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CADTH OPTIMAL USE REPORT

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

PROSPERO REGISTRATION NUMBER: CRD42018082587

Service Line:	CADTH Optimal Use Report
Issue Number:	Vol. 9, no. 2b
Publication Date:	March 2019
Report Length:	201 Pages

CADTH

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Cite As: *Dual Antiplatelet Therapy Following Percutaneous Coronary Intervention: Clinical and Economic Impact of Standard Versus Extended Duration*. Ottawa: CADTH; 2019 Mar. (CADTH Optimal Use Report; vol. 9, no. 2b).

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ISSN: 1927-0127

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Conflicts of Interest

Dr. Wells declared having received funding from Abbott within five years preceding this project. Funding was received for educational activities.

Dr. Welsh declared having received funding from the following companies within five years preceding this project: Astra Zeneca, Bayer, BMS/Pfizer, Boehringer Ingelheim. Funding was received for advisory work, as well as educational and research activities.

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Table of Contents

Tables

Figures

Abbreviations

ACS	acute coronary syndrome
BARC	Bleeding Academic Research Consortium
BMS	bare-metal stent
CI	confidence interval
DAPT	dual antiplatelet therapy
DES	drug-eluting stent
EQ-5D	EuroQol 5-Dimensions questionnaire
ESC	European Society of Cardiology
GUSTO	Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries
ICUR	incremental cost-utility ratio
HR	hazard ratio
MACCE	major adverse cardiac and cerebrovascular event
MI	myocardial infarction
NMA	network meta-analysis
NNT	number needed to treat
OCCI	Ontario Case Costing Initiative
PCI	percutaneous coronary intervention
QALY	quality-adjusted life-year
RCT	randomized controlled trial
RR	relative risk
STEMI	ST-elevation myocardial infarction
TIA	transient ischemic attack
TIMI	thrombolysis in myocardial infarction

Executive Summary

Rationale and Policy Issues

Dual antiplatelet therapy (DAPT) — the combination of a P2Y12 inhibitor (clopidogrel, prasugrel, or ticagrelor) together with 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 (MACCEs). 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, although clinicians also need to consider the associated bleeding risk. It is therefore important for clinicians to identify those patients most likely to benefit from extended DAPT, 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 that extended therapy will result in optimal outcomes for patients after PCI and not result in more harm. Accordingly, given the current uncertainty about the benefits and harms of extended DAPT beyond one year, further elucidation of the available evidence, including the assessment of both the 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 P2Y12 inhibitors used as part of extended DAPT following PCI with stent insertion should be reimbursed by publicly funded drug programs. The second question sought to determine whether there may be a preferred P2Y12 inhibitor that should be reimbursed for extended DAPT.

Policy Question 1

Should P2Y12 inhibitors (i.e., clopidogrel, prasugrel, or ticagrelor) be reimbursed for use beyond 12 months in combination with ASA for patients who recently underwent PCI with bare-metal stent (BMS) or drug-eluting stent (DES) insertion?

Policy Question 2

Which of the P2Y12 inhibitors (clopidogrel, prasugrel, or ticagrelor) should be reimbursed for use beyond 12 months in combination with ASA for patients who underwent PCI with BMS or DES insertion?

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.

Research Question 1

What is the comparative clinical efficacy and safety of shorter-duration DAPT (six to 12 months) versus longer duration (i.e., more than 12 months) 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 the time of PCI
- those with diabetes
- different age subgroups
- those who smoke?

Research Question 2

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

- all post-PCI patients
- those with a prior MI
- those presenting with ACS at the time of PCI
- those with diabetes
- different age subgroups
- those who smoke?

Research Question 3

Compared with shorter treatment duration (six to 12 months), what is the comparative clinical efficacy and safety of ASA plus clopidogrel, prasugrel, or ticagrelor when DAPT is used for longer (i.e., more than 12 months) duration following PCI with BMS or DES insertion in:

- all post-PCI patients
- those with a prior MI
- those presenting with ACS at the time of PCI
- those with diabetes
- different age subgroups
- those who smoke?

Research Question 4

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

- all post-PCI patients
- those with a prior MI
- those presenting with ACS at the time of PCI
- those with diabetes
- different age subgroups
- those who smoke?

Of note, Research Questions 1 and 3 were addressed 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 standard DAPT (i.e., for six to 12 months) after stenting compared with extended DAPT (i.e., for 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 less than 75 years or aged 75 years and older). 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 a majority of the participants in the RCTs, and limited data were available to address Research Question 3 (re: the 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 an MI (relative risk [RR] 0.58, 95% confidence interval (CI), 0.48 to 0.70; number needed to treat [NNT] 174) and probable or definite stent thrombosis (RR 0.38, 95% CI, 0.21 to 0.67; NNT 348) compared with DAPT for six to12 months (Table 1). These benefits were associated with an increased risk of bleeding, Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO), moderate bleeding (RR 1.68, 95%CI, 1.22 to 2.30, number needed to harm 156); of note, estimates varied depending on the bleeding classification system. One large RCT (the DAPT trial) reported a significant increase in non-cardiovascular death (RR 2.15, 95%CI, 1.30 to 3.55) among participants who received DAPT for more than 12 months; however, no significant difference in risk was observed in two smaller trials.

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 in Table 1.

Table 1: Summary of Findings — Outcomes

	> 12 Versus 6 to 12 Months		
Outcome	**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)
Non-cardiovascular death	**↑[a] (N = 14,666)**	NA	**↑[a] (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[b]	↔ (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)

↓ = 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; 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 event; NA = no evidence was available to inform the comparison; TIMI = thrombolysis in myocardial infarction.

[a] Inconsistent findings across studies. One large randomized, controlled trial (DAPT trial) reported a significant increase in non-cardiovascular death among patients who received extended DAPT, while two smaller randomized, controlled trial s (OPTIDUAL, NIPPON) reported no significant difference between DAPT durations.

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

The following sections provide a summary of findings in clinically important patient subgroups. RRs and additional information are provided in the main body of the report.

Prior Myocardial Infarction

Compared with DAPT for six to 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.

Among patients without a prior MI, an increased risk of all-cause death and moderate bleeding was observed. A decreased risk of MI and probable or definite stent thrombosis was also observed in this population (Table 2).

Table 2: Summary of Findings — Prior Myocardial Infarction

	> 12 Versus 6 to 12 Months	
Outcome	**Prior MI**	**No Prior MI**
All-cause death	↔ (N = 5,622)	**↑ (N = 6,308)**
Cardiovascular death	↔ (N = 282)	NA
Non-cardiovascular 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)**

↓ = 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; 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; NA = no evidence was available to inform the comparison; TIMI = thrombolysis in myocardial infarction.

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

Acute Coronary Syndrome at Time of Percutaneous Coronary Intervention

Compared with DAPT for six to 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 acute coronary syndrome (ACS) at presentation. Limited data were available for participants without ACS (Table 3).

Table 3: Summary of Findings — Acute Coronary Syndrome

	> 12 Versus 6 to 12 months	
Outcome	**ACS**	**No ACS**
All-cause death	↔ (N = 4,382)	NA
Cardiovascular death	↔ (N = 806)	NA
Non-cardiovascular 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

↓ = 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; 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; NA = no evidence was available to inform the comparison;TIMI = thrombolysis in myocardial infarction.

[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 4).

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 4).

Table 4: Summary of Findings — Diabetes

	> 12 Versus 6 to 12 Months	
Outcome	**Diabetes**	**No Diabetes**
All-cause death	↔ (N = 4,076)	↔ (N = 8,257)
Cardiovascular death	↔ (N = 4,076)	NA
Non-cardiovascular 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)**
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

↓ = 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 DAP; 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; NA = no evidence was available to inform the comparison;TIMI = thrombolysis in myocardial infarction.

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

Age

Among those aged 75 years and older, extending DAPT for more than 12 months may increase the risk of stroke and bleeding (Table 5).

Among those aged less than 75 years, extended DAPT may reduce the risk of MI and probable or definite stent thrombosis, although the supporting evidence is inconsistent for both outcomes. Extended DAPT is also associated with an increased risk of bleeding (Table 5).

Table 5: Summary of Findings — Age

	> 12 Versus 6 to12 months	
Outcome	**≥ 75 Years**	**< 75 Years**
All-cause death	↔ (N = 848)	↔ (N = 1,383)
Cardiovascular death	↔ (N = 848)	↔ (N = 1,383)
Non-cardiovascular death	NA	NA
Myocardial infarction	↔ (N = 1,880)	**↓[a] (N = 8,929)**
Stroke	**↑ (N = 587)**	↔ (N = 1,383)
Stent thrombosis: Definite	↔ (N = 587)	↔ (N = 1,383)
Stent thrombosis: Probable or definite	↔ (N = 1,624)	**↓[b] (N = 1,383)**
Urgent revascularization	↔ (N = 261)	NA
MACCE[c]	↔ (N = 1,624)	**↓[d] (N = 8,929)**
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)**

↓ = 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; 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; NA = no evidence was available to inform the comparison; TIMI = thrombolysis in myocardial infarction.

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

[b] 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).

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

[d] Inconsistent evidence: One large RCT (DAPT trial) reported a significantly lower risk of MACCE among participants aged less than 75 years who received extended DAPT (HR 0.69, 95%CI 0.57, 0.83), while one smaller RCT (PRODIGY) reported no significant difference (RR 1.59, 95%CI 0.92 to 2.75).

Smoking

Among smokers, extending DAPT for more than 12 months may reduce the risk of MI, definite or probable stent thrombosis, and MACCE (Table 6).

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 6).

