorprin).tw,kw.
116 ("2 acetoxybenzoate" or "8-hour bayer" or acenterine or acesal or acetan or acetard or aceticil or aceticyl or acetonyl or acetophen or acetosal or acetosalicylic acid or acetosalin or acetosalum or acetyl salicylate or acetyl salicylic acid or acetylic salicylic acid or acetylin or acetylo or acetylon or acetylosalicylic acid or acetylsal or acetylsalicyclic acid or acetylsalicyl or acetylsalicylate or acetylsalicylic acid or acetylsalycic acid or acetylsalycylic acid or acetysal or acidulatum or acidum acetyl salicylicum or acidum acetylosalicylicum or acidum acetylsalicylicum).tw,kw.
117 (actorin or acylpyrine or acytosal or adiro or alabukun or alasil or albyl-e or alka seltzer or alkaspirin or anasprin or andol or anopyrin or ansin or anthrom or aptor or arthralgyl or asaflow or asaphen or asapor or asatard or asawin or aspec or aspent or aspex or aspilets or aspirem or aspirgran or aspirina or aspirine or aspirinine or aspirisucre or aspisol or aspo cid or aspro or asrina or asrivo or asta or asteric or astrix).tw,kw.
118 (bebesan or biprin or bokey or boxazin or breoprin or bufferin or cafenol or caprin or cardioaspirina or caspirin or catalgine or catalgix or cemerit or cemirit or claradin or claragine or comoprin or contrheuma).tw,kw.
119 (darosal or dispirin or dolean or dolean or dusil or ecasil or ecosprin or egalgic or emocin or empirin or encaprin or encine or endosprin or entaprin or entericin or enteroprin or enterosarine or enterospirine or entrophen or eskotrin or euthermine or extren).tw,kw.
120 (genasprin or globentyl or godamed or gotosan or helicon or idotyl or infatabs or istopirin or istopyrine or ivepirine or juvepirine or keypo or kilios or "mcn r 358" or measurin or mejoral or melabon or micropyrin or mikristin or miniasal or mycristin).tw,kw.
121 (naspro or novasen or nu seal or nu seals or nuseal? or ortho acetoxybenzoate or ortho acetoxybenzoic or ostoprin or pancemol or paracin or paynocil or pengo or platet 300 cleartab or plewin or polopiryna or premaspin or primaspan or proprin or pyronoval).tw,kw.
122 (reumyl or rhodine or rhonal or ronal or salacetin or salacetogen or saletin or salisalido or sargepirine or soldral or solpyron or solucetyl or solupsa or spren).tw,kw.
123 (tapal or temagin or tevapirin or "th 2152" or thrombo-aspilets or treupahlin or treuphalin or tromalyt or tromcor or turivital or verin or vitalink or xaxa or zero-order release).tw,kw.
124 acetylsalicylic acid.rn.
125 or/94-124
126 acetylsalicylic acid/cb
127 antithrombocytic agent/cb
128 clopidogrel/cb

129 prasugrel/cb
130 purinergic P2Y receptor antagonist/cb
131 ticagrelor/cb
132 drug combination/
133 ((combination* or combine* or combining) adj2 (agent or agents or drug or drugs)).tw,kw.
134 ((combination* or combine* or combining) adj2 (therap* or treatment*)).tw,kw.
135 ((dual or double) adj2 (therap* or treatment*)).tw,kw.
136 or/126-135
137 125 and 136
138 93 or 137
139 88 and 138
140 exp percutaneous coronary intervention/
141 (percutaneous coronary adj3 (intervention? or revascular* or re-vascular*)).tw,kw.
142 (PCI or PCIs or PPCI or PPCIs).tw,kw.
143 (coronary adj2 balloon adj (dilation* or dilatation*)).tw,kw.
144 (coronary angioplast* adj2 balloon).tw,kw.
145 PTCA.tw,kw.
146 laser angioplasty/
147 (laser-assisted adj2 angioplast*).tw,kw.
148 (laser balloon* adj2 angioplast*).tw,kw.
149 percutaneous transluminal laser angioplast*.tw,kw.
150 PTLA.tw,kw.
151 or/140-150
152 138 and 151
153 139 or 152
154 randomized controlled trial/ or controlled clinical trial/
155 exp "clinical trial (topic)"/
156 (randomi#ed or randomly or RCT$1 or placebo*).tw,kw.
157 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kw.
158 trial.ti.
159 or/154-158
160 153 and 159
161 exp juvenile/ not (exp juvenile/ and exp adult/)
162 adolescent/ not (exp adult/ and adolescent/)
163 exp child/ not (exp adult/ and exp child/)
164 exp infant/ not (exp adult/ and exp Infant/)
165 or/161-164
166 160 not 165
167 exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/
168 exp human/ or exp human experimentation/ or exp human experiment/
169 167 not 168
170 166 not 169
171 editorial.pt.
172 letter.pt. not (letter.pt. and randomized controlled trial/)
173 170 not (171 or 172)

174	conference abstract.pt.
175	173 not 174
176	175 use oemezd
177	83 or 176
178	remove duplicates from 177

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Cochrane Library	Same MeSH, keywords, and date limits used as per Medline search, excluding study types and Human restrictions. Syntax adjusted for Cochrane Library databases.

GREY LITERATURE

Dates for Search:	Nov 24-25, 2017, Clinicaltrials.gov and ICTRP only
Keywords:	DAPT; DAPTs; "dual antiplatelet"; "dual anti-platelet"; "platelet aggregation inhibitor"; "platelet aggregation inhibitors"**; "**Purinergic P2Y Receptor Antagonist"; "Purinergic P2Y Receptor Antagonists"; P2Y; P2Y1; P2Y12; P2Y2; clopidogrel; prasugrel; ticagrelor, DES and associated synoyms
Limits:	No limits

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Databases (free)
- Internet Search
- Open Access Journals

Appendix 2: List of included records

1. Abbot Vascular. XIENCE V USA dual antiplatelet therapy (DAPT) cohort (XVU-AV DAPT). NCT01106534. 2016. In: Clinical trials.gov. Bethesda (MD): U.S. National Library of Medicine. https://clinicaltrials.gov/ct2/show/NCT01106534
2. Adamo M, Costa F, Vranckx P, Leonardi S, Navarese EP, Garcia-Garcia HM, et al. Does smoking habit affect the randomized comparison of 6 versus 24-month dual antiplatelet therapy duration? Insights from the PRODIGY trial. *Int J Cardiol*. 2015;190:242.
3. Beijing Anzhen Hospital. Twelve vs 24 months of dual antiplatelet therapy in patients with coronary revascularization for in-stent restenosis. NCT02402491. In: Clinical trials.gov. Bethesda (MD): U.S. National Library of Medicine. https://clinicaltrials.gov/ct2/show/NCT02402491
4. Campo G, Tebaldi M, Vranckx P, Biscaglia S, Tumscitz, Ferrari R, et al. Short- versus long-term duration of dual antiplatelet therapy in patients treated for in-stent restenosis: A PRODIGY trial substudy (Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia). *J Am Coll Cardiol*. 2014;63(6):506.
5. Collet JP, Cayla G, Cuisset T, Elhadad S, Range G, Vicaut E, et al. Randomized comparison of platelet function monitoring to adjust antiplatelet therapy versus standard of care: Rationale and design of the assessment with a double randomization of (1) a fixed dose versus a monitoring-guided dose of aspirin and clopidogrel after DES implantation, and (2) treatment interruption versus continuation, 1 year after stenting (ARCTIC) study. *Am Heart J*. 2011;161(1):5.
6. Collet JP, Silvain J, Barthelemy O, Range O, Cayla G, Van Belle E, et al. Dual-antiplatelet treatment beyond 1 year after drug-eluting stent implantation (ARCTIC-interruption): A randomised trial. *Lancet*. 2014;384:1577-1585.
7. Collet JP, Silvain J, Kerneis M, Cuisset T, Meneveau N, Boueri Z, et al. Clinical outcome of first- vs second-generation DES according to DAPT duration: Results of ARCTIC-Generation. *Clin Cardiol*. 2016;39(4):192.
8. Cordis Corporation. CYPRESS-CYPHER for evaluating sustained safety. NCT00954707. 2016. In: Clinical trials.gov. Bethesda (MD): U.S. National Library of Medicine. https://clinicaltrials.gov/ct2/show/NCT00954707
9. Costa F, Adamo M, Ariotti S, Ferrante G, Navarese EP, Leonardi S, et al. Left main or proximal left anterior descending coronary artery disease location identifies high-risk patients deriving potentially greater benefit from prolonged dual antiplatelet therapy duration. *EuroIntervention*. 2016;11(11):e1222.
10. Costa F, Vranckx P, Leonardi S, Moscarella E, Ando G, Calabro P,et al. Impact of clinical presentation on ischaemic and bleeding outcomes in patients receiving 6- or 24-month duration of dual-antiplatelet therapy after stent implantation: a pre-specified analysis from the PRODIGY (Prolonging Dual-Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia) trial. *Eur Heart J*. 2015;36(20):1242.
11. Crimi G, Leonardi S, Costa F, Adamo M, Ariotti S, Valgimigli M. Role of stent type and of duration of dual antiplatelet therapy in patients with chronic kidney disease undergoing percutaneous coronary interventions. Is bare metal stent implantation still a justifiable choice? A post-hoc analysis of the all comer PRODIGY trial. *Int J Cardiol*. 2016;212:110.
12. Crimi G, Leonardi S, Costa F, Ariotti S, Tebaldi M, Biscaglia S, et al. Incidence, prognostic impact, and optimal definition of contrast-induced acute kidney injury in consecutive patients with stable or unstable coronary artery disease undergoing percutaneous coronary intervention. Insights from the all-comer PRODIGY trial. *Catheter Cardiovasc Interv*. 2015;86(1):E19.

13. Dadjou Y, Safavi S, Kojuri J. Risks and benefits of dual antiplatelet therapy beyond 12 months after coronary stenting: A prospective randomized cohort study. *Medicine (Baltimore)*. 2016;95(22):e3663.
14. Didier R, Morice MC, Barragan P, Noryani AAL, Noor HA, Majwal T, et al. 6- versus 24-month dual antiplatelet therapy after implantation of drug-eluting stents in patients nonresistant to aspirin: Final results of the ITALIC trial (Is There a Life for DES After Discontinuation of Clopidogrel). *JACC Cardiovasc Interv*. 2017;10(12):1202.
15. Franzone A, Piccolo R, Gargiulo G, Ariotti S, Marino M, Santucci A, et al. Prolonged vs short duration of dual antiplatelet therapy after percutaneous coronary intervention in patients with or without peripheral arterial disease: A subgroup analysis of the PRODIGY randomized clinical trial. *JAMA Cardiol*. 2016;1(7):795.
16. Gargiulo G, Ariotti S, Santucci A, Piccolo R, Baldo A, Franzone A, et al. Impact of sex on 2-year clinical outcomes in patients treated with 6-month or 24-month dual-antiplatelet therapy duration: A pre-specified analysis from the PRODIGY trial. *JACC Cardiovasc Interv*. 2016;9(17):1780.
17. Gargiulo G, Costa F, Ariotti S, Biscaglia S, Campo G, Esposito G, et al. Impact of proton pump inhibitors on clinical outcomes in patients treated with a 6- or 24-month dual-antiplatelet therapy duration: Insights from the PROlonging Dual-antiplatelet treatment after Grading stent-induced Intimal hyperplasia studY trial. *Am Heart J*. 2016;174:95.
18. Gargiulo G, Santucci A, Piccolo R, Franzone A, Ariotti S, Baldo A, et al. Impact of chronic kidney disease on 2-year clinical outcomes in patients treated with 6-month or 24-month DAPT duration: An analysis from the PRODIGY trial. *Catheter Cardiovasc Interv*. 2017;90(4):E73-E84.
19. Garratt KN, Weaver WD, Jenkins RG, Pow TK, Mauri L, Kereiakes DJ, et al. Prasugrel plus aspirin beyond 12 months is associated with improved outcomes after TAXUS Liberte paclitaxel-eluting coronary stent placement. *Circulation*. 2015;131(1):62.
20. Gilard M, Barragan P, Noryani AAL, Noor HA, Majwal T, Hovasse T, et al. 6- versus 24-month dual antiplatelet therapy after implantation of drug-eluting stents in patients nonresistant to aspirin: The randomized, multicenter ITALIC trial. *J Am Coll Cardiol*. 2015;65:777-786.
21. Helft G, Le Feuvew C, Georges JL, Carrie D, Leclercq F, Eltchaninoff H, et al. Efficacy and safety of 12 versus 48 months of dual antiplatelet therapy after implantation of a drug-eluting stent: the OPTImal DUAL antiplatelet therapy (OPTIDUAL) trial: Study protocol for a randomized controlled trial. *Trials*. 2013;14(56):1-6.
22. Helft G, Steg PG, Le Feuvre C, Georges JL, Carrie D, Dreyfus X, et al. Stopping or continuing clopidogrel 12 months after drug-eluting stent placement: the OPTIDUAL randomized trial. *Eur Heart J*. 2016;37(4):365.
23. Hermiller JB, Krucoff MW, Kereiakes DJ, Windecker S, Steg PG, Yeh RW, et al. Benefits and risks of extended dual antiplatelet therapy after everolimus-eluting stents. *JACC Cardiovasc Interv*. 2016;9(2):138.
24. Kereiakes DJ, Yeh RW, Massaro JM, Cutlip DE, Steg PG, Wiviott SD, et al. DAPT score utility for risk prediction in patients with or without previous myocardial infarction. *J Am Coll Cardiol*. 2016;67(21):2492.
25. Kereiakes DJ, Yeh RW, Massaro JM, Driscoll-Shempp P, Cutlip DE, Steg PG, et al. Antiplatelet therapy duration following bare metal or drug-eluting coronary stents: The dual antiplatelet therapy randomized clinical trial. *JAMA*. 2015;313(11):1113.
26. Kereiakes DJ, Yeh RW, Massaro JM, Driscoll-Shempp P, Cutlip DR, Steg PG, et al. Stent thrombosis in drug-eluting or bare-metal stents in patients receiving dual antiplatelet therapy. *JACC Cardiovasc Interv*. 2015;8(12):1552.

27. Lee CW, Ahn JM, Park DW, Kang SJ, Lee SW, Kim YH, et al. Optimal duration of dual antiplatelet therapy after drug-eluting stent implantation a randomized, controlled trial. *Circulation*. 2014;129:304-312.
28. Lee JM, Cho DK, Hahn JY, Song YB, Park TK, Oh JH, et al. Safety of 6-month duration of dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndromes: Rationale and design of the Smart Angioplasty Research Team-safety of 6-month duration of Dual Antiplatelet Therapy after percutaneous coronary intervention in patients with acute coronary syndromes (SMART-DATE) prospective multicenter randomized trial. *Am Heart J*. 2016;182:1.
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30. Matteau A, Yeh RW, Kereiakes D, Orav EJ, Massaro J, Steg PG, et al. Frequency of the use of low- versus high-dose aspirin in dual antiplatelet therapy after percutaneous coronary intervention (from the Dual Antiplatelet Therapy study). *Am J Cardiol*. 2014;113(7):1146.
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34. Meredith IT, Tanguay JF, Kereiakes DJ, Cutlip DE, Yeh RW, Garratt KN, et al. Diabetes mellitus and prevention of late myocardial infarction after coronary stenting in the randomized Dual Antiplatelet Therapy Study. *Circulation*. 2016;133(18):1772.
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39. Schmidt ACS, Kereiakes DJ, Cutlip DE, Yeh, D'Agostino RB, Massaro, et al. Myocardial infarction risk after discontinuation of thienopyridine therapy in the randomized DAPT Study (Dual Antiplatelet Therapy). *Circulation*. 2017;135(18):1720.
40. Secemsky EA, Yeh RW, Kereiakes DJ, Cutlip DE, Cohen DJ, Steg PG, et al. Mortality following cardiovascular and bleeding events occurring beyond 1 year after coronary stenting: A secondary analysis of the Dual Antiplatelet Therapy (DAPT) study. *JAMA Cardiol*. 2017;2:478-487.

41. Secemsky EA, Yeh RW, Kereiakes DJ, Cutlip DE, Steg PG, Massaro JM, et al. Extended duration dual antiplatelet therapy after coronary stenting among patients with peripheral arterial disease: A subanalysis of the dual antiplatelet therapy study. *JACC Cardiovasc Interv*. 2017;10:942-954.
42. Valgimigli M, Borghesi M, Tebaldi M, Vranckx P, Parrinello G, Ferrari R, et al. Should duration of dual antiplatelet therapy depend on the type and/or potency of implanted stent? A pre-specified analysis from the PROlonging Dual antiplatelet treatment after Grading stent-induced Intimal hyperplasia studY (PRODIGY). *Eur Heart J*. 2013;34(12):909.
43. Valgimigli M, Campo G, Monti M, Vranckx P, Percoco G, Tumscitz C, et al. Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting: A randomized multicenter trial. *Circulation*. 2012 Apr 24;125(16):2015-26
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45. Valgimigli M, Tebaldi M, Borghesi M, Vranckx P, Campo G, Tumscitz C, et al. Two-year outcomes after first- or second-generation drug-eluting or bare-metal stent implantation in all-comer patients undergoing percutaneous coronary intervention: A pre-specified analysis from the PRODIGY study (PROlonging Dual Antiplatelet Treatment After Grading stent-induced Intimal hyperplasia studY). *JACC Cardiovasc Interv*. 2014;7(1):20.
46. Vranckx P, Leonardi S, Tebaldi M, Biscaglia S, Parrinello G, Rao SV, et al. Prospective validation of the Bleeding Academic Research Consortium classification in the all-comer PRODIGY trial. *Eur Heart J*. 2014;35(37):2524.
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49. Yeh RW, Secemsky EA, Kereiakes DJ, Normand ST, Gershlick AH, Cohen DJ, et al. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. *JAMA - J Am Med Assoc*. 2016;315(16):1735.

Appendix 3: List of studies excluded at full-text review

1. Bang VV, Levy MS. Duration of dual anti-platelet therapy following drug eluting stents: Less Is More? *Catheter Cardiovasc Interv.* 2016;87(4):733-734.
2. Bonaca MP, Murphy SA, Miller D, Herrman JP, Gottlieb S, Keltai M, et al. Patterns of long-term thienopyridine therapy and outcomes in patients with acute coronary syndrome treated with coronary stenting: Observations from the timi-38 coronary stent registry. *Clin Cardiol.* 2014;37(5):293-299.
3. Brener SJ. Are at least 12 months of dual antiplatelet therapy needed for all patients with drug-eluting stents? All patients with drug-eluting stents need at least 12 months of dual antiplatelet therapy. *Circulation.* 2015;131(22):2001-2009.
4. Chevalier B, Cequier A, Dudek D, Haude M, Carrie D, Sabate M, et al. Four-year follow-up of the randomised comparison between an everolimus-eluting bioresorbable scaffold and an everolimus-eluting metallic stent for the treatment of coronary artery stenosis (ABSORB II trial). *EuroIntervention.* 2017;13(13):1561-1564.
5. Costa F, Tijssen JG, Ariotti S, Giatti S, Moscarella E, Guastaroba P, et al. Incremental Value of the CRUSADE, ACUITY, and HAS-BLED Risk Scores for the Prediction of Hemorrhagic Events After Coronary Stent Implantation in Patients Undergoing Long or Short Duration of Dual Antiplatelet Therapy. *J Am Heart Assoc.* 2015 Dec 7;4(12). pii: e002524. doi: 10.1161/JAHA.115.002524.
6. Costa F, van Klaveren D, James S, Heg D, Raber L, Feres F, et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. *Lancet.* 2017;389(10073):1025-1034.
7. Crawford-Faucher A. Prolonged clopidogrel use after cardiac stenting is not beneficial. *Am Fam Physician.* 2012;86(9):853. (This is `Tips from other journals`)
8. Dadjou Y, Safavi S, Kojuri J. Risks and benefits of dual antiplatelet therapy beyond 12 months after coronary stenting: A Prospective Randomized Cohort Study. *Medicine (Baltimore).* 2016;95(22):e3663.
9. Dalby AJ, Gottlieb S, Cyr DD, Magnus Ohman E, McGuire DK, Ruzyllo W, et al. Dual antiplatelet therapy in patients with diabetes and acute coronary syndromes managed without revascularization. *Am Heart J.* 2017;188:156-166.
10. Ebell MH. No benefit to prolonged dual antiplatelet therapy after drug-eluting stent placement. *Am Fam Physician.* 2014;90(7):502.
11. Eisen A, Bhatt DL. Antiplatelet therapy: Defining the optimal duration of DAPT after PCI with DES. *Nat Rev Cardiol.* 2015;12(8):445-446.
12. Elmariah S. Formal comment to Toyota et al.: Short versus prolonged dual antiplatelet therapy (DAPT) duration after coronary stent implantation: A comparison between the DAPT study and 9 other trials evaluating DAPT duration. *PLoS One.* 2017;12(9):e0184513.
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Appendix 4: Characteristics of Included Studies

RCT	Study design	Population	Stent types	Treatments	Timing of randomization	Primary outcome	Country	Funding Source
Mauri 2014, p. 2155; (DAPT; NCT00977938)[24]	Multi-centre, placebo-controlled, superiority RCT	≥ 18 yr who had undergone PCI with a drug-eluting or bare-metal stent. Patients who had no MACCE, repeat revascularization, or moderate or severe bleeding, and who had been adherent to thienopyridine therapy were randomized 12 months after PCI	SES, ZES, PES, BMS	ASA 75–162 mg/d+ clopidogrel (75 mg/d) or prasugrel (10 mg/d) for 12 months, followed by continuation on DAPT or discontinuation of P2Y12 inhibitor (ASA continued) for 18 months DAPT: 12 vs. 30 months Mean/median treatment duration or follow-up not reported	12 months post PCI	Co-primary outcomes: cumulative incidence of definite or probable stent thrombosis and major adverse cardiovascular and cerebrovascular events (composite of death, myocardial infarction, or stroke)	Multi-national	Abbott, Boston Scientific, Cordis, and Medtronic, Bristol-Myers Squibb–Sanofi Pharmaceuticals Partnership, Eli Lilly, and Daiichi Sankyo, and the Department of Health and Human Services
Valgimigli 2012 (PRODIGY; NCT00611286)[25]	Multi-centre, open-label, superiority RCT	≥ 18 yr undergoing elective, urgent, or emergent coronary angioplasty with intended stent implantation, with chronic stable coronary artery disease or acute coronary syndromes, including non–STEMI and STEMI	ZES, EES, PES, BMS	ASA (160 to 325 mg orally or 500 mg IV as a loading dose, 80 to 160 mg orally indefinitely) + clopidogrel (300 or 600 mg orally as a loading dose), then 75 mg/d for 6 or 24 months	30d +/- 5 days post PCI	Composite: death of any cause, myocardial infarction, cerebrovascular accident	Italy	University of Ferrara; no external funding