Table 6: Summary of Findings — Smoking

	> 12 Versus 6 to 12 months	
Outcome	**Smoking**	**No smoking**
All-cause death	↔ (N = 469)	↔ (N = 1,493)
Cardiovascular death	NA	NA
Non-cardiovascular 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)**

↓ = 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; 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; 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 included participants in the eligible RCTs were administered clopidogrel. Because the analyses intended to address Research Question 1 and 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 the 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 = 3,456). In the DAPT trial, participants who received prasugrel for at least 12 months (N = 1,745) were at lower risk of MI, definite or probable stent thrombosis, and MACCE compared with those who received DAPT for six to 12 months (N = 1,711); however, patients who received extended DAPT were at higher risk of GUSTO moderate or severe bleeding. No data were available for death, stroke, urgent revascularization, or thrombolysis in myocardial infarction (TIMI) bleeding.

Ticagrelor was one of the eligible P2Y12 inhibitors in one RCT (ITALIC); however, no participants in the 24-month DAPT group and 0.1% of participants in the six-month DAPT group received ticagrelor. There were therefore insufficient data available to assess the benefits and harms of extended DAPT involving ticagrelor. During the review process, one large RCT (PEGASUS-TIMI 54) involving ticagrelor was identified; however, it did not meet the eligibility criteria. The main reasons for excluding this trial were: not all included patients had undergone PCI before randomization, there was uncertainty about the proportion of

participants who received a P2Y12 inhibitor prior to randomization, and the duration of potential DAPT before randomization was longer than the eligibility criteria for the present review. 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 Clinical Data Synthesis section 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 (the extended DAPT phase) was built to reflect the results of CADTH meta-analysis and the end points 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 CADTH 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 (the post-extended DAPT phase), which reflected the rest of their lives; 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 cardiovascular events (e.g., stroke or second MI in an MI patient, MI or second stroke in stroke patients). Published literature supplemented results from the CADTH 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, and quality-adjusted life-years (QALYs) were discounted at 1.5% per annum (0% and 3% in sensitivity analyses). 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 (0.0160 QALYs) and savings ($707) were small. This dominance was observed in 71.6% of the 5,000 iterations, while extended DAPT was dominated (i.e., less effective and more expensive than six to 12 months DAPT) in only 1.5% of the iterations. However, 13.8% of the iterations resulted in an incremental cost-utility ratio (ICUR) above $50,000 per QALY. The incremental benefits associated with extended DAPT came largely (98%) from the lifetime analysis. When the analysis was limited to the duration of the trials included in CADTH meta-analysis (i.e., an average of 19 months beyond the initial six- to 12-month DAPT), the incremental benefit of extended DAPT was only 0.0003 QALYs, with incremental costs of $161, resulting in an ICUR of $546,427 per QALY. Uncertainty exists regarding the impact of extended DAPT beyond the duration of studies included in CADTH meta-analysis (i.e., three to four 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 7). 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 (assuming a similar efficacy across products) when the analysis was performed on a shorter time horizon (i.e., 19 months beyond the initial six to 12 month DAPT), as well as 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 because the data to inform these analyses were obtained from few studies (one or two) and required additional assumptions to be made (Table 7). 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 ACS. In patients less than 75-years-old, the ICUR was $37,901. However, extended DAPT resulted in a loss of health benefit in patients with diabetes, those with no prior MI and, those older than 75 years of age, and thus may not be the preferred option in these patients.

Table 7: Key Results of the Economic Analysis

Scenario	6- to 12-months DAPT		Extended DAPT		Incremental (Versus Extended DAPT)		
	Costs	QALY	Costs	QALY	ΔCosts	ΔQALY	ICUR
Base case	$40,227	13.64	$39,520	13.65	–$707	0.0160	Extended DAPT dominant
Alternative proportion for antiplatelet agents							
100% clopidogrel	$40,233	13.63	$39,340	13.65	–$893	0.0157	Extended DAPT dominant
100% prasugrel	$40,319	13.64	$40,324	13.65	$5	0.0156	$322
100% ticagrelor	$40,243	13.63	$40,895	13.65	$653	0.0160	$40,696
Shorter time horizon (19 months)	$787	1.23	$947	1.23	$161	0.0003	$546,427
No CV event post-extended DAPT treatment	$5,929	14.65	$5,225	14.69	–$704	0.0376	Extended DAPT dominant
DAPT duration in control: 6 months	$29,562	14.06	$29,640	14.08	$78	0.0264	$2,958
DAPT duration in control: 12 months	$43,589	13.49	$42,336	13.51	–$1,253	0.0186	Extended DAPT dominant
Extended DAPT duration: 18 months	$29,033	14.11	$28,912	14.21	–$121	0.1048	Extended DAPT dominant
Extended DAPT duration: 24 to 30 months	$45,840	13.42	$44,904	13.42	–$937	–0.0033	$284,371
Extended DAPT duration: 36 to 48 months	$30,904	14.02	$30,448	14.01	–$456	–0.0084	$54,413
Rebound effect							
Maximal rebound at 3 months	$40,157	13.64	$39,737	13.65	–$420	0.0078	Extended DAPT dominant
Rates reaching control rates at 6 months	$40,214	13.63	$40,171	13.62	–$43	–0.0070	$6,132

Scenario	6 to 12 months DAPT		Extended DAPT		Incremental (versus Extended DAPT)		
	Costs	QALY	Costs	QALY	ΔCosts	ΔQALY	ICUR
Subgroup Analyses							
Prior MI	$56,045	12.94	$53,936	13.00	–$2,109	0.0583	Extended DAPT dominant
No prior MI	$46,773	13.48	$45,697	13.42	–$1,076	–0.0575	$18,706
ACS	$48,826	13.17	$47,229	13.24	–$1,597	0.0685	Extended DAPT dominant
Diabetes	$51,880	13.14	$51,749	13.08	–$130	–0.0640	$2,035
No diabetes	$45,525	13.41	$44,239	13.43	-$1,286	0.0177	Extended DAPT dominant
Older than 75-years-old	$9,596	6.51	$14,491	6.47	$4,895	–0.0394	6- to 12-month DAPT dominant
Less than 75-years-old	$33,016	14.10	$37,406	14.22	$4,390	0.1158	$37,901

ΔCosts = incremental costs; ΔQALY = incremental QALY; ACS = acute coronary syndrome; CV = cardiovascular; DAPT = dual anti-platelet therapy; MI = myocardial infarction; QALY = quality-adjusted life-year. MI = myocardial infarction.

Discussion

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

- Limited data were available for most of the clinically important subgroups of interest in this review; accordingly there is uncertainty about the benefits and harms of extended DAPT. Most of the available subgroup data are from one RCT (the DAPT trial); therefore, the results of the subgroup analyses should be interpreted with caution. The longest duration of DAPT in the RCTs was 48 months; as such, the benefits and harms of DAPT beyond that time point are uncertain.
- 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 results of the clinical review indicate that the use of DAPT beyond 12 months after PCI is associated with a reduced risk of MI and a reduced risk of probable or definite stent thrombosis. This strategy is, however, associated with an increased risk of bleeding. These are important considerations for clinicians, in particular the need to identify which patients are at higher risk of bleeding. Clinicians may also consider other factors in

determining which patients would benefit most from extended DAPT, such as age, presence of diabetes, smoking status, and previous MI.

As the economic analysis used the results of the CADTH meta-analysis, the identified limitations to the CADTH 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 three to four years' study duration) effect 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 CADTH 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 that most study participants received clopidogrel, these findings mainly apply to clopidogrel-based DAPT regimens. Although limited data were available, similar results were found for participants who received prasugrel. Indeed, among participants who received prasugrel, DAPT for more than12 months was associated with a lower risk of MI, definite or probable stent thrombosis, and MACCE but a 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 patients after PCI because of a lack of data.

Of note, among those who received extended clopidogrel-based DAPT, an increased risk of death was observed among participants without prior MI, and an increased risk of stroke was observed among those aged more than 75 years. In general, from a clinical perspective, patients with prior MI, those with ACS at presentation, as well as patients with no diabetes or aged less than 75 years, may derive the most benefit from extended DAPT provided that the increased risk of bleeding is accounted for when deciding to extend DAPT beyond 12 months.

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 therefore not preferred in patients with diabetes, patients with no prior MI, and patients older than 75 years of age. As such, our economic findings are in line with the findings of the clinical review and call for a careful selection of patients who may benefit most from extended DAPT beyond 12 months in order to ensure it leads to improved clinical and economic outcomes for them.

Rationale and Policy Issues

Background and Rationale

Dual antiplatelet therapy (DAPT) — the combination of a P2Y12 inhibitor (clopidogrel, prasugrel, or ticagrelor) together with ASA — is routinely given for six to 12 months following percutaneous coronary intervention (PCI) with stenting, with the aim of preventing stent thrombosis and major adverse cardiac and cerebrovascular events (MACCEs). 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., in patients with a high risk of bleeding), while other patients may derive a greater benefit from extended DAPT (e.g., those with a high risk of stent thrombosis and a 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[2] guidelines recommend DAPT for six 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 one-year minimum duration of DAPT for patients with ACS. Recent Canadian guidelines also support a one-year 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 et al.[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 the consideration of findings from a recent clinical review,[1] 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.

Patient Group Input Summary

At the onset of this project in the late winter of 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 but no feedback was received from patient groups at that time.

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.

Policy Questions

There were two policy questions for this project. The first question sought to determine whether P2Y12 inhibitors used as part of extended DAPT following PCI with stent insertion should be reimbursed by publicly funded drug programs. The second question sought to determine whether there may be a preferred P2Y12 inhibitor that should be reimbursed for extended DAPT.

Policy Question 1

Should P2Y12 inhibitors (i.e., clopidogrel, prasugrel, or ticagrelor) be reimbursed for use beyond 12 months in combination with ASA for patients who recently underwent PCI with bare-metal stent (BMS) or drug-eluting stent (DES) insertion?

Policy Question 2

Which of the P2Y12 inhibitors (clopidogrel, prasugrel, or ticagrelor) should be reimbursed for use beyond 12 months in combination with ASA for patients who underwent PCI with BMS or DES insertion?