RCT	Study design	Population	Stent types	Treatments	Timing of randomization	Primary outcome	Country	Funding Source
				DAPT: 6 vs. 24 months Mean/median treatment duration or follow-up not reported				
Collet 2014 (ARCTIC-Interruption; NCT00827411)[34]	Multi-centre, open-label, superiority RCT	≥ 18 yr who underwent DES stent implantation, who did not ischaemic event of the primary endpoint or any event of the primary safety endpoint during the first 12 months	SES, PES, ZES, EES	ASA (75-100 mg/d) alone or ASA (75-100 mg/d) + clopidogrel (75-150 mg/d) or prasugrel (10 mg/d) DAPT: 12 vs. 18–30 months Mean/median treatment duration not reported Median follow-up: 17 months (IQR 15-18)	12 mo post PCI	Composite: death, myocardial infarction, stent thrombosis, stroke, urgent revascularisation	France	Allies in Cardiovascular Trials Initiatives and Organized Networks (ACTION Study Group), Fondation de France, Sanofi - Aventis, Cordis, Medtronic, Boston Scientific, Fondation SGAM.
Lee 2014 (DES-LATE; NCT01186146)[27]	Multi-centre, open-label RCT	≥ 18 yr who had undergone implantation with a DES ³ 12 months before enrollment, had not had a major adverse cardiovascular event (myocardial infarction, stroke, or repeat revascularization) or major bleeding since	SES, PES, ZES, EES and "other DES"	ASA (100 to 200 mg/d) alone or ASA (100 to 200 mg/d)+ clopidogrel (75 mg/d) DAPT: 12 vs. 24 months Mean/median treatment duration not	12-18 mo post PCI	Composite: death resulting from cardiac causes, myocardial infarction, or stroke	Korea	CardioVascular Research Foundation, Seoul, Korea, and the Health 21 R&D Project, Ministry of Health & Welfare, Korea

RCT	Study design	Population	Stent types	Treatments	Timing of randomization	Primary outcome	Country	Funding Source
		implantation, and were receiving dual antiplatelet therapy at the time of enrollment		reported Median follow-up: 42 months (IQR 24.7-50.7)				
Gilard 2015 (ITALIC; NCT01476020)[31]	Multi-centre, open-label, non-inferiority RCT	≥ 18 yr, undergoing PCI with a DES for any indication, with the exception of acute MI and treatment of the left main artery, with confirmed non-resistance to ASA	EES	ASA 75 to 325 mg/d + clopidogrel 75 mg/d, prasugrel 60 mg/d, or ticagrelor 90 mg twice daily DAPT: 6 vs. 24 months Mean/median treatment duration or follow-up not reported	During PCI hospitalization; Patients were withdrawn if an endpoint occurred during the first 6 months of DAPT	Composite: death, myocardial infarction, urgent target vessel revascularization, stroke, and major bleeding	Multi-national	Abbott Vascular Devices
Helft 2016 (OPTIDUAL; NCT00822536)[30]	Multi-centre, open-label, superiority RCT	≥ 18 yr with symptoms of stable angina, silent ischaemia, or acute coronary syndrome (unstable angina, non–STEMI, , or STEMI), who had not experienced a major cardiovascular, cerebrovascular, or major bleeding event in the first12 months post PCI	SES, PES, ZES, EES, BES	ASA (75–160 mg/d) alone or ASA (75–160 mg/d) + clopidogrel (75 mg/d) DAPT: 12 vs.18-48 months Mean/median treatment duration not reported Median follow-up: 22 months after randomization (median follow-	12 +/- 3 months post PCI	Composite: death, myocardial infarction, stroke, major bleeding	France	Assistance Publique-Hopitaux de Paris (Departement de la Recherche Clinique et du Developpement), Programme Hospitalier de Recherche Publique-PHRC 2008, and unrestricted research grants from Federation francaise de Cardiologie, Cordis, Boston, Medtronic,

RCT	Study design	Population	Stent types	Treatments	Timing of randomization	Primary outcome	Country	Funding Source
				up after stenting: 33.4 months)				Terumo, and Biotronik
Nakamura 2017 (NIPPON; NCT01514227)[23]	Multi-centre, non-inferiority, open-label RCT	21-79 yr, with coronary artery disease, including acute myocardial infarction	DES (Nobori*)	ASA (81-162 mg/d) + clopidogrel (75 mg/d) or ticlopidine (200 mg/d)† DAPT: 6 vs. 18 months Mean/median treatment duration not reported Median follow-up: 435 days (14.5 months) in the long-term DAPT group and 430 days (14.3 months) in the short-term DAPT group.	During hospitalization for PCI	Composite: all-cause mortality, myocardial infarction, stroke, major bleeding	Japan	Association for Establishment of Evidence in Interventions
Dadjou 2016 (NCT02327741)[32]	Multi-centre, open-label‡ randomized	50-70 yr, with stenosis more than 70% in any coronary vessel with reference diameter of more than 2.25 which was suitable for PCI	Mixed DES, BMS	ASA (325 mg loading dose, 240 mg/d for 2 mo, followed by 75 mg/d) + clopidogrel (600 mg loading dose, then 75 mg/d) DAPT: < 1 yr vs. > 1 yr Mean/median treatment	At PCI	Composite: cardiovascular death, the incidence of stent reocclusion, bleeding outcomes (not defined)	Iran	Baghiatollah University and the Education Development Center of Shiraz University of Medical Sciences

RCT	Study design	Population	Stent types	Treatments	Timing of randomization	Primary outcome	Country	Funding Source
				duration not reported Follow-up duration was at least 36 months				

Note: ASA = acetylsalicylic acid, BES = biolimus-eluting stent, BMS = bare-metal stent, RCT = randomized controlled trial, d = day, DAPT = dual anti-platelet therapy, DES = drug-eluting stent, EES = everolimus-eluting stent, MACCE = major adverse cardiac and cerebrovascular events, MI = myocardial infarction, mo = months, PCI = percutaneous coronary intervention, PES = paclitaxel-eluting stent, RCT = randomized controlled trial, SES = sirolimus-eluting stent, STEMI = ST-elevation myocardial infarction, vs. = versus, yr = year, ZES = zotarolimus-eluting stent.
*Biodegradable polymer-coated DES.
†Less than 3% of patients received ticlopidine.
‡Open-label inferred from description of methods; not explicitly stated.

Appendix 5: Baseline participant characteristics

Author, year	DAPT duration, mo (no. randomized)	Age, yr, mean (SD)	No. (%) of participants					
			Male	Diabetes	Current smoking	Former smoking	Prior MI	History of heart failure
Nakamura 2017 (NIPPON)*	6 mo (1886) 18 mo (1887)	67.4 (9.6) 67.2 (9.9)	1304 (78.8) 1312 (79.4)	619 (37.4) 635 (38.4)	960 (58.0) 997 (60.3)	NR	201 (12.2) 195 (11.8)	NR
Dadjou 2016¶	< 12 mo (502) > 12 mo (508)	60 (10†)	647 (64.0)	283 (28.0)	341 (33.8)	NR	NR	NR
Helft 2016 (OPTIDUAL)	12 mo (697) 48 mo (701)	64.2 (11.5) 64.1 (10.8)	547 (79.3) 568 (81.7)	222 (32.2) 213 (30.6)	399 (57.8) 425 (61.2)	NR	122 (17.7) 119 (17.1)	8 (1.2) 4 (0.6)
Gilard 2015 (ITALIC)	6 mo (926) 24 mo (924)	61.7 (10.9) 61.5 (11.1)	737 (81.0) 721 (79.3)	331 (36.3) 344 (37.8)	464 (50.9) 480 (52.7)	NR	142 (15.6) 134 (14.7)	NR
Mauri 2014 (DAPT)	12 mo (5786) 30 mo (5862)	61.2 (10.3) 61.4 (10.3)	4318 (74.6) 4405 (75.1)	1654 (28.7) 1737 (29.8)	1560 (27.4) 1582 (27.4)	NR	1204 (21.1) 1252 (21.7)	251 (4.4) 273 (4.7)
Lee 2014 (DES-LATE)	12 mo (2415) 24 mo (2531)	62.3 (10.1) 62.5 (10.0)	1749 (69.6) 1749 (69.1)	709 (28.2) 709 (28.0)	722 (28.7) 693 (27.4)	NR	92 (3.7) 103 (4.1)	NR
Collet 2014 (ARCTIC-INT)	12 mo (641) 18–30 mo (645)	64.0 (11.9) 64.0 (11.9)	503 (81.0) 508 (80.0)	222 (36.0) 198 (31.0)	152 (24.4) 147 (23.1)	NR	186 (29.8) 197 (31.0)	23 (3.7) 20 (3.1)
Valgimigli 2012 (PRODIGY)	6 mo (983) 24 mo (987)	67.9 (11.0) 67.8 (11.0)	747 (76.0) 764 (77.4)	233 (23.7) 244 (24.7)	247 (25.1) 222 (22.5)	NR	258 (26.2) 270 (27.3)	NR

Note: DAPT = dual anti-platelet therapy, MI = myocardial infarction, mo = months, NR = not reported, SD = standard deviation, yr = year
*Characteristics data for patients who did not experience an event in the first 6 months of DAPT.
†Assumed to be SD
¶Data reported for whole population, not by treatment arm.

Appendix 6: Baseline participant characteristics, continued

Author, year	DAPT duration, mo (no. randomized)	No. (%) of participants*			
		Complex lesions†	STEMI	NSTEMI	Unstable angina
Nakamura 2017 (NIPPON)*	6 mo (1886) 18 mo (1887)	NR	198 (12.0) 196 (11.9)	33 (2.0) 26 (1.6)	296 (17.9) 230 (20.0)
Dadjou 2016	< 12 mo (502) > 12 mo (508)	NR	NR	NR	NR
Helft 2016 (OPTIDUAL)	12 mo (697) 48 mo (701)	NR	82 (11.9) 74 (10.7)	117 (17.0) 99 (14.2)	63 (9.1) 66 (9.5)
Gilard 2015 (ITALIC)	6 mo (926) 24 mo (924)	NR	1 (0.1) 3 (0.3)	67 (7.3) 65 (7.1)	143 (15.7) 149 (16.4)
Mauri 2014 (DAPT)	12 mo (5786) 30 mo (5862)	450 (47.8) 440 (47.6	511 (10.3) 534 (10.6)	936 (16.2) 960 (16.4)	825 (16.7) 838 (16.7)
Lee 2014 (DES-LATE)	12 mo (2415) 24 mo (2531)	2734 (78.2) 2838 (78.8)	314 (12.5) 314 (12.4)	266 (10.6) 268 (10.6)	971 (38.6) 930 (36.7)
Collet 2014 (ARCTIC-INT)	12 mo (641) 18 to 30 mo (645)	NR	NR	NR	NR
Valgimigli 2012 (PRODIGY)	6 mo (983) 24 mo (987)	664 (67.6) 642 (65.1)	327 (33.3) 321 (32.5)	224 (22.8) 226 (22.9)	182 (18.5) 183 (18.5)

Note: DAPT = dual anti-platelet therapy, mo = months, NR = not reported, NSTEMI = Non-ST-elevation myocardial infarction, STEMI = ST-elevation myocardial infarction.
*Characteristics data for patients who did not experience an event in the first 6 months of DAPT.
*unless otherwise stated
† No. (%) of lesions; Type B2 or C based on the American College of Cardiology and American Heart Association classification system.

Appendix 7: Characteristics: Type of implanted drug-eluting stents among randomized participants

Author, year	Group	No. (%) of participants			
		Everolimus	Paclitaxel	Zotarolimus	Sirolimus
Mauri 2014 (DAPT)*	12 mo 30 mo	2358 (47.7) 2345 (46.7)	1316 (26.6) 1350 (26.9)	622 (12.6) 642 (12.8)	541 (10.9) 577 (11.5)
Helft 2016 (OPTIDUAL)	12 mo 48 mo	522 (49.2) 540 (50.2)	169 (16.0) 164 (15.2)	114 (10.8) 89 (8.3)	186 (17.5) 214 (19.9)
Gilard 2015 (ITALIC)	6 mo 24 mo	912 (100) 910 (100)	NA	NA	NA
Lee 2014 (DES-LATE)	12 mo 24 mo	364 (10.4) 427 (11.9)	709 (20.3) 738 (20.5)	664 (19) 682 (18.9)	1551 (44.3) 1566 (43.5)
Collet 2014 (ARCTIC-INT)¶	12 mo 18 to 30 mo	NR	NR	NR	NR
Valgimigli 2012 (PRODIGY)*	6 mo 24 mo	247 (25.1) 248 (25.1)	245 (24.9) 245 (24.8)	245 (24.9) 248 (25.1)	NR
Nakamura 2017 (NIPPON)†	6 mo 18 mo	NA	NA	NA	NA
Dadjou 2016‡	< 12 mo > 12 mo	NR	NR	NR	NR

Note: DES = drug-eluting stent, mo = months, NA = not applicable, NR = not reported.
*Participants with an implanted DES.
†All patients received Nobori DES.
‡Included participants with a wide range of stent types (24 individual types); Data for each stent type are available in Table 3 of Dadjou 2016.[32]
¶Described stents as first- or second-generation DES. In the 12 month group, 40% of participants received a first-generation stent and 64% received a second-generation stent. In the 18-30 month group, 43% received a first-generation stent, and 62% received a second-generation stent.

Appendix 8: Inclusion and exclusion criteria for included studies

Major Inclusion and Exclusion Criteria of Included Randomized Controlled Trials

RCT	Major Inclusion Criteria	Major Exclusion Criteria
PRODIGY	Chronic Stable coronary artery disease or ACS including non-ST-elevation and STEMI with at least 1 lesion with a diameter stenosis of ≥50% with a reference vessel diameter of ≥ 2.25 mm	Known allergy to acetylsalicylic acid or clopidogrel, history of bleeding diathesis, active bleeding or previous stroke in the past 6 months, concomitant need of oral anticoagulant therapy, scheduled elective surgery within 24 months of PCI, major surgery within 15 days
DES-LATE	All candidates for DAPT after DES implantation who had not had a major adverse cardiovascular event or major bleeding for12 months after PCI	Life expectancy < 1 year, concomitant vascular disease that required the long-term use of clopidogrel or other established indications for clopidogrel therapy
ARCTIC-Interruption	Planned DES implantation	Primary PCI for STEMI, planned use of GPIIb/IIIa inhibitors, chronic anticoagulationtreatment, or bleeding diathesis
ITALIC	Candidates pre-treated with DAPT after implanted with at least 1 Xience V DES	Primary PCI for acute MI and treatment of the left main artery, nonresponders to Aspirin resistance test, prior DES implantation within 1 year, oral anticoagulation therapy or abciximab treatment during hospital stay, scheduled elective surgery within 12 months, known hemorrhagic diathesis
DAPT	All candidates for DAPT after treatment with FDA-approved DES or BMS who had not had a major adverse cardiovascular or cerebrovascular event, repeat revascularization, or moderate or severe bleeding12 months after PCI	Use of stent with diameter <2.25 mm or >4.0 mm, scheduled elective surgery within 30 months, concomitant need of oral anticoagulant therapy, patient treated with both DES and BMS, a life expectancy < 3 years
OPTIDUAL	Symptoms of stable angina, silent ischemia, or ACS with ≥ 1 lesion with stenosis > 50% located in a native vessel ≥ 2.25 mm in diameter and implanted with ≥ 1 DES or BMS and treated with clopidogrel plus aspirin for 12 months	Requirement for oral anticoagulant, DES implantation in an unprotected left main coronary artery, malignancy or other coexisting conditions associated with life expectancy < 2 years, other revascularization with a DES within 9 months or a BMS within 4 weeks prior to this study
NIPPON[23]	"Optimal indication for percutaneous coronary intervention" and no known contraindications to dual antiplatelet therapy, including patients with acute MI	Cardiogenic shock at the time of PCI, concomitant disease for which a thienopyridine was essential for treatment, history of stent thrombosis, ejection fraction <30%, Life expectancy < 1year, active bleeding condition, planned surgery necessitating discontinuation of antiplatelet therapy (>14 days) within 18 months, index stent procedure for a saphenous vein graft, in-stent restenosis of DES, or unprotected LMT lesion; history of intracranial bleeding or ischemic stroke within 6 months before enrollment. DES for another lesion within 6 months prior to index PCI

Dadjou 2016[32]	Patients with stenosis more than 70% in any coronary vessel with reference diameter of more than 2.25 which was suitable for coronary stenting	planned surgery within 6 months of PCI unless the DAPT could be continued throughout the perioperation period, history of bleeding diathesis, major surgery within 15 days, active bleeding, previous hemorrhagic stroke in the past 6 months which contraindicated use of DAT, pregnancy, life expectancy < 24 months
Note: ACS = Acute coronary syndrome, BMS = bare-metal stent, DAPT = dual anti-platelet therapy, DES = drug-eluting stent, MI = myocardial infarction, PCI = percutaneous coronary intervention, STEMI = ST-elevation myocardial infarction.		

Appendix 9: Study-level risk of bias assessment

Author, yr (trial name)	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Collet 2014 (ARCTIC-INT)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Dadjou 2016	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Gilard 2015 (ITALIC)	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear
Helft 2016 (OPTIDUAL)	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear
Lee 2014 (DES-LATE)	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk
Mauri 2014 (DAPT)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Nakamura 2017 (NIPPON)	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear
Valgimigli 2012 (PRODIGY)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Appendix 10: Bleeding classification system definitions

TIMI (Thrombolysis in Myocardial Infarction (non-coronary artery bypass grafting–related bleeding)

Major: Any intracranial bleeding (excluding microhemorrhages <10 mm evident only on gradient-echo MRI); Clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥5 g/dL; Fatal bleeding (bleeding that directly results in death within 7 d)

Minor: Clinically overt (including imaging), resulting in hemoglobin drop of 3 to <5 g/dL

BARC (Bleeding Academic Research Consortium)

Type 1: bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional

Type 2: any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation

Type 3a: Overt bleeding plus hemoglobin drop of 3 to 5 g/dL* (provided hemoglobin drop is related to bleed) Any transfusion with overt bleeding

Type 3b: Overt bleeding plus hemoglobin drop 5 g/dL* (provided hemoglobin drop is related to bleed) Cardiac tamponade Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid) Bleeding requiring intravenous vasoactive agents

Type 3c: Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal) Subcategories confirmed by autopsy or imaging or lumbar puncture Intraocular bleed compromising vision

Type 4: CABG (coronary artery bypass grafting)-related bleeding Perioperative intracranial bleeding within 48 h Reoperation after closure of sternotomy for the purpose of controlling bleeding Transfusion of 5 U whole blood or packed red blood cells within a 48-h period† Chest tube output 2L within a 24-h period

Type 5a: Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious

Type 5b: Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

GUSTO (Global Use of Strategies to Open Occluded Arteries)

Severe (or life threatening): Intracerebral hemorrhage; Resulting in substantial hemodynamic compromise requiring treatment

Moderate: Requiring blood transfusion but not resulting in hemodynamic compromise

REPLACE-2 (Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events)

Major: Intracranial, intraocular, or retroperitoneal; Overt blood loss with hemoglobin decrease >3 g/dl; Any hemoglobin decrease >4 g/dL; Transfusion of ≥2 U blood products

Minor: Overt bleeding not meeting criteria for major bleeding

ISTH

Major: Fatal bleeding, and/or Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or Bleeding causing a fall in haemoglobin level of ≥1.24 mmol/L (≥20 g/L), or leading to transfusion of ≥2 units of whole blood or red cells.

Minor: All reported bleedings not classified as major.

STEEPLE (Safety and Efficacy of Enoxaparin in PCI Patients, an International Randomized Evaluation)

Major: Fatal bleeding; Retroperitoneal, intracranial, or intraocular bleeding; Bleeding that causes hemodynamic compromise requiring specific treatment; Bleeding that requires intervention (surgical or endoscopic) or decompression of a closed space to stop or control the event; Clinically overt bleeding, requiring any transfusion of ≥1 U packed red blood cells or whole blood; Clinically overt bleeding, causing a decrease in hemoglobin of ≥3 g/dL (or, if hemoglobin level is not available, a decrease in hematocrit of ≥10%)

Minor: Gross hematuria not associated with trauma (eg, from instrumentation); Epistaxis that is prolonged, is repeated, or requires plugging or intervention; Gastrointestinal hemorrhage; Hemoptysis; Subconjunctival hemorrhage; Hematoma >5 cm or leading to prolonged or new hospitalization; Clinically overt bleeding, causing a decrease in hemoglobin of 2 to 3 g/dL; Uncontrolled bleeding requiring protamine sulfate administration

Appendix 11: Definitions used in randomized controlled trials

Adapted from Spencer et al. 2015[86] and Wells et al. 2017[18]

PRODIGY[25]

Myocardial Infarction

The diagnosis of acute myocardial infarction was based on the universal definition of myocardial infarction. The term "myocardial infarction" should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Under these conditions, any one of the following criteria meets the diagnosis of myocardial infarction:
1. Detection of an increase or decrease in the levels of cardiac biomarkers (preferably troponin) with at least 1 value above the 99th percentile of the upper reference limit, together with evidence of myocardial ischemia with at least one of the following: symptoms of ischemia; electrocardiography changes indicative of new ischemia (new ST-T changes or new left bundle branch block); development of pathologic Q waves on ECG; or imaging evidence of new loss of viable myocardium or new regional wall-motion abnormality.

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

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

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

5. Pathologic findings of acute myocardial infarction.

Stroke

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

Death

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

DES-LATE[27]

Myocardial Infarction

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

Stroke

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

Death

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

ARCTIC-Interruption[34]

Myocardial Infarction

Periprocedural myocardial infarction, was defined as follows:

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

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

Stroke

Not described.

Death

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

DAPT[24]

Myocardial Infarction

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

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

1. New pathologic Q waves or LBBB.

2. New native or graft vessel occlusion.

3. Imaging evidence of loss of viable myocardium.

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

1. Symptoms of ischemia.

2. ECG changes indicative of new ischemia (new ST-T changes or new LBBB).

3. Development of pathologic Q waves.

4. Imaging evidence of a new loss of viable myocardium or a new regional wall-motion abnormality.

Silent myocardial infarction: No biomarker data available and new pathologic Q waves or LBBB.

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

1. New ST elevation or LBBB.

2. Documented thrombus by angiography or autopsy.

3. Reinfarction, spontaneous, and periprocedural myocardial infarction: Stable or decreasing values on 2 samples obtained more than 6 hours apart and a 20% increase 3 to 6 hours after the second sample was obtained.

Stroke

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

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

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

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

Death

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

ITALIC[31]

Myocardial Infarction

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

Stroke

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

Death

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

OPTIDUAL[30]

MACCE

Composite endpoint including all-cause mortality, myocardial infarction, stroke and major bleeding events.

Myocardial infarction

Classified and adjudicated according to the Academic Research Consortium (ARC) definition

NIPPON[23]

Death (ARC Definition)

All deaths are considered to be cardiac deaths unless an unequivocal non-cardiac cause can be

established. Specifically, any unexpected death should be classified as cardiac, even in subjects with coexisting potentially fatal non-cardiac disease (e.g. cancer, infection).

1. Cardiac death

Any death due to an immediate cardiac cause (e.g. myocardial infarction, low-output failure, or fatal arrhythmia). Unwitnessed death and death of unknown cause was classified as cardiac death. This included all procedure-related deaths, including those related to concomitant treatment.

2. Vascular death

Death due to cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular cause.