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:

Research Question 1

What is the comparative clinical efficacy and safety of shorter-duration DAPT (six to 12 months) versus longer duration (i.e., more than 12 months) following PCI with BMS or DES insertion in:

- all post-PCI patients
- those with a prior MI
- those presenting with ACS at the time of PCI
- those with diabetes
- different age subgroups
- those who smoke?

Research Question 2

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

- all post-PCI patients
- those with a prior MI
- those presenting with ACS at the time of PCI
- those with diabetes
- different age subgroups
- those who smoke?

Research Question 3

Compared with shorter treatment duration (six to 12 months), what is the comparative clinical efficacy and safety of ASA plus clopidogrel, prasugrel, or ticagrelor when DAPT is used for longer (i.e., more than 12 months) duration following PCI with BMS or DES insertion in:

- all post-PCI patients
- those with a prior MI
- those presenting with ACS at the time of PCI
- those with diabetes
- different age subgroups
- those who smoke?

Research Question 4

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

- all post-PCI patients
- those with a prior MI
- those presenting with ACS at the time of PCI
- those with diabetes
- different age subgroups
- those who smoke?

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 of Interventions* and the PRISMA checklist for systematic reviews.[18]

Clinical Evaluation

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 and daily updates) via Ovid; Embase (1974 to the present) via Ovid; the Cochrane Library via Wiley; and PubMed (November 17, 2017). 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 antiplatelet therapy (DAPT) [Intervention] and patients requiring 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/resources/finding-evidence/grey-matters); i.e., ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform (ICTRP) search portal.

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 8: Selection Criteria

PICO Components	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 six 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, non-cardiovascular) 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

DAPT = dual antiplatelet therapy; PCI = percutaneous coronary intervention.
Note: Studies were not selected for inclusion based on reported outcomes.

Population and Subgroups

The population of interest is adult patients (aged 18 years or older) 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 less than 75 years or aged 75 years and older. Where available, diabetes was dichotomized as type 1 diabetes or type 2 diabetes.

Intervention and Comparators

Intervention: DAPT following PCI with stenting for an extended duration (more than 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 six to 12 months. Other DAPT regimens or durations are beyond the scope of this review.

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, and 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 (zero to six months after PCI) were not pooled with data from studies that reported outcomes data from the period starting six to 12 months following PCI.

Study Designs

RCTs that meet the abovementioned population, intervention, and comparator criteria were eligible for inclusion.

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).

Quality Assessment

We applied the Cochrane risk-of-bias tool (RoB) version 2.0 (RoB 2.0)[19] 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.

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.[20]

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:

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

If included studies reported multiple time points for outcomes 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 following 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.

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., more than 12 months of DAPT versus six to12 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.

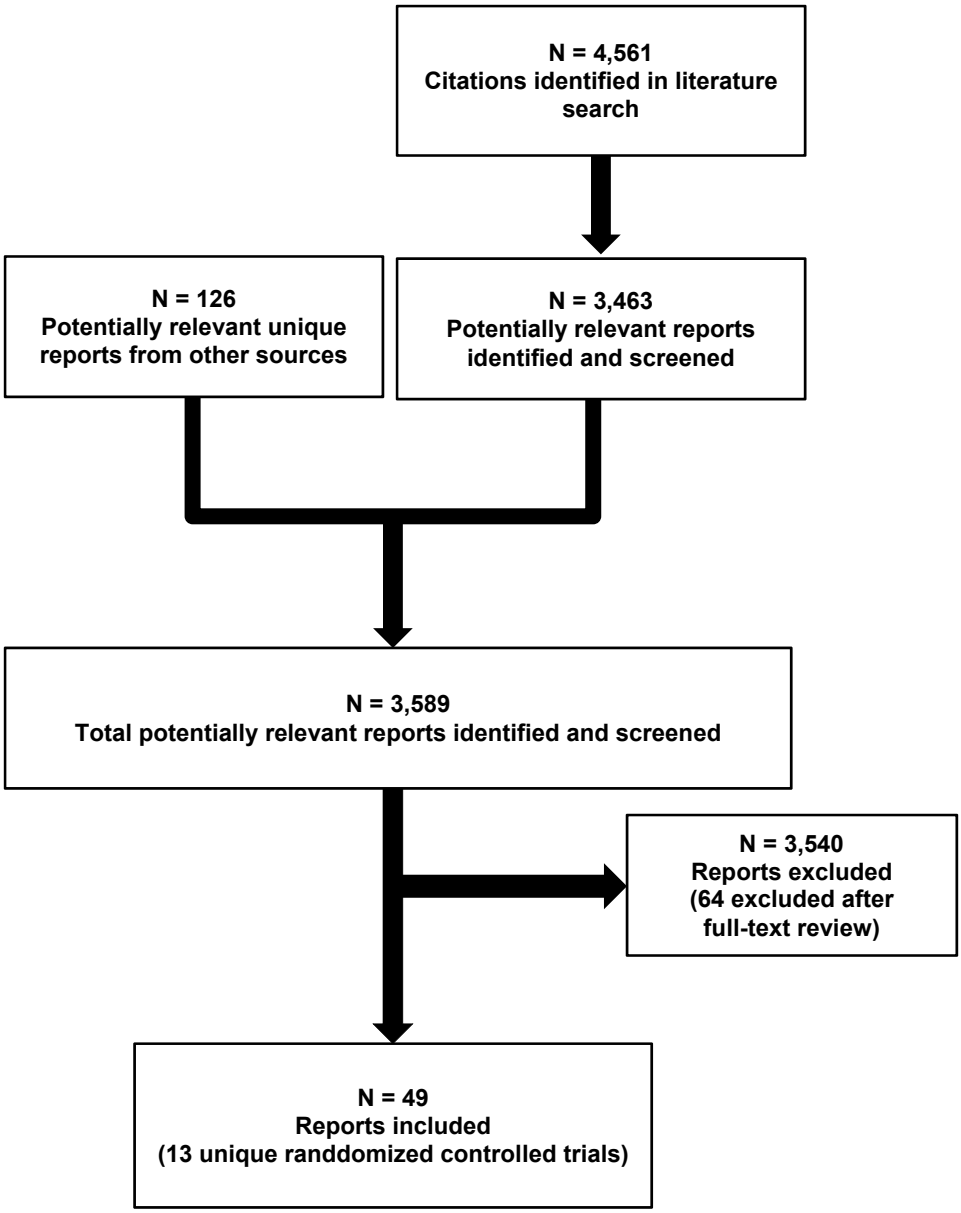
In the following sections, the term “significant” is used to express statistical significance; otherwise, “clinical importance” is used.

Results of Clinical Evaluation

Selection of Primary Studies

The initial literature search returned 4,561 records (Figure 1), with 3,463 records remaining after the removal of duplicates. An additional 126 unique citations were identified through grey literature searching. Of the 3,589 records screened based on titles or abstracts, 118 records were considered potentially relevant. The full text of five records could not be located (Appendix 3) so that 113 records were examined in full-text format. After a full-text review, 49 records corresponding to 13 unique RCTs[21-33] 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.

Study Characteristics

In total, 13 unique RCTs were included. Of these, no data were reported for five RCTs[21,25,27,28,32]; thus, the evidence base for this review is formed by eight RCTs.[22-24,26,29-31,33] Of the RCTs that did not report data, one was a protocol,[25] while four RCTs were available only as ClinicalTrials.gov registrations.[21,27,28,32]

Of the studies registered in ClinicalTrials.gov but that had no results posted, the status of two RCTs is unknown (NCT record last updated prior to 2015: NCT02402491[28] and NCT00954707[32]). One RCT was terminated because of slow enrolment (NCT02494284[27]). The outcomes of participants in one trial were reported as part of the DAPT trial (NCT01106534[21]).

The study characteristics for the eight RCTs that reported study results are subsequently summarized 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 9). The largest RCT was the DAPT trial,[23] with initial outcomes data published in 2014. None of the included studies were conducted in Canada or the US, although one multinational study included sites in the US.[23]

Most of the included studies were open-label (k = 7), with one placebo-controlled trial (Table 9). 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,[22,24,30,31] while the remaining four RCTs randomized participants who completed six to 12 months of DAPT with no adverse events; these patients therefore 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 9: Summary of Study Characteristics

Trial Characteristic	Category	Number 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**	**Number of Included Studies (k = 8)**
Number 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

PCI = percutaneous coronary intervention; RCT = randomized controlled trial.

The most frequently used P2Y12 inhibitor was clopidogrel (Table 10). Four RCTs involved only clopidogrel (PRODIGY,[24] DES-LATE,[26] OPTIDUAL,[29] Dadjou 2016[31]), while four RCTs involved more than one type of P2Y12 inhibitor (DAPT,[23] ARCTIC-Interruption,[33] ITALIC,[30] NIPPON[22]). Additional information about the P2Y12 inhibitors, including dose, is provided in Appendix 4.

Table 10: P2Y12 Inhibitors Used as Part of DAPT Regimens

Author, Year (Trial)	Group	Eligible P2Y12 Inhibitors	Number (%) of Participants			
			Clopidogrel	Prasugrel	Ticagrelor	Other P2Y12 Inhibitor
Nakamura et al., 2017 (NIPPON)[22]	6 mo 18 mo	Clopidogrel, ticlopidine	1,619 (97.9) 1,605 (97.1)	1 (0.1) 3 (0.2)	NA	32 (1.9) 44 (2.7)
Helft 2016 et al., (OPTIDUAL)[29]	12 mo 48 mo	Clopidogrel	100%	NR	NR	NR
Gilard et al., 2015 (ITALIC)[30]	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 et al., 2014 (DAPT)[23a]	12 mo 30 mo	Clopidogrel, prasugrel	3,230 (65.4) 3,275 (65.2)	1,711 (34.6) 1,745 (34.8)	NA	NA
Lee et al., 2014 (DES-LATE)[26]	12 mo 24 mo	Clopidogrel	2,502 (99.5) 2,521 (99.6)	NR	NR	NR
Collet et al., 2014 (ARCTIC-INT)[33]	12 mo 18 to 30 mo	Clopidogrel, prasugrel	562 (90.1) 569 (89.6)	53 (8.5) 54 (8.5)	NR	NR
Valgimigli et al., 2012 (PRODIGY)[24]	6 mo 24 mo	Clopidogrel	983 (100)[b] 987 (100)[b]	NA	NA	NA
Dadjou et al., 2016[31]	< 12 mo > 12 mo	Clopidogrel	100%*	NR	NR	NR

DAPT = dual antiplatelet therapy, mo = months, NA = not applicable, NR = not reported.

[a] P2Y12 inhibitor use among randomized participants with an implanted drug-eluting stent.
[b] At randomization (30 days post-percutaneous coronary intervention). At six months post-percutaneous coronary intervention, 83.6% of participants in the six-month DAPT group were receiving clopidogrel (98.3% among participants with a drug-eluting stent, 39.2% among participants with a bare-metal stent), and 99.4% of participants in the 24-month DAPT group.

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,[23,24,33] with between 0.6% and 5% of participants reporting a history of heart failure.

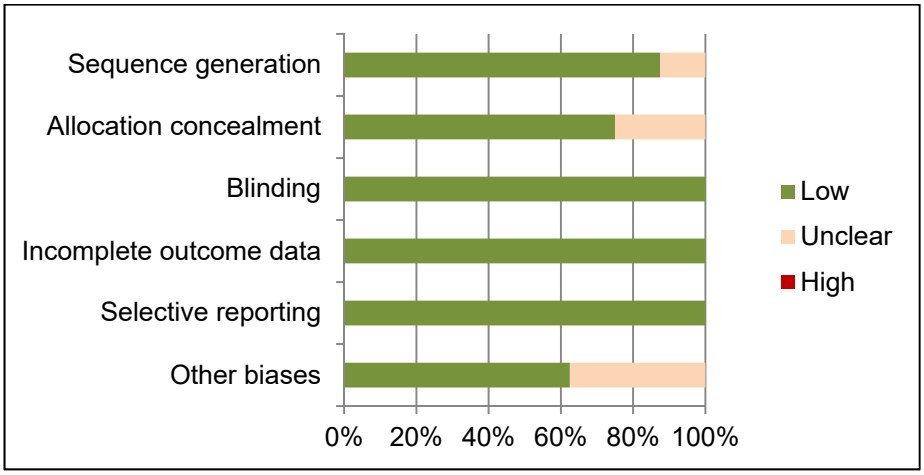
There was wide variation in the percentage of participants with ACS within the RCTs (Appendix 6). Between 0.1% and 33% of participants had ST-elevation MI (STEMI), between 2% and 23% of participants had non-STEMI, and between 9% and 39% of participants had unstable angina. Two RCTs[31,33] did not report the proportion of participants with STEMI, non-STEMI, 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,[30] while the PRODIGY trial enrolled "all-comers," including participants with STEMI.[24]

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,[24] DAPT[23], and Dadjou 2016[31]). Approximately 25% of participants in the PRODIGY trial received a BMS,[24] while about 15% of participants in the DAPT trial[23] included participants with a BMS. No studies involved only participants with an implanted BMS.

Risk of Bias

Risk of bias was assessed by using the Cochrane'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[26] and Dadjou 2016,[31] which did not provide sufficient details to permit judgment. 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,[30] OPTIDUAL,[29] NIPPON[22]) were considered to be at unclear risk of "other sources of bias" because all were terminated early. Two RCTs (ITALIC,[30] OPTIDUAL[29]) were terminated for problems with recruitment, while the NIPPON[22] 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



Data Synthesis

Research Question 1: What is the comparative clinical efficacy and safety of shorter-duration DAPT (six to 12 months) versus longer duration (i.e., more than 12 months) following PCI with BMS or DES insertion in:

- all post-PCI patients
- those with a prior MI
- those presenting with ACS at the time of PCI
- those with diabetes
- different age subgroups
- those who smoke?

In total, eight of the included RCTs addressed this research question.[22-24,26,29-31,33] The remaining RCTs reported no data (ClinicalTrials.gov records)[21,27,28,32] or were available only as published protocols.[25] Of the eight RCTs that reported data, four randomized participants

within 30 days of PCI.[22,24,30,31] Nakamura et al. (NIPPON)[22] and Valgimigli et al. (PRODIGY)[24] reported outcomes 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 six-month milestone as the denominator. Although the ITALIC trial[30] 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.[31]) 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. The following analyses are therefore based on data from seven RCTs,[22-24,26,29,30,33] representing the treatment period starting six months after PCI.

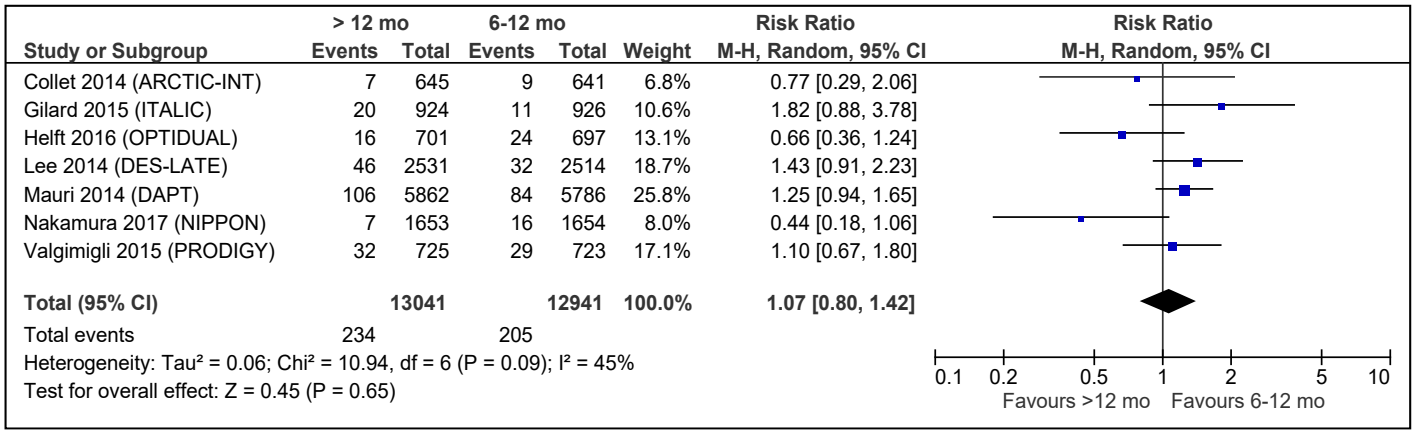
All Patients

Overall, based on data from the seven included studies,[22-24,26,29,30,33] extending DAPT beyond 12 months was associated with a reduced risk of MI (RR 0.58, 95% CI, 0.48 to 0.70; number needed to treat 174) and probable or definite stent thrombosis (RR 38, 95% CI, 0.21 to 0.67; number needed to treat 348), compared with DAPT for six to 12 months. These benefits were associated with an increased risk of bleeding, (GUSTO moderate bleeding RR 1.68, 95% CI, 1.22 to 2.30; number needed to harm 156), although estimates varied depending on the bleeding classification system. One large RCT (DAPT[23]) reported a significant increase in non-cardiovascular death (RR 2.15, 95% CI, 1.30 to 3.55) among participants who received DAPT for more than 12 months; however, no significant difference in risk was observed in two smaller trials (NIPPON[22] and OPTIDUAL[29]). A detailed description of these analyses is provided in the sections that follow.

All-Cause Death

In total, seven RCTs[22-24,26,29,30,33] involving 25,982 participants assessed all-cause death associated with six to 12 months of DAPT compared with extended DAPT more than 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

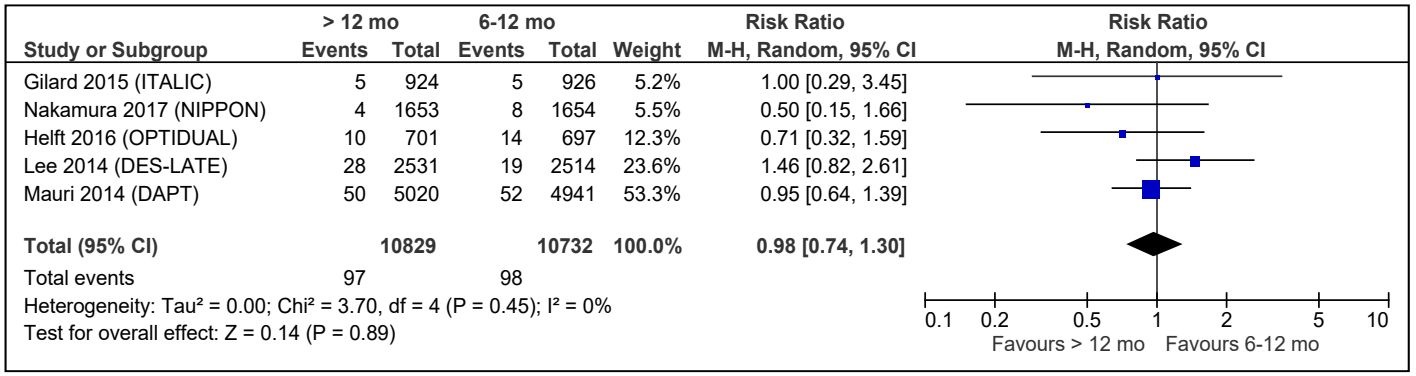


CI = confidence interval; mo = months.