3. Non-cardiovascular death

Any death not covered by the above definitions, including death due to infection, sepsis, pulmonary causes, accident, suicide or trauma.

Stroke

A cerebrovascular accident was defined as the occurrence of cerebral infarction (ischemic stroke) or cerebral hemorrhage or subarachnoid hemorrhage (hemorrhagic stroke). Stroke was defined as the sudden onset of vertigo, numbness, dysphasia, weakness, visual field defects, dysarthria or other focal neurological deficits due to vascular lesions of the brain such as hemorrhage, embolism, thrombosis, or ruptured aneurysm.

Myocardial Infarction

Classified as Q-wave (new pathological Q waves in 2 or more continuous ECG leads) or non-Q-wave Q-wave, and:

1. Periprocedural—A serum CK-MB level exceeding the upper limit of normal should not be considered as new myocardial infarction, but as myocardial infarction at registration;, a serum troponin or serum CK-MB level exceeding 3 times the upper limit of normal within 48 hours after PCI; a serum troponin or serum CK-MB level exceeding 5 times the upper limit of normal within 72 hours after CABG; and a new Q-wave, left bundle block, new occlusion of the native vessel or graft, or reduction of viable myocardium on diagnostic imaging.
2. Spontaneous—When myocardial enzymes are at or above the upper limit of normal, it should be considered as myocardial infarction at registration, and when the serum level of troponin or CK-MB exceeds the upper limit of normal more than 48 hours after PCI or within 72 hours after CABG.
3. Re-infarction— Blood levels of biomarkers measured twice after the onset of myocardial infarction are stable or decrease and the values at 3 to 6 hours after PCI show a > 20% increase compared with those obtained at index PCI

Appendix 12: Use of ticagrelor in the PEGASUS-TIMI 54 trial

The PEGASUS-TIMI 54[35] RCT involved participants in 31 countries with a prior myocardial infarction 1–3 years before enrollment (median 1.7, interquartile range [1.2 to 2.3]) years. Participants were aged at least 50 years and had at least one other high risk feature (>65 yr, diabetes, second prior myocardial infarction, multivessel coronary artery disease, chronic renal dysfunction). In total, 83% of participants underwent stenting. About 17% of participants had more than one prior myocardial infarction, and about 54% of these were STEMI.

At study enrollment, all participants were taking ASA 75-100 mg once daily. The use of P2Y12 inhibitors before enrollment was at the discretion of the treating physician, and the percentage of participants who received a P2Y12 inhibitor was not reported. Because of uncertainty about whether all participants received a P2Y12 inhibitor, and because the duration of potential DAPT before randomization was longer than the eligibility criteria (6-12 months), the PEGASUS-TIMI 54[35] RCT was not eligible for inclusion in the current systematic review.

Participants in PEGASUS-TIMI 54[35] were randomized to ticagrelor 60 or 90 mg BID or placebo (n = 21,162) and were followed for a median of 33 months (IQR 28-37 months). The primary efficacy outcome was a composite of cardiovascular death, myocardial infarction, or stroke. The primary safety outcome was Thrombolysis in Myocardial Infarction (TIMI) major bleeding.

Among all participants (with or without PCI), both ticagrelor 60 mg and 90 mg BID reduced the primary outcome (cardiovascular death, myocardial infarction, or stroke) relative to placebo (ticagrelor 60 mg vs. placebo: HR 0.84, 95%CI 0.74 to 0.95; ticagrelor 90 mg vs. placebo HR 0.85, 95%CI 0.75 to 0.96), with the outcome experienced by 7.85% among participants who received 90 mg ticagrelor, 7.77% among those who received 60 mg, and 9.04% in the placebo group in 3-year Kaplan-Meier analysis.[35]

For both doses, ticagrelor use was associated with a lower risk of myocardial infarction compared with placebo (ticagrelor 60 mg vs. placebo: HR 0.84, 95%CI 0.72 to 0.98; ticagrelor 90 mg vs. placebo HR 0.81, 95%CI 0.69 to 0.95), with no significant differences in all-cause death (ticagrelor 60 mg vs. placebo: HR 0.89, 95%CI 0.76 to 1.04; ticagrelor 90 mg vs. placebo: HR 1.00, 95%CI 0.86 to 1.16) or cardiovascular death (ticagrelor 60 mg vs. placebo: HR 0.83, 95%CI 0.68 to 1.01; ticagrelor 90 mg vs. placebo: HR 0.87, 95%CI 0.71 to 1.06). Ticagrelor 60 mg, but not 90 mg was associated with a reduction in the risk of stroke (ticagrelor 60 mg vs. placebo: HR 0.75, 95%CI 0.57 to 0.98; ticagrelor 90 mg vs. placebo HR 0.82, 95%CI 0.63 to 1.07). The risk of TIMI major bleeding was significantly higher with both doses of ticagrelor (ticagrelor 60 mg vs. placebo: HR 2.32, 95%CI 1.68 to 3.21; ticagrelor 90 mg vs. placebo HR 2.69, 95%CI 1.96 to 3.70), as well as TIMI minor bleeding (ticagrelor 60 mg vs. placebo: HR 3.31, 95%CI 1.94 to 5.63; ticagrelor 90 mg vs. placebo HR 4.15, 95%CI 2.47 to 7.00).[35] Premature discontinuations of treatment were 32.0%, 28.7%, and 21.4% in ticagrelor 90mg, 60mg and placebo group, respectively, mainly due to adverse events in the two ticagrelor groups.

Among participants who had prior PCI, the risk of the primary outcome (cardiovascular death, myocardial infarction, or stroke) was significantly lower among those who had received ticagrelor (ticagrelor 60 mg vs. placebo: HR 0.83, 95%CI 0.72 to 0.96; ticagrelor 90 mg vs. placebo HR 0.86, 95%CI 0.74 to 0.98), and a higher risk of TIMI major bleeding (ticagrelor 60 mg vs. placebo: HR 2.42, 95%CI 1.70 to 3.44; ticagrelor 90 mg vs. placebo HR 2.76, 95%CI 1.95 to 3.91).[35]

Appendix 13: Pharmacoeconomics

Table 36: Previously published pharmacoeconomic analyses

First author	Year published	Country of analysis	Patient population	Interventions	Type of model	Model details
Treatment duration (most relevant)						
Arbel Y[36]	2018	Canada	Patients undergoing PCI	DAPT 3-6 months Versus DAPT 12 months Versus DAPT 30-36 months	Markov patient-level simulation (lifetime horizon in 63 years old individuals, 1-month cycles)	Efficacy populated by NMA (stable angina and ACS patients) Markov states: • Bleeding • death • MI • PCI • Stent thrombosis • Stroke
Garg P[39]	2015	USA	Patients undergoing PCI with DES	DAPT (clopidogrel + ASA) 6 months versus DAPT 12 months versus DAPT 30 months	Markov cohort (lifetime) to identify threshold of benefits to outweigh harm. Sensitivity analysis on ACS (12 and 18 months only) and non-ACS patients.	Markov states: • Bleeding (major & minor) • Death (CV & non-CV) • MI (non-fatal) • Stent thrombosis • Stroke (hemorrhagic)
Jiang M[43]	2017	US	ACS patients who had DAPT for 12 months after PCI (DES)	ASA 75-162 mg + clopidogrel for 12 months Versus Further DAPT (ASA+clopidogrel) for 18 months post-PCI	Markov (lifetime in 60 years old individual)	Markov states: • Bleeding (major) • Death (CV) • MI (non-fatal) • Stent thrombosis • Stroke (non-fatal)
DAPT vs ASA						
Beinart SC[37]	2005	US (using results from multinational CREDO trial)	Patients with coronary artery disease undergoing PCI	Clopidogrel 75 mg + aspirin daily for 1 year Versus Clopidrogrel 75 mg daily for 28 days + aspirin daily for 1	Decision-tree (lifetime horizon)	Using: 1) Health care resources and clinical events collected during the trial: major cv healthcare-related resources for death, bleeding, MI, stroke; revascularization procedures; in and outpatient medications (all other

First author	Year published	Country of analysis	Patient population	Interventions	Type of model	Model details
				year		ambulatory care excluded). 2) Framingham Study and Swedish database for long-term survival
Kolm P[45]	2007	Canada	ACS	Clopidogrel + ASA Versus ASA + placebo For 1 year (CURE study) (PCI-CURE: subset who had a PCI)	Decision-tree (1 year)	Healthcare resources from CURE trial. Clinical events: bleeding, death, MI, stroke
Lindgren P[46]	2005	Sweden	Unstable angina undergoing PCI (PCI-CURE study)	ASA + placebo Versus ASA + clopidogrel for 1 year	Markov	Markov states: • Death (CV) • Death (other causes) • MI year 1 • MI subsequent years
Mahoney EM[47]	2006	US	ACS without ST-segment elevation undergoing PCI (PCI-CURE patient-level data)	ASA Versus ASA+Clopidogrel for up to 1 year	Decision-tree	Hospitalizations and treatment taken from PCI-CURE study. Assigned DRG post-hoc. Costs per DRG from Medicare and/or Medstat for trial duration. Long-term costs and survival from Saskatchewan healthcare database. Clinical events: bleeding, death, MI, stroke
Ringborg A[52]	2005	Sweden	Patients undergoing PCI	Clopidogrel for 28 days +ASA for 12 months Versus Clopidogrel+ASA for 12 months	Markov	Using CREDO trial results Markov states: • death • MI year 1 • MI subsequent years • Stroke year 1 • Stroke subsequent years
Zhang Z[54]	2009	US	Patients presenting at ER with suspected MI and STEMI within 24 hours undergoing PCI (COMMIT)	Clopidogrel 75 mg Versus Clopidogrel + ASA 162 mg for 1 year	Decision-tree	Using COMMIT trial for 28-day outcomes, long-term outcomes assumed to be similar to CURE trial. Outcomes: • Bleeding (major) • CABG • death • Ischemia (refractory) • MI complication • PCI • Stroke
P2Y12 agents in DAPT						

First author	Year published	Country of analysis	Patient population	Interventions	Type of model	Model details
Davies A[38]	2013	Germany, Sweden, NL, Turkey (using results of TRITON-TIMI trial)	ACS patients undergoing PCI	Prasugrel + ASA Versus Clopidrogrel + ASA for 1 year	Markov patient-level simulation (40 year horizon; 12 monthly cycles; risk equations derived from TRITON-TIMI trial)	Markov states: a. 3-day acute phase b. Bleeds (major, minor) c. Death (CV) d. MI (non-fatal) e. Stroke (non-fatal) Using TRITON-TIMI trial Restricted to 1 primary event and 1 bleed event per patient Risks are implemented in 2 stages: i) risk of composite endpoint from TRITON-TIMI trial; ii) risk of respective events. Same process for bleeds No event beyond 12 month is modelled, but lifetime related costs (e.g., ischaemic events) are accounted for.
Gasche D[40]	2013	Switzerland	ACS patients (including stent installation in 60%)	Ticagrelor + ASA Versus Generic clopidrogrel + ASA For 1 year	1 year decision-tree and lifetime Markov model (original model developed by Nikolic)	Using: 1) Healthcare resources and clinical events from PLATO trial 2) Markov states (populated with external sources): a. death b. MI (non-fatal) c. MI (post-MI) d. Stroke (non-fatal) e. Stroke (post-stroke)
Greenhalgh J[41]	2015	UK (NICE TA182)	ACS patients with PCI divided in 4 subgroups: • ACS with PCI for STEMI with and without diabetes • ACS with PCI for unstable angina or NSTEMI	Prasugrel +ASA Versus Clopidogrel + ASA for 1 year post PCI	Patient-level simulation using statistical model from TRITON-TIMI trial (1 year) followed by Markov for 39 years.	Clinical outcomes: • Non-fatal and fatal cv events, adverse effects of treatment and utility • Markov states: o Death (other vascular) o Death (non-vascular) o MI (fatal) o MI (non-fatal) o Stroke (fatal hemorrhagic) o Stroke (non-fatal hemorrhagic – not disabling) o Stroke (non-fatal hemorrhagic – disabling) o Stroke (ischemic)/TIA (fatal) o Stroke (ischemic)/TIA – non-