Cardiovascular Death

In total, five RCTs[22,23,26,29,30] involving 21,561 participants assessed cardiovascular death associated with six to 12 months of DAPT compared with extended DAPT (more than 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

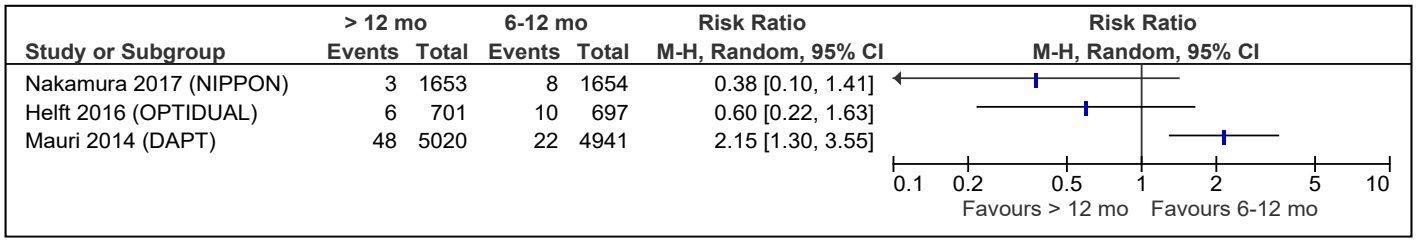


CI = confidence interval; mo = months.

Non-Cardiovascular Death

In total, three RCTs[22,23,29] involving 14,666 participants assessed non-cardiovascular death associated with six to 12 months of DAPT compared with extended DAPT (more than 12 months). No pooled analysis was performed, as there was high heterogeneity between trials (I^2 = 79%). Of note, two RCTs (NIPPON[22] and OPTIDUAL[29]) found no significant difference in the risk of non-cardiovascular death, while one RCT (DAPT[23]) 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

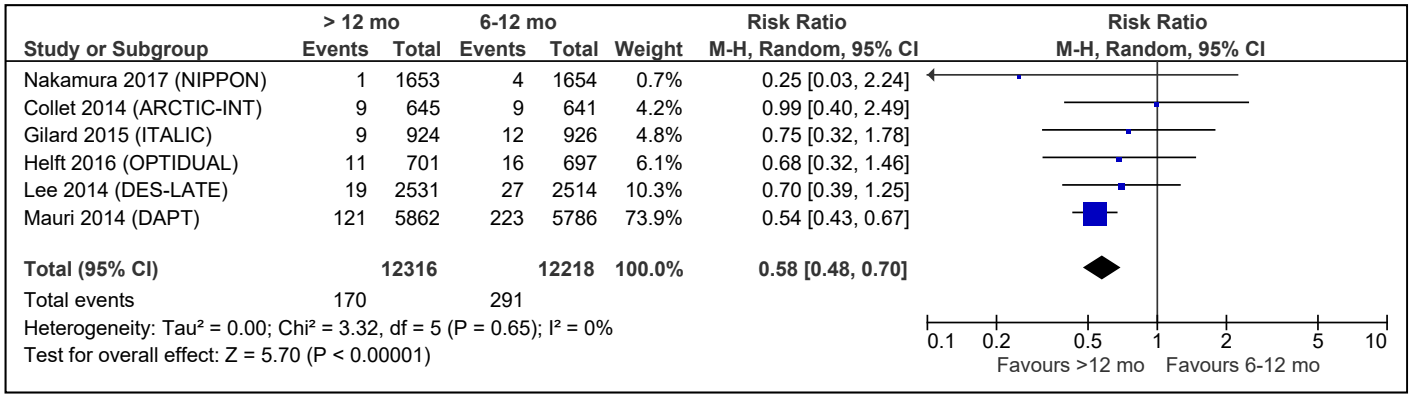


CI = confidence interval; mo = months.

Myocardial Infarction

In total, six RCTs[22,23,26,29,30,33] involving 24,534 participants assessed myocardial infarction (MI) associated with six to 12 months of DAPT compared with extended DAPT (more than 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

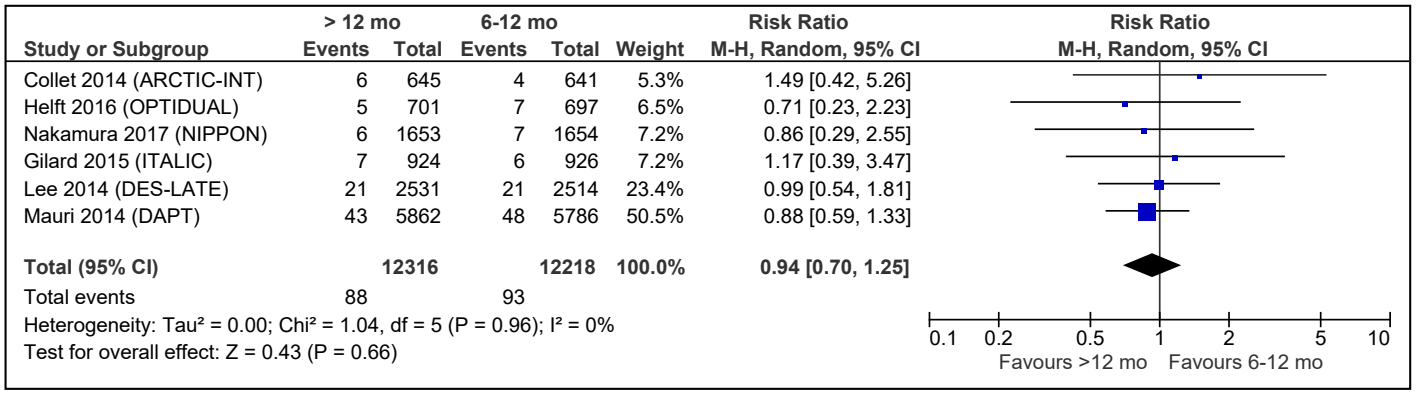


CI = confidence interval; mo = months.

Stroke

In total, six RCTs[22,23,26,29,30,33] involving 24,534 participants assessed stroke associated with six to 12 months of DAPT compared with extended DAPT (more than 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



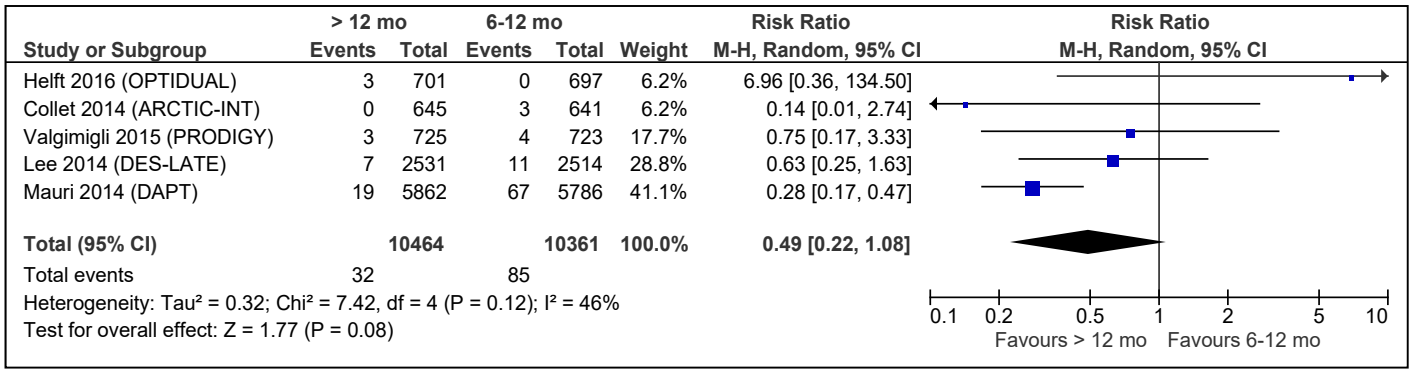
CI = confidence interval; mo = months.

Stent Thrombosis

Definite Stent Thrombosis

In total, five RCTs[23,24,26,29,33] involving 20,825 participants assessed definite stent thrombosis associated with six to 12 months of DAPT compared with extended DAPT (more than 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

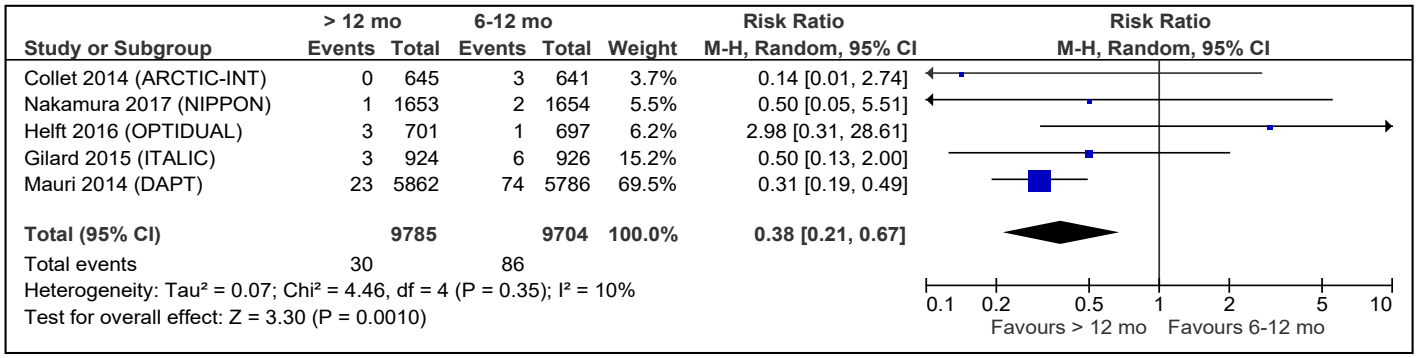


CI = confidence interval; mo = months.