First author	Year published	Country of analysis	Patient population	Interventions	Type of model	Model details
						fatal, not disabling o Stroke (ischemic)/TIA – non-fatal, disabling
Kazi DS[44]	2014	US	PCI in ACS patients	Clopidogrel + ASA Versus Prasugrel + ASA Versus Ticagrelor + ASA Versus Genotype-guided treatment with ticagrelor or prasugrel and non carrier with clopidogrel	Markov	Markov states: • Bleeding (intracranial) • Bleeding (extracranial) • Death (CV) • Death (non-CV) • MI (non-fatal) • MI (post-MI) • Revascularization (percutaneous or surgical) • Stent thrombosis
Mahoney EM[48]	2010	US	PCI in ACS	Prasugrel + ASA Versus Clopidogrel + ASA For 6 to 15 months (TRITON-TIMI 38 trial)	Decision-tree (15 months)	Healthcare resources from TRITON-TIMI 38 trial (USA, Australia, Canada, Germany, Italy, Spain, UK, France) Clinical events; bleeding, death, ischemia, MI, revascularization, stroke
Mauskopf J[49]	2012	US	PCI in ACS	Prasugrel + ASA Versus Clopidogrel + ASA For 15 months	Lifetime 'disease-progression' model (separate rates for 1st month and months 2-15)	Model outcomes: • Costs: medication; ER visits; inpatient stays • Clinical: cv events (MI, stroke, angina, death); bleeding events; revascularization; rehospitalizations; LYG
Nikolic[50]	2013	Sweden	ACS	Ticagrelor + ASA Versus Clopidogrel+ASA For 12 months	Decision-tree for 1-year data from PLATO clinical study + Markov	Decision-tree events: • Death • MI (non-fatal) • Stroke (non-fatal) Markov states: • Death (from other causes) • Death (CV) • MI (non-fatal) • MI (post-MI) • Stroke (non-fatal) • Stroke (post-stroke)
Patel V[51]	2014	US	PCI in ACS	Prasugrel + ASA	Decision-tree (15	Event subtree:

First author	Year published	Country of analysis	Patient population	Interventions	Type of model	Model details
				Versus Clopidogrel + ASA Versus Genotype-guided treatment	months)	• Bleeding (major) • Death • MI • Revascularization • Stroke Separate probabilities for month 1 and months 2-15
Wein B[53]	2017	Denmark Germany Switzerland	ACS undergoing PCI	ASA 100 mg lifelong + clopidogrel 75 mg for 12 months Versus ASA 100 mg lifelong + prasugrel 5 of 10 mg per day for 12 months	Decision-tree (12 months)	Using BASKET-PROVE cohort. Clinical events; MACCE, death, MI, revascularization, bleeding
Other regimens						
Heeg[42]	2007	UK	Secondary prevention in patients at high risk of CV events or stroke or ACS	Antiplatelets in secondary prevention; multiple comparisons: clopidogrel versus ASA; clopidrogrel 1 year versus clopidogrel 28 days; dipyridamole + ASA versus ASA; Dipyridamole + ASA versus clopidogrel; ASA versus placebo	Markov (lifetime in a 60 yo individual)	Health states: • Death • MI (first) • MI (second) • Stroke (first) • Stroke (second) • CV event (third) Transition probabilities depend on time since start of treatment (0-6 months; 6-12 months; after 12 months)

ACS: acute coronary syndrome; ASA: acetyl-salicylic acid; CABG: coronary artery bypass graft; CV: cardio-vascular; DAPT: dual anti-platelet therapy; DES: drug eluting stent: DRG: diagnosis related group; ER: emergency room; LYG: life-year gain; MACCE: major adverse cardio-vascular and cerebrovascular event; MI: myocardial infarction; NMA: network meta-analysis; NSTEMI: non-ST segment elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST segment elevation myocardial infarction; TIA: transient ischemic attack; UK: United Kingdom; US: United States

Table 37: Detailed inputs used to estimate transition probabilities in the extended DAPT phase of the model

Parameter	Study	Treatment	Monthly rate	Alpha	Beta	Study duration (months)	Distribution
All-cause death	NIPPON	6 to 12 month-DAPT	0.000806	16	1638	12	Beta
		Extended DAPT	0.000353	7	1646		
	OPTIDUAL	6 to 12 month-DAPT	0.000956	24	673	36	
		Extended DAPT	0.000634	16	685		
	ITALIC	6 to 12 month-DAPT	0.000660	11	915	18	
		Extended DAPT	0.001203	20	904		
	PRODIGY	6 to 12 month-DAPT	0.002228	29	694	18	
		Extended DAPT	0.002452	32	693		
	ARCTIC	6 to 12 month-DAPT	0.000826	9	632	17	
		Extended DAPT	0.000638	7	638		
	DAPT	6 to 12 month-DAPT	0.000807	84	5702	18	
		Extended DAPT	0.001005	106	5756		
	DES-LATE	6 to 12 month-DAPT	0.000530	32	2482	24	
		Extended DAPT	0.000757	46	2485		
	Weighted average	6 to 12 month-DAPT	0.000831				
		Extended DAPT	0.000930				
Bleeding	OPTIDUAL	6 to 12 month-DAPT-all	0.000797			36	Beta
		6 to 12 month-DAPT-major	*0.000159*	*4*	*693*		
		6 to 12 month-DAPT-minor	*0.000638*	*16*	*681*		
		Extended DAPT all	0.000753				
		Extended DAPT - major	*0.000159*	*4*	*697*		
		Extended DAPT - minor	*0.000601*	*15*	*686*		
	ITALIC	6 to 12 month-DAPT-all	0.000360			18	
		6 to 12 month-DAPT-major	*0.000000*	*0*	*926*		
		6 to 12 month-DAPT-minor	*0.000360*	*6*	*920*		
		Extended DAPT all	0.000601				
		Extended DAPT - major	*0.000241*	*4*	*920*		
		Extended DAPT - minor	*0.000361*	*6*	*918*		
	ARCTIC	6 to 12 month-DAPT-major	0.000000	0	641	17	
		Extended DAPT - major	0.000000	0	643		
	DES-LATE	6 to 12 month-DAPT-all	0.000398	24	2490	24	
		Extended DAPT -all	0.000560	34	2497		
	Weighted average	6 to 12 month-DAPT-all	0.000712				
		Extended DAPT -all	0.000826				
		6 to 12 month-DAPT-major	*0.000233*				
		Extended DAPT - major	*0.000365*				

Parameter	Study	Treatment	Monthly rate	Alpha	Beta	Study duration (months)	Distribution
		6 to 12 month-DAPT-minor	*0.000479*				
		Extended DAPT - minor	*0.000462*				
Non-fatal MI	NIPPON	6 to 12 month-DAPT	0.000202	4	1650	12	Beta
		Extended DAPT	0.000050	1	1652		
	OPTIDUAL	6 to 12 month-DAPT	0.000638	16	681	36	
		Extended DAPT	0.000436	11	690		
	ITALIC	6 to 12 month-DAPT	0.000720	12	914	18	
		Extended DAPT	0.000541	9	915		
	ARCTIC	6 to 12 month-DAPT	0.000826	9	632	17	
		Extended DAPT	0.000821	9	636		
	DAPT	6 to 12 month-DAPT	0.002141	223	5563	18	
		Extended DAPT	0.001147	121	5741		
	DES-LATE	6 to 12 month-DAPT	0.000447	27	2487	24	
		Extended DAPT	0.000313	19	2512		
	Weighted average	6 to 12 month-DAPT	0.001268				
		Extended DAPT	0.000725				
Non-fatal stroke	NIPPON	6 to 12 month-DAPT	0.000353	7	1647	12	Beta
		Extended DAPT	0.000302	6	1647		
	OPTIDUAL	6 to 12 month-DAPT	0.000279	7	690	36	
		Extended DAPT	0.000198	5	696		
	ITALIC	6 to 12 month-DAPT	0.000360	6	920	18	
		Extended DAPT	0.000421	7	917		
	ARCTIC	6 to 12 month-DAPT	0.000367	4	637	17	
		Extended DAPT	0.000547	6	639		
	DAPT	6 to 12 month-DAPT	0.000461	48	5738	18	
		Extended DAPT	0.000408	43	5819		
	DES-LATE	6 to 12 month-DAPT	0.000348	21	2493	24	
		Extended DAPT	0.000346	21	2510		
	Weighted average	6 to 12 month-DAPT	0.000400				
		Extended DAPT	0.000377				
Stent thrombosis	NIPPON	6 to 12 month-DAPT	0.000101	2	1652	12	Beta
		Extended DAPT	0.000050	1	1652		
	OPTIDUAL	6 to 12 month-DAPT	0.000040	1	696	36	
		Extended DAPT	0.000119	3	698		
	ITALIC	6 to 12 month-DAPT	0.000360	6	920	18	
		Extended DAPT	0.000180	3	921		
	ARCTIC	6 to 12 month-DAPT	0.000275	3	638	17	
		Extended DAPT	0.000000	0	645		
	DAPT	6 to 12 month-DAPT	0.000711	74	5712	18	
		Extended DAPT	0.000218	23	5829		
	Weighted average	6 to 12 month-DAPT	0.000496				
		Extended DAPT	0.000165				
Urgent revasc-ularization	ITALIC	6 to 12 month-DAPT	0.000540	9	917	18	Beta
		Extended DAPT	0.000481	8	916		
	ARCTIC	6 to 12 month-DAPT	0.000826	9	632	17	
		Extended DAPT	0.000274	3	642		
	Weighted average	6 to 12 month-DAPT	0.000657				
		Extended DAPT	0.000396				

DAPT: dual anti-platelet therapy; MI: myocardial infarction

Table 38: Detailed inputs used to estimate transition probability in the post-extended DAPT phase of the model

Parameter		Value	Alpha	Beta	95%CI LL	95%CI UL	Distribution
MI in MI patient	Overall (annual)	0.052995					Beta
	Year 1 (annual)	0.124573	1058	7435			
	Year 2 (annual	0.018077	244	6505			
	Years 3&4 (annual)	0.016336	441	6308			
Stroke in MI patient	Overall (annual)	0.010947					Beta
	Year 1 (annual)	0.022136	188	8305			
	Year 2 (annual	0.005482	74	6675			
	Years 3&4 (annual)	0.005223	141	6608			
Stroke in stroke patient	Overall	0.019660					Beta
	Year 1	0.030533	487	15463			
	Year 3	0.017513	838	15112			
	Year 5	0.010934	872	15078			
MI in stroke patient	Overall	0.007512					Beta
	Year 1	0.010408	166	15784			
	Year 3	0.007315	350	15600			
	Year 5	0.004815	384	15566			
Post-MI death rate	Overall	2.301395					Log normal
	Years 1 to 3 men	2.14			2.00	2.28	
	Years 1 to 3 women	2.92			2.72	3.13	
	Years 3 to 5 men	2.10			1.86	2.34	
	Years 3 to 5 women	2.77			2.42	3.17	
HR death post-stroke	Overall	1.633333					Log normal
	Year 1	1.4			1.3	1.5	
	Year 3	1.7			1.6	1.7	
	Year 5	1.8			1.7	1.8	

95%CI LL: 95% confidence interval lower limit; 95%CI UL: 95% confidence interval upper limit; DAPT: dual anti-platelet therapy; MI: myocardial infarction; HR: hazard ratio