Definite or Probable Stent Thrombosis

In total, five RCTs[22,23,29,30,33] involving 19,489 participants assessed probable or definite stent thrombosis associated with six to 12 months of DAPT compared with extended DAPT (more than 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

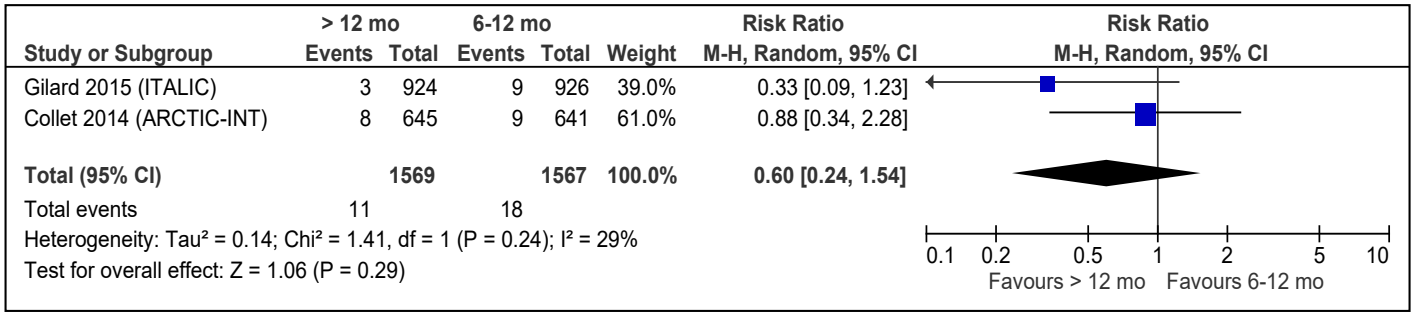


CI = confidence interval; mo = months.

Urgent Revascularization

Two RCTs[30,33] involving 3,136 participants assessed urgent revascularization associated with six to 12 months of DAPT compared with extended DAPT (more than 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



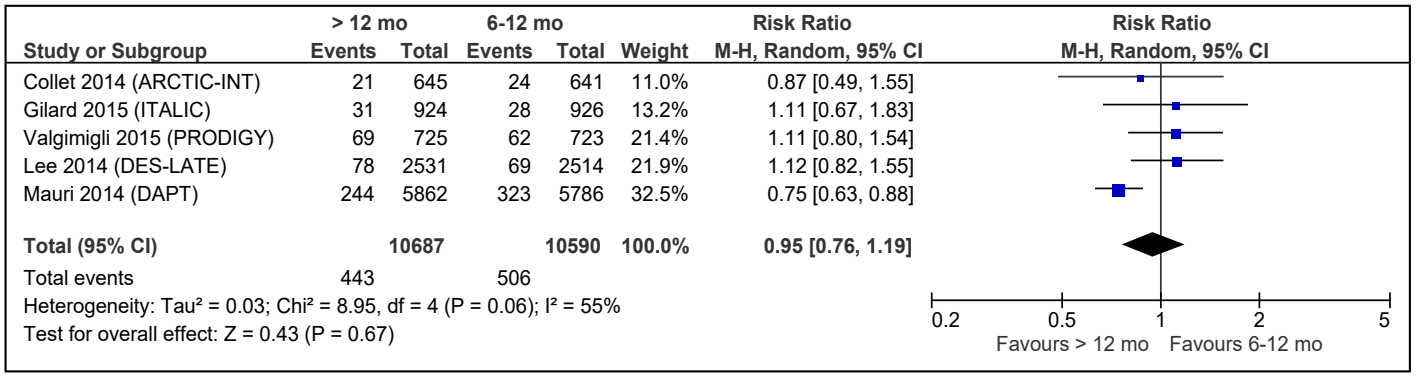
CI = confidence interval; mo = months.

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, MI, or stroke.

Five RCTs[23,24,26,30,33] reported the occurrence of MACCE during the treatment period, defined as a composite outcome involving death, MI, or stroke. In total, 21,277 participants were randomized to six to 12 months or more than 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



CI = confidence interval; MACCE = major adverse cardiac and cerebrovascular event; mo = months.

Two additional RCTs reported MACCE by use of an alternative definition that included major bleeding (Table 11), with no significant difference in the risk of an event between DAPT for more than12 months or DAPT for six to 12 months.

Table 11: MACCE Reported by Use of Alternative Definitions

Author, Date, Trial	MACCE Definition	Number of Events/ Number of Participants	RR (95% CI)
Nakamura et al., 2017 (NIPPON)[22]	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 et al., 2016 (OPTIDUAL)[29]	All-cause death, non-fatal MI, stroke, or major bleeding	12 mo: 52/697 48 mo: 40/701	0.76 (0.51, 1.14)

CI = confidence interval; MACCE = major adverse cardiac and cerebrovascular event; MI = myocardial infarction; mo = months; RR = relative risk.

Gastrointestinal Bleeding

Gastrointestinal bleeding was reported by one RCT,[22] with no significant difference in risk between participants who received DAPT for six or 18 months (Figure 12).

Figure 12: Relative Risk of Gastrointestinal Bleeding

CI = confidence interval; mo = months.

Major Bleeding

A variety of bleeding classification systems was used among the included trials to assess bleeding severity (Table 12). The TIMI classification system was most commonly used among the included trials.

Table 12: Bleeding Classification Systems Used by the Included RCTs to Assess Bleeding Severity

Trial	Bleeding Classification Systems[a]
Mauri et al., 2014 (DAPT)[23]	GUSTO, BARC
Valgimigli et al., 2012 (PRODIGY)[24]	TIMI, BARC
Collet et al., 2014 (ARCTIC-INT)[33]	TIMI, STEEPLE
Gilard et al., 2015 (ITALIC)[30]	TIMI
Helft et al., 2016 (OPTIDUAL)[29]	TIMI, BARC, GUSTO, ISTH
Nakamura et al., 2017 (NIPPON)[22]	BARC, REPLACE
Lee 2014 et al., (DES-LATE)[26]	TIMI

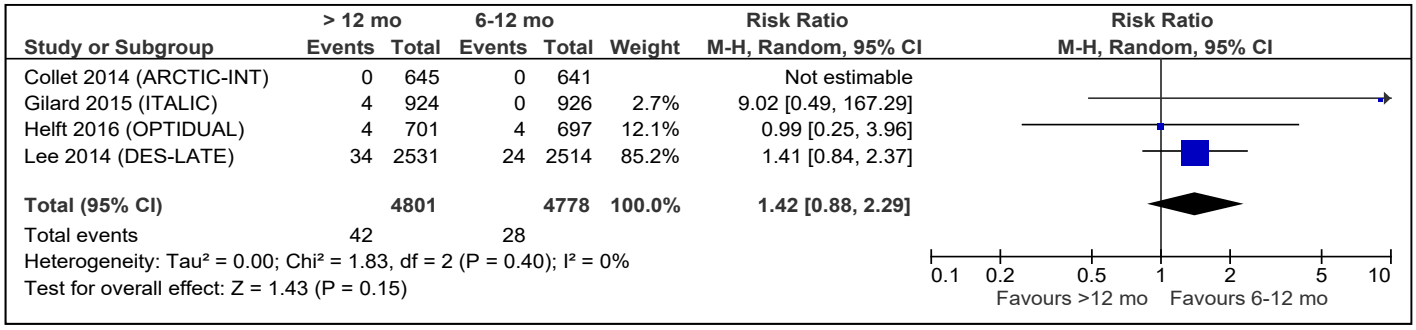
RCT = randomized controlled trial.

[a] A description of each bleeding classification system is available in Appendix 10.

TIMI Major Bleeding

TIMI major bleeds were reported in four RCTs[26,29,30,33] 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

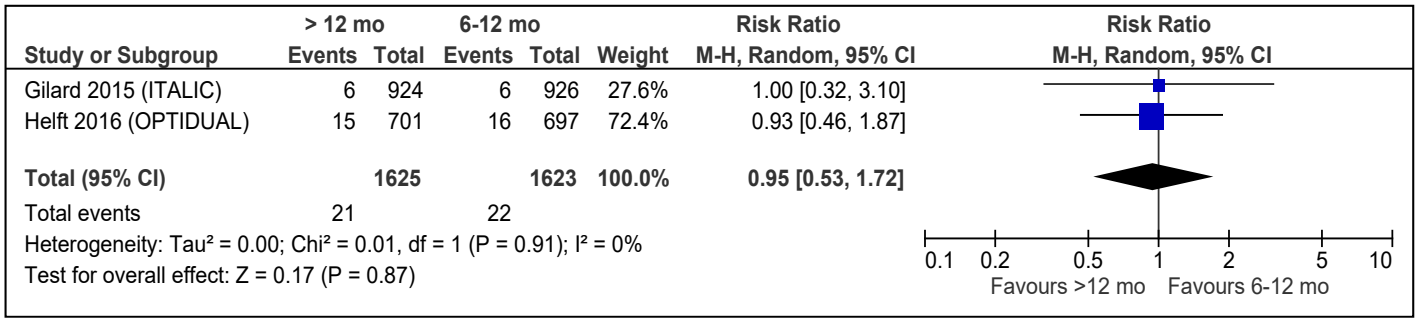


CI = confidence interval; mo = months; TIMI = thrombolysis in myocardial infarction.

TIMI Minor Bleeding

TIMI minor bleeds were reported in two RCTs[29,30] 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 14).

Figure 14: Relative Risk of TIMI Minor Bleeding



CI = confidence interval; mo = months; TIMI = thrombolysis in myocardial infarction.

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 six to12 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, 95% CI, 1.17, 2.11). Results from the DAPT trial suggest that there is a trend toward increased major bleeding with extended DAPT.