Table 39: List of ICD10 codes used for extracting costs for bleeding events from the OCCI database

Bleeding site	ICD10 code	Description
Gastrointestinal	I850	Oesophageal varices with bleeding
	K250	Gastric ulcer, acute with hemorrhage
	K252	Gastric ulcer, acute with both hemorrhage and perforation
	K254	Gastric ulcer, chronic or unspecified with hemorrhage
	K256	Gastric ulcer, chronic or unspecified with both hemorrhage and perforation
	K260	Duodenal ulcer, acute with hemorrhage
	K262	Duodenal ulcer, acute with both hemorrhage and perforation
	K264	Duodenal ulcer, chronic or unspecified with hemorrhage
	K266	Duodenal ulcer, chronic or unspecified with both hemorrhage and perforation
	K270	Peptic ulcer, acute with hemorrhage
	K272	Peptic ulcer, acute with both hemorrhage and perforation
	K274	Peptic ulcer, chronic or unspecified with hemorrhage
	K276	Peptic ulcer, chronic or unspecified with both hemorrhage and perforation
	K280	Gastrojejunal ulcer, acute with hemorrhage
	K282	Gastrojejunal ulcer, acute with both hemorrhage and perforation
	K284	Gastrojejunal ulcer, chronic or unspecified with hemorrhage
	K286	Gastrojejunal ulcer, chronic or unspecified with both hemorrhage and perforation
	K290	Acute hemorrhagic gastritis
	K625	Hemorrhage of anus and rectum
	K661	Hemoperitoneum
	K920	Hematemesis
	K921	Melena
	K922	Gastrointestinal hemorrhage, unspecified
Hematology	R58	Hemorrhage, not elsewhere classified
Intracranial (other than hemorrhagic stroke)	I629	Intracranial hemorrhage (non-traumatic), unspecified
Respiratory	R040	Epistaxis
	R041	Hemorrhage from throat
	R042	Hemoptysis
	R048	Hemorrhage form other site in respiratory passages
	R049	Hemorrhage from respiratory passages, unspecified
Urogenital	N020-029	Recurrent and persistent hematuria
	R310, 311, 318	Unspecified hematuria

ICD-10: International Classification of Diseases 10th Revision

Table 40: Detailed cost inputs

Parameter	Value	SE	Alpha	Beta	95%CI LL	95%CI UL	Distribution
Medications							
ASA (monthly)	*$9.25*						Not varied
Clopidogrel	*$16.72*						
Prasugrel	*$66.31*						
Pharmacist dispensing fees	*$8.83*						
% clopidogrel	*0.80*		*10553*	*2488*			Beta
Stroke (event)	$12,889.65						
Hospitalization	*$11,420.37*	*$247.72*	*$2,125.31*	*$5.37*			Gamma
Physician (unadjusted)	*$1,469.28*	*$393.36*	*$13.95*	*$105.31*			Gamma
Age adjustment	*0.0053*	*0.0007*					Normal
Gender adjustment	*0.0387*	*0.0163*					Normal
MI (event)	$10,763.33						
Hospitalization	*$8,731.63*	*$87.23*	*$10,018.79*	*$0.87*			Gamma
Physician (unadjusted)	*$2,031.70*	*$15.91*	*$16,316.46*	*$0.12*			Gamma
Age adjustment	*0.9930*	*0.001*			*0.991*	*0.995*	Normal
Gender adjustment	*1.1100*	*0.015*			*1.080*	*1.140*	Normal
Major bleed	$6,541.22	$124.16	$2,775.51	$2.36			Gamma
Minor bleed	$222.64						Gamma
General Emergency	*$227.72*	*$1.15*	*$0.01*	*$222.64*			
Urgent Care center	*$120.68*	*$2.07*	*$0.04*	*$227.72*			
% minor bleed	84.62		22	4			Beta
Post-stroke (age and gender adjusted)	$2,245.24						
Post-stroke (unadjusted)	*$1,711.73*	*$208.52*	*$67.38*	*$25.40*			Gamma
Post-MI (per month, age and gender adjusted)	$308.28						
Post-MI (per day unadjusted)	*$7.22*	*$0.13*	*$3,173.06*	*$0.00*			Gamma
PCI	$567.09						Not varied

SE: standard error: 95%CI LL: lower limit of the 95% confidence interval; 95%CI UL: upper limit of the 95% confidence interval; ASA: acetyl-salicylic acid; MI: myocardial infarction; PCI: percutaneous coronary intervention

Table 41: Exploratory subgroup analysis data inputs – prior myocardial infarction¥

Parameter	Study	Treatment	Monthly rate	Alpha	Beta	Study duration (months)	Distribution
All-cause death	ITALIC	6 to 12 month-DAPT	0.001543	4	140	18	Beta
		Extended DAPT	0.001610	4	134		
	DAPT	6 to 12 month-DAPT	0.001058	50	2575	18	
		Extended DAPT	0.001105	54	2661		
	Weighted average	6 to 12 month-DAPT	0.001083				
		Extended DAPT	0.001129				
Bleeding	ITALIC	6 to 12 month-DAPT-all	0.000386			18	Beta
		6 to 12 month-DAPT-major					
		6 to 12 month-DAPT-minor	*0.000386*	*1*	*143*		
		Extended DAPT all	0.000000				
		Extended DAPT-major					
		Extended DAPT-minor	*0.000000*	*0*	*144*		
	DAPT	6 to 12 month-DAPT-all	0.001164	55	2570	18	
		6 to 12 month-DAPT-major					
		6 to 12 month-DAPT-minor					
		Extended DAPT all	0.002394	117	2598		
		Extended DAPT-major					
		Extended DAPT-minor					
	Weighted average	6 to 12 month-DAPT-all	0.001124				
		Extended DAPT all	0.002353				
Non-fatal MI	ITALIC	6 to 12 month-DAPT	0.000772	2	142	18	Beta
		Extended DAPT	0.000403	1	137		
	DAPT	6 to 12 month-DAPT	0.002899	137	2488	18	
		Extended DAPT	0.001391	68	2647		
	Weighted average	6 to 12 month-DAPT	0.002789				
		Extended DAPT	0.001344				
Non-fatal stroke	DAPT	6 to 12 month-DAPT	0.000508	24	2601	18	Beta
		Extended DAPT	0.000389	19	2696		
Stent thrombosis	DAPT	6 to 12 month-DAPT	0.000995	47	2578	18	Beta
		Extended DAPT	0.000286	14	2701		
Urgent revasc-ularization	ITALIC	6 to 12 month-DAPT	0.001157	3	141	18	Beta
		Extended DAPT	0.000400	1	138		

¥Cohort assumed to have same average age and gender distribution as full cohort; DAPT: dual anti-platelet therapy; MI: myocardial infarction

Table 42: Exploratory subgroup analysis data inputs – no prior myocardial infarction¥

Parameter	Study	Treatment	Monthly rate	Alpha	Beta	Study duration (months)	Distribution
All-cause death	DAPT	6 to 12 month-DAPT	0.000615	35	3126	18	Beta
		Extended DAPT	0.001006	57	3090		
Bleeding	DAPT	6 to 12 month-DAPT-all	0.001775	101	3060	18	Beta
		Extended DAPT-all	0.003389	192	2955		
Non-fatal MI	DAPT	6 to 12 month-DAPT	0.001670	95	3066	18	Beta
		Extended DAPT	0.001059	60	3087		
Non-fatal stroke	DAPT	6 to 12 month-DAPT	0.000492	28	3133	18	Beta
		Extended DAPT	0.000441	25	3122		
Stent thrombosis	DAPT	6 to 12 month-DAPT	0.000492	28	3133	18	Beta
		Extended DAPT	0.000159	9	3138		
Urgent revasc-ularization*		6 to 12 month-DAPT	0.000657				Beta
		Extended DAPT	0.000396				

¥Cohort assumed to have same average age and gender distribution as full cohort; *Assumed to be the same as the entire population (16% had a prior myocardial infarction); DAPT: dual anti-platelet therapy; MI: myocardial infarction

Table 43: Exploratory subgroup analysis – Acute coronary syndrome patients[¥]

Parameter	Study	Treatment	Monthly rate	Alpha	Beta	Study duration (months)	Distribution
All-cause death	ITALIC	6 to 12 month-DAPT	0.000556	4	396	18	Beta
		Extended DAPT	0.001232	9	397		
	DAPT	6 to 12 month-DAPT	0.000878	28	1743	18	
		Extended DAPT	0.000769	25	1780		
	Weighted average	6 to 12 month-DAPT	0.000819				
		Extended DAPT	0.000854				
Bleeding	ITALIC	6 to 12 month-DAPT-all				18	Beta
		6 to 12 month-DAPT-major					
		6 to 12 month-DAPT-minor	*0.000278*	*2*			
		Extended DAPT all					
		Extended DAPT-major					
		Extended DAPT-minor	*0.000547*	*4*			
	DAPT	6 to 12 month-DAPT-all	0.001161	37		18	
		6 to 12 month-DAPT-major					
		6 to 12 month-DAPT-minor					
		Extended DAPT all	0.002401	78			
		Extended DAPT-major					
		Extended DAPT-minor					
	Weighted average	6 to 12 month-DAPT-all	0.000998				
		Extended DAPT all	0.002091				
Non-fatal MI	ITALIC	6 to 12 month-DAPT	0.000972	7		18	Beta
		Extended DAPT	0.000821	6			
	DAPT	6 to 12 month-DAPT	0.002886	92		18	
		Extended DAPT	0.001231	40			
	Weighted average	6 to 12 month-DAPT	0.002533				
		Extended DAPT	0.001156				
Non-fatal stroke	DAPT	6 to 12 month-DAPT	0.000376	12		18	Beta
		Extended DAPT	0.000400	13			
Stent thrombosis	DAPT	6 to 12 month-DAPT	0.001067	34		18	Beta
		Extended DAPT	0.000277	9			
Urgent revasc-ularization	ITALIC	6 to 12 month-DAPT	0.000833	6		18	Beta
		Extended DAPT	0.000000	0			

¥Cohort assumed to have the same average age and gender distribution as full cohort; DAPT: dual anti-platelet therapy; MI: myocardial infarction

Table 44: Exploratory subgroup analysis – diabetes mellitus patients[¥]

Parameter	Study	Treatment	Monthly rate	Alpha	Beta	Study duration (months)	Distribution
All-cause death	ITALIC	6 to 12 month-DAPT	0.001157	7		18	Beta
		Extended DAPT	0.001592	10			
	DAPT	6 to 12 month-DAPT	0.001176	35		18	
		Extended DAPT	0.001471	46			
	Weighted average	6 to 12 month-DAPT	0.001173				
		Extended DAPT	0.001491				
Bleeding	ITALIC	6 to 12 month-DAPT-all				18	Beta
		6 to 12 month-DAPT-major					
		6 to 12 month-DAPT-minor	*0.000496*	*3*			
		Extended DAPT all					
		Extended DAPT-major					
		Extended DAPT-minor	*0.000318*	*2*			
	DAPT	6 to 12 month-DAPT-all	0.001982			18	
		6 to 12 month-DAPT-major	*0.001108*	*33*			
		6 to 12 month-DAPT-minor	*0.000873*	*26*			
		Extended DAPT all	0.003294				
		Extended DAPT-major	*0.001439*	*45*			
		Extended DAPT-minor	*0.001855*	*58*			
	Weighted average	6 to 12 month-DAPT-all	0.001731				
		Extended DAPT-all	0.002846				
Non-fatal MI	ITALIC	6 to 12 month-DAPT	0.000661	4		18	Beta
		Extended DAPT	0.000637	4			
	DAPT	6 to 12 month-DAPT	0.002586	77		18	
		Extended DAPT	0.001887	59			
	Weighted average	6 to 12 month-DAPT	0.002261				
		Extended DAPT	0.001678				
Non-fatal stroke	DAPT	6 to 12 month-DAPT	0.000571	17		18	Beta
		Extended DAPT	0.000576	18			
Stent thrombosis	DAPT	6 to 12 month-DAPT	0.000605	18		18	Beta
		Extended DAPT	0.000288	9			
Urgent revascularization	ITALIC	6 to 12 month-DAPT	0.000496	3		18	Beta
		Extended DAPT	0.000478	3			

¥Cohort assumed to have the same average age and gender distribution as the full cohort; DAPT: dual anti-platelet therapy; MI: myocardial infarction

Table 45: Exploratory subgroup analysis: patients without diabetes mellitus¥

Parameter	Study	Treatment	Monthly rate	Alpha	Beta	Study duration (months)	Distribution
All-cause death	DAPT	6 to 12 month-DAPT	0.000622	50	4082	18	Beta
		Long-DAPT	0.000770	62	4063		
Bleeding*	Weighted average	6 to 12 month-DAPT-all	0.000712				Beta
		Extended DAPT -all	0.000826				
		6 to 12 month-DAPT-major	*0.000233*				
		Extended DAPT - major	*0.000365*				
		6 to 12 month-DAPT-minor	*0.000479*				
		Extended DAPT - minor	*0.000462*				
Non-fatal MI	DAPT	6 to 12 month-DAPT	0.002003	149	3983	18	Beta
		Long-DAPT	0.000889	66	4059		
Non-fatal stroke*	Weighted average	6 to 12 month-DAPT	0.000400				Beta
		Extended DAPT	0.000377				
Stent thrombosis	DAPT	6 to 12 month-DAPT	0.000780	58	4074	18	Beta
		Long-DAPT	0.000229	17	4108		
Urgent revascularization*	Weighted average	6 to 12 month-DAPT	0.000657				Beta
		Extended DAPT	0.000396				

¥Cohort assumed to have the same average age and gender distribution as the full cohort; *Assumed to be similar to the entire patient population (69% without diabetes); DAPT: dual anti-platelet therapy; MI: myocardial infarction

Parameter	Study	Treatment	Monthly rate	Alpha	Beta	Study duration (months)	Distribution

Table 46: Exploratory subgroup analysis – patients above 75 years old¥

Parameter	Study	Treatment	Monthly rate	Alpha	Beta	Study duration (months)	Distribution
All-cause death	ITALIC	6 to 12 month-DAPT	0.000896	2	122	18	Beta
		Extended DAPT	0.002839	7	130		
	PRODIGY	6 to 12 month-DAPT	0.006031	33	271	18	
		Extended DAPT	0.005104	26	257		
	Weighted average	6 to 12 month-DAPT	0.004543				
		Extended DAPT	0.004365				
Bleeding	ITALIC	6 to 12 month-DAPT-all				18	Beta
		6 to 12 month-DAPT-major					
		6 to 12 month-DAPT-minor	*0.001344*	*3*	*121*		
		Extended DAPT all					
		Extended DAPT-major					
		Extended DAPT-minor	*0.001622*	*4*	*133*		
	PRODIGY	6 to 12 month-DAPT-all	0.001645			18	
		6 to 12 month-DAPT-major	*0.000914*	*5*	*299*		
		6 to 12 month-DAPT-minor	*0.000731*	*4*	*300*		
		Extended DAPT all	0.007263				
		Extended DAPT-major	*0.004515*	*14*	*260*		
		Extended DAPT-minor	*0.002748*	*9*	*269*		
	Weighted average	6 to 12 month-DAPT-all	0.001558				
		Extended DAPT-all	0.005423				
Non-fatal MI	ITALIC	6 to 12 month-DAPT	0.000000	0	124	18	Beta
		Extended DAPT	0.001217	3	134		
	PRODIGY	6 to 12 month-DAPT	0.002558	14	290	18	
		Extended DAPT	0.003337	17	266		
	Weighted average	6 to 12 month-DAPT	0.001817				
		Extended DAPT	0.002646				
Non-fatal stroke	PRODIGY	6 to 12 month-DAPT	0.000183	1	303	18	Beta
		Extended DAPT	0.001570	8	275		
Stent thrombosis	PRODIGY	6 to 12 month-DAPT	0.001096	6	298	18	Beta
		Extended DAPT	0.000785	4	279		
Urgent revascularization	ITALIC	6 to 12 month-DAPT	0.000448	1	123	18	Beta
		Extended DAPT	0.000406	1	136		

¥Age and gender distribution from PRODIGY study only: 80.4 (SE: 4.0) years old; 65.8% men, DAPT: dual anti-platelet therapy; MI: myocardial infarction

Table 47: Exploratory subgroup analysis – below 75 years old[¥]

Parameter	Study	Treatment	Monthly rate	Alpha	Beta	Study duration (months)	Distribution
All-cause death	PRODIGY	6 to 12 month-DAPT	0.000818	10	669	18	Beta
		Extended DAPT	0.001342	17	687		
Bleeding	PRODIGY	6 to 12 month-DAPT-all	0.000900			18	Beta
		6 to 12 month-DAPT-major	*0.000409*	*5*	*674*		
		6 to 12 month-DAPT-minor	*0.000491*	*6*	*673*		
		Extended DAPT all	0.002367				
		Extended DAPT-major	*0.000789*	*10*	*694*		
		Extended DAPT-minor	*0.001578*	*20*	*684*		
Non-fatal MI	PRODIGY	6 to 12 month-DAPT	0.000736	9	670	18	Beta
		Extended DAPT	0.000789	10	694		
Non-fatal stroke	PRODIGY	6 to 12 month-DAPT	0.000245	3	676	18	Beta
		Extended DAPT	0.000710	9	695		
Stent thrombosis	PRODIGY	6 to 12 month-DAPT	0.000327	4	675	18	Beta
		Extended DAPT	0.000316	4	700		
Urgent revascularization*	Weighted average	6 to 12 month-DAPT	0.000657				Beta
		Extended DAPT	0.000396				

¥Age and gender from the PRODIGY STUDY, i.e.,
*Assumed to be similar to entire patient population
DAPT: dual anti-platelet therapy; MI: myocardial infarction

Table 48: Scenario and sensitivity analysis inputs

Analysis	Parameter	Group	Value	95% CI LL	95%CI UL
Risk ratios from meta-analysis	HR overall death	Extended DAPT	1.068079	0.802612	1.421352
	HR major bleed	Extended DAPT	1.418856	0.878175	2.292429
	HR minor bleed	Extended DAPT	0.951977	0.525755	1.720110
	HR non-fatal MI	Extended DAPT	0.579459	0.480307	0.699080
	HR stent thrombosis	Extended DAPT	0.379765	0.213703	0.674868
	HR non-fatal stroke	Extended DAPT	0.937225	0.698896	1.256827
	HR urgent revascularization	Extended DAPT	0.604943	0.238838	1.532236
Alternative calculation for bleeding – method A	All bleeding	6 to 12 month-DAPT – all	0.001223		
	Major bleeding	*6 to 12 month-DAPT – major*	*0.000525*		
	Minor bleeding	*6 to 12 month-DAPT -minor*	*0.000697*		
	All bleeding	Extended DAPT – all	0.002234		
	Major bleeding	*Extended DAPT – major*	*0.000877*		
	Minor bleeding	*Extended DAPT - minor*	*0.001357*		
Alternative calculation for bleeding – method B	All bleeding	6 to 12 month-DAPT – all	0.003419		
	Major bleeding	*6 to 12 month-DAPT – major*	*0.000525*		
	Minor bleeding	*6 to 12 month-DAPT -minor*	*0.002894*		
	All bleeding	Extended DAPT – all	0.005705		
	Major bleeding	*Extended DAPT – major*	*0.000877*		
	Minor bleeding	*Extended DAPT - minor*	*0.004828*		
Initial DAPT 6 months (NIPPON, ITALIC, PRODIGY)	Overall death	6 to 12 month-DAPT	0.001076		
		Extended DAPT	0.001052		
	Bleeding all	6 to 12 month-DAPT	0.000360		
		Extended DAPT	0.000601		
	Non-fatal MI	6 to 12 month-DAPT	0.000388		
		Extended DAPT	0.000226		
	Non-fatal stroke	6 to 12 month-DAPT	0.000355		
		Extended DAPT	0.000345		
	Stent thrombosis	6 to 12 month-DAPT	0.000194		

Analysis	Parameter	Group	Value	95% CI LL	95%CI UL
		Extended DAPT	0.000097		
	Urgent revascularization	6 to 12 month-DAPT	0.000540		
		Extended DAPT	0.000481		
Initial DAPT 12 months (DAPT, OPTIDUAL, ARCTIC, DES-LATE)	Overall death	6 to 12 month-DAPT	0.000747		
		Extended DAPT	0.000889		
	Bleeding all	6 to 12 month-DAPT	0.000926		
		Extended DAPT	0.000988		
	Non-fatal MI	6 to 12 month-DAPT	0.001503		
		Extended DAPT	0.000857		
	Non-fatal stroke	6 to 12 month-DAPT	0.000412		
		Extended DAPT	0.000386		
	Stent thrombosis	6 to 12 month-DAPT	0.000606		
		Extended DAPT	0.000189		
	Urgent revascularization	6 to 12 month-DAPT	0.000826		
		Extended DAPT	0.000274		
DAPT duration 18 months (NIPPON)	Overall death	6 to 12 month-DAPT	0.000806		
		Extended DAPT	0.000353		
	Bleeding all*	6 to 12 month-DAPT	0.000712		
		Extended DAPT	0.000826		
	Non-fatal MI	6 to 12 month-DAPT	0.000202		
		Extended DAPT	0.000050		
	Non-fatal stroke	6 to 12 month-DAPT	0.000353		
		Extended DAPT	0.000302		
	Stent thrombosis	6 to 12 month-DAPT	0.000101		
		Extended DAPT	0.000050		
	Urgent revascularization*	6 to 12 month-DAPT	0.000657		
		Extended DAPT	0.000396		
DAPT duration 24 to 30 months (ITALIC, PRODIGY, ARCTIC, DAPT)	Overall death	6 to 12 month-DAPT	0.000919		
		Extended DAPT	0.001127		
	Bleeding all	6 to 12 month-DAPT	0.000360		
		Extended DAPT	0.000502		
	Non-fatal MI	6 to 12 month-DAPT	0.001848		
		Extended DAPT	0.001043		

Analysis	Parameter	Group	Value	95% CI LL	95%CI UL
	Non-fatal stroke	6 to 12 month-DAPT	0.000440		
		Extended DAPT	0.000421		
	Stent thrombosis	6 to 12 month-DAPT	0.000628		
		Extended DAPT	0.000194		
	Urgent revascularization	6 to 12 month-DAPT	0.000657		
		Extended DAPT	0.000396		
DAPT duration 36 to 48 months (OPTIDUAL, DES-LATE)	Overall death	6 to 12 month-DAPT	0.000623		
		Extended DAPT	0.000731		
	Bleeding all	6 to 12 month-DAPT	0.000672		
		Extended DAPT	0.001067		
	Non-fatal MI	6 to 12 month-DAPT	0.000489		
		Extended DAPT	0.000339		
	Non-fatal stroke	6 to 12 month-DAPT	0.000333		
		Extended DAPT	0.000314		
	Stent thrombosis	6 to 12 month-DAPT	0.000040		
		Extended DAPT	0.000119		
	Urgent revascularization*	6 to 12 month-DAPT	0.000657		
		Extended DAPT	0.000396		

*assumed to be the same as the full analysis
95% CI LL: lower limit of the 95% confidence interval; 95%CI UL: upper limit of the 95% confidence interval; DAPT: dual anti-platelet therapy; HR: hazard ratio