Table 13: Relative Risk of Bleeding, Assessed by Use of Alternative Bleeding Classification Systems

Bleeding Classification System[a]	Trial	Number of Events/ Number Randomized	RR (95% CI); I^2
BARC			
Type 2	DAPT[23]	12 mo: 79/5,786 30 mo: 167/5,862	1.41 (0.51, 3.90); 69%
	OPTIDUAL[29]	12 mo: 7/697 48 mo: 5/701	
Type 3	DAPT[23]	12 mo: 74/5,786 30 mo: 138/5,862	1.29 (0.76, 2.22); 58%
	OPTIDUAL[29]	12 mo: 14/697 48 mo: 13/701	
	NIPPON[22]	6 mo: 11/1,654[b] 18 mo: 10/1,653[b]	
Type 5	DAPT[23]	12 mo: 5/5,786 30 mo: 7/5,862	1.72 (0.62, 4.47); 0%
	OPTIDUAL[29]	12 mo: 0/697 48 mo: 1/701	
	NIPPON[22]	6 mo: 0/1,654[b] 18 mo: 2/1,653[b]	
Type 2,3,5	OPTIDUAL[29]	12 mo: 20/697 48 mo: 18/701	0.89 (0.48, 1.68); NA
GUSTO			
Moderate	DAPT[23]	12 mo: 52/5,786 30 mo: 91/5,862	1.68 (1.22, 2.30); 0%
	OPTIDUAL[29]	12 mo: 8/697 48 mo: 11/701	

Bleeding Classification System[a]	Trial	Number of Events/ Number Randomized	RR (95% CI); I^2
Severe	DAPT[23]	12 mo: 29/5,786 30 mo: 44/5,862	1.41 (0.90, 2.20); 0%
	OPTIDUAL[29]	12 mo: 4/697 48 mo: 3/701	
Moderate or severe	DAPT[23]	12 mo: 80/5,786 30 mo: 135/5,862	1.57 (1.17, 2.11); 7%
	OPTIDUAL[29]	12 mo: 12/697 48 mo: 13/701	
Replace			
Major	NIPPON[22]	6 mo: 11/1,654 [b] 18 mo: 22/1,653 [b]	2.00 (0.97, 4.11); NA
ISTH			
Major	OPTIDUAL[29]	12 mo: 14/697 48 mo: 14/701	0.99 (0.48, 2.07); NA
Minor	OPTIDUAL[29]	12 mo: 7/697 48 mo: 6/701	0.85 (0.29, 2.52); NA
STEEPLE			
Major	ARCTIC-INT[33]	12 mo: 1/641 18-30 mo: 7/645	6.96 (0.86, 56.38); NA
Minor	ARCTIC-INT[33]	12 mo: 2/641 18-30 mo: 5/645	2.48 (0.48, 12.76); NA

CI = confidence interval; mo = months; NA = not applicable; RR = relative risk.
[a] Definitions for each bleeding classification system are available in Appendix 10.
[b] Number of randomized who reached the 6-month landmark without experiencing the primary outcome.

Patients With an Implanted BMS

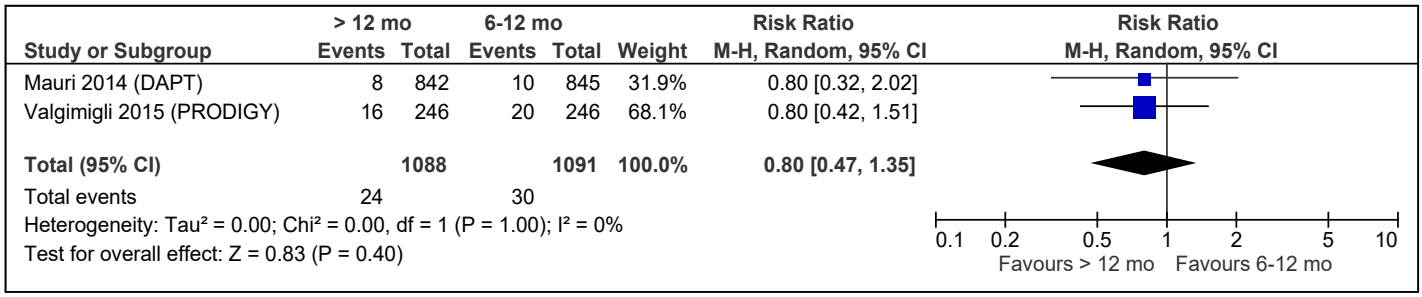
Two of the included RCTs involved participants with an implanted BMS (PRODIGY[24] and DAPT trials[23]) or DES. Approximately 25% of participants in the PRODIGY trial received a BMS,[24] whereas approximately 15% of participants in the DAPT trial[23] included participants with a BMS. These RCTs each reported data separately for participants with a BMS and form the evidence base for this subgroup.

In the PRODIGY trial,[24] participants were randomized within 30 days of PCI, and data were presented in two ways: zero to 24 months of DAPT or six to 24 months of DAPT. For participants with a BMS, subgroup data were provided for the period from zero to 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 six months. In the following analyses, the included data from the PRODIGY trial includes these participants. Hazard ratios (HRs) for the risk of an event during the period from six months onward (i.e., excluding participants who experienced an early event) were available for some outcomes and are subsequently reported.

All-Cause Death

Two RCTs[23,24] 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

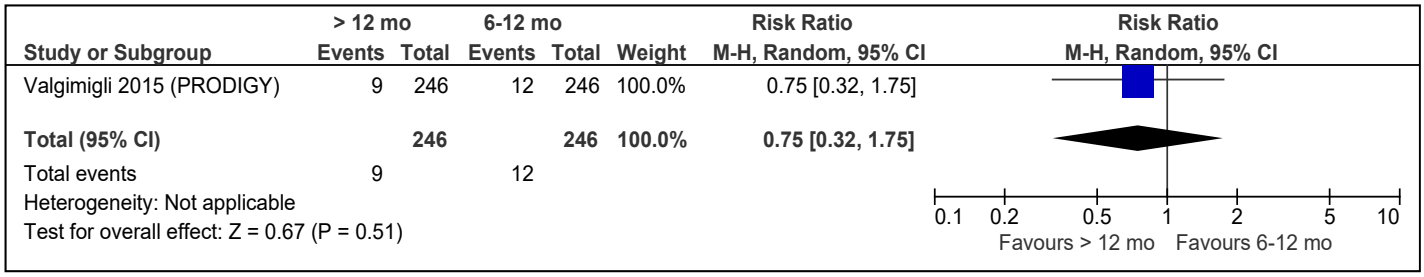


BMS = bare-metal stent; CI = confidence interval; mo = months.

Cardiovascular Death

One RCT[24] 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



BMS = bare-metal stent; CI = confidence interval; mo = months.

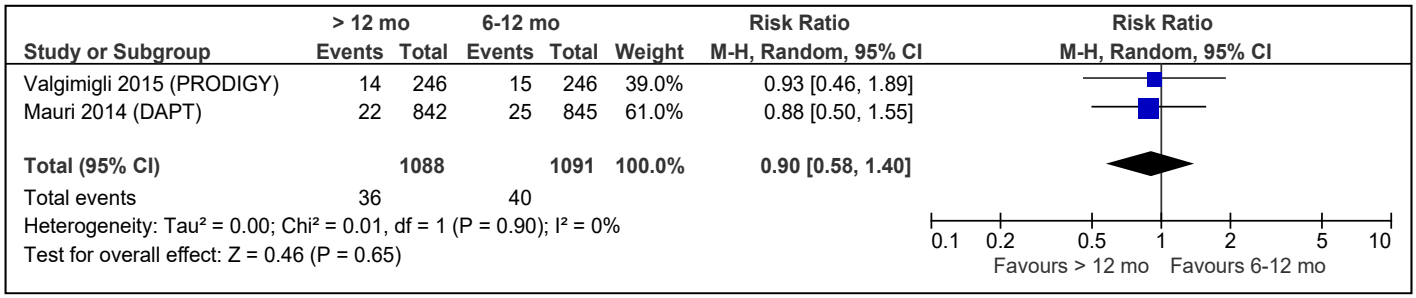
Non-cardiovascular Death

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

Myocardial Infarction

Two RCTs[23,24] 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

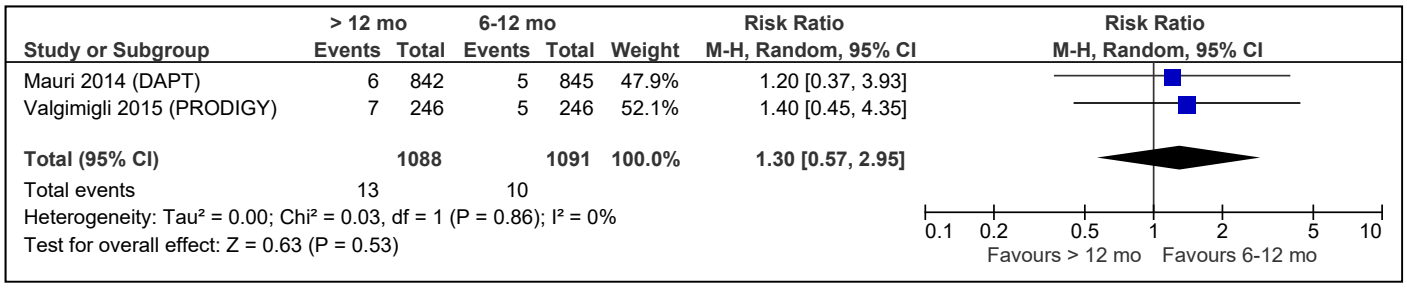


BMS = bare-metal stent; CI = confidence interval; mo = months.

Stroke

Two RCTs[23,24] 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



BMS = bare-metal stent; CI = confidence interval; mo = months.

Stent Thrombosis

Two RCTs[23,24] involving 2,179 participants with a BMS assessed stent thrombosis.

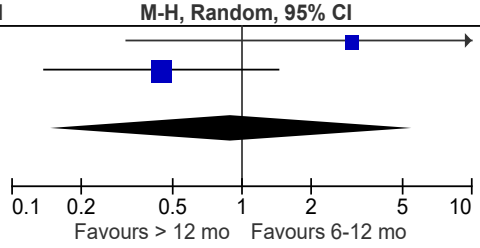
Definite Stent Thrombosis

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

Study or Subgroup	> 12 mo Events	> 12 mo Total	6-12 mo Events	6-12 mo Total	Weight	Risk Ratio M-H, Random, 95% CI
Valgimigli 2015 (PRODIGY)	3	246	1	246	36.7%	3.00 [0.31, 28.64]
Mauri 2014 (DAPT)	4	842	9	845	63.3%	0.45 [0.14, 1.44]
Total (95% CI)		**1088**		**1091**	**100.0%**	**0.90 [0.15, 5.46]**
Total events	7		10			

Heterogeneity: Tau² = 0.98; Chi² = 2.17, df = 1 (P = 0.14); I² = 54%
Test for overall effect: Z = 0.12 (P = 0.91)



BMS = bare-metal stent; CI = confidence interval; mo = months.

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

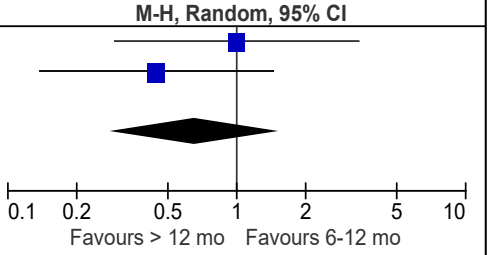
Definite or Probable Stent Thrombosis

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

Study or Subgroup	> 12 mo Events	> 12 mo Total	6-12 mo Events	6-12 mo Total	Weight	Risk Ratio M-H, Random, 95% CI
Valgimigli 2015 (PRODIGY)	5	246	5	246	47.8%	1.00 [0.29, 3.41]
Mauri 2014 (DAPT)	4	842	9	845	52.2%	0.45 [0.14, 1.44]
Total (95% CI)		**1088**		**1091**	**100.0%**	**0.66 [0.28, 1.53]**
Total events	9		14			

Heterogeneity: Tau² = 0.00; Chi² = 0.87, df = 1 (P = 0.35); I² = 0%
Test for overall effect: Z = 0.97 (P = 0.33)



BMS = bare-metal stent; CI = confidence interval; mo = months.

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

Urgent Revascularization

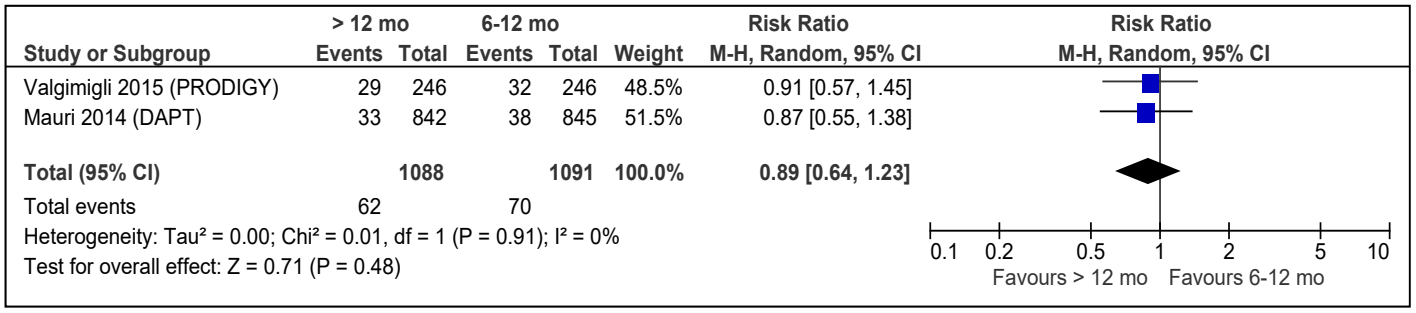
No studies assessed urgent revascularization among participants with an implanted BMS.

MACCE

Two RCTs[23,24] involving 2,179 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



MACCE = major adverse cardiac and cerebrovascular event; CI = confidence interval; mo = months.

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

Gastrointestinal Bleeding

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

Major and Minor Bleeding

None 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 14). 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[24] for participants with a BMS.

Table 14: Relative Risk of Bleeding Among Participants With an Implanted BMS

Trial	Bleeding Classification System*	Number of Events/ Number of Participants	RR (95% CI)
Mauri et al., 2014 (DAPT)[23]	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)

BMS = bare-metal stent; CI = confidence interval; DAPT = dual antiplatelet therapy; mo = months; RR = relative risk.
*Definitions for each bleeding classification system are available in Appendix 10.

Participants With an Implanted Drug-Eluting Stent

Of the included RCTS, five involved only participants with an implanted drug-eluting stent (DES).[22,26,29,30,33] Two additional RCTs[23,24] provided subgroup data for participants with a DES. These seven RCTs form the evidence basis to address this subgroup.

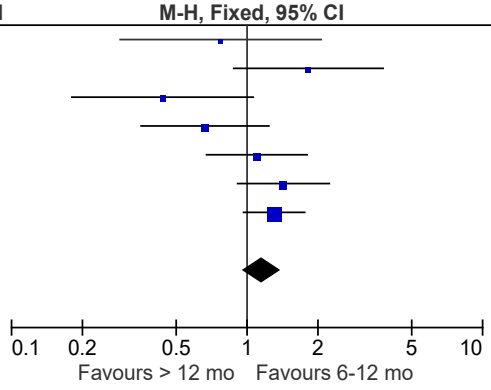
All-Cause Death

Seven RCTs[22-24,26,29,30,33] 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

Study or Subgroup	> 12 mo Events	> 12 mo Total	6-12 mo Events	6-12 mo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Collet 2014 (ARCTIC-INT)	7	645	9	641	4.6%	0.77 [0.29, 2.06]
Gilard 2015 (ITALIC)	20	924	11	926	5.6%	1.82 [0.88, 3.78]
Nakamura 2017 (NIPPON)	7	1653	16	1654	8.2%	0.44 [0.18, 1.06]
Helft 2016 (OPTIDUAL)	16	701	24	697	12.3%	0.66 [0.36, 1.24]
Valgimigli 2015 (PRODIGY)	32	725	29	723	14.8%	1.10 [0.67, 1.80]
Lee 2014 (DES-LATE)	46	2531	32	2514	16.4%	1.43 [0.91, 2.23]
Mauri 2014 (DAPT)	98	5020	74	4941	38.1%	1.30 [0.97, 1.76]
Total (95% CI)		**12199**		**12096**	**100.0%**	**1.15 [0.95, 1.39]**
Total events	226		195			

Heterogeneity: Chi² = 11.32, df = 6 (P = 0.08); I² = 47%
Test for overall effect: Z = 1.43 (P = 0.15)



CI = confidence interval; DES = drug-eluting stent; mo = months.

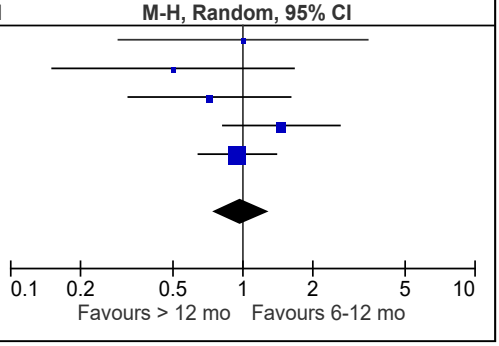
Cardiovascular Death

Five RCTs[22,23,26,29,30] 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

Study or Subgroup	> 12 mo Events	> 12 mo Total	6-12 mo Events	6-12 mo Total	Weight	Risk Ratio M-H, Random, 95% CI
Gilard 2015 (ITALIC)	5	924	5	926	5.2%	1.00 [0.29, 3.45]
Nakamura 2017 (NIPPON)	4	1653	8	1654	5.5%	0.50 [0.15, 1.66]
Helft 2016 (OPTIDUAL)	10	697	14	701	12.3%	0.72 [0.32, 1.61]
Lee 2014 (DES-LATE)	28	2531	19	2514	23.6%	1.46 [0.82, 2.61]
Mauri 2014 (DAPT)	50	5020	52	4941	53.3%	0.95 [0.64, 1.39]
Total (95% CI)		**10825**		**10736**	**100.0%**	**0.98 [0.74, 1.30]**
Total events	97		98			

Heterogeneity: Tau² = 0.00; Chi² = 3.65, df = 4 (P = 0.46); I² = 0%
Test for overall effect: Z = 0.13 (P = 0.90)



CI = confidence interval; DES = drug-eluting stent; mo = months.

Non-cardiovascular Death

Three RCTs[22,23,29] involving 14,666 participants assessed non-cardiovascular death associated with six to 12 months of DAPT compared with extended DAPT (more than 12 months). When pooled, there was a high heterogeneity between trials (I^2 = 79%). Of note, two RCTs (NIPPON[22] and OPTIDUAL[29]) found no significant difference in the risk of non-cardiovascular death, while one RCT (DAPT[23]) 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).

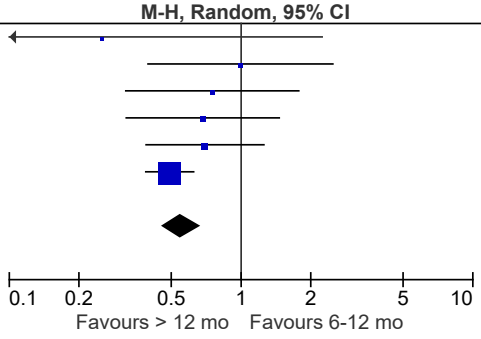
Myocardial Infarction

Six RCTs[22,23,26,29,30,33] involving 22,847 participants with a DES assessed MI. Among those with an implanted DES, DAPT for more than 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

	> 12 mo		6-12 mo			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Nakamura 2017 (NIPPON)	1	1653	4	1654	0.8%	0.25 [0.03, 2.24]	
Collet 2014 (ARCTIC-INT)	9	645	9	641	4.7%	0.99 [0.40, 2.49]	
Gilard 2015 (ITALIC)	9	924	12	926	5.4%	0.75 [0.32, 1.78]	
Helft 2016 (OPTIDUAL)	11	701	16	697	6.9%	0.68 [0.32, 1.46]	
Lee 2014 (DES-LATE)	19	2531	27	2514	11.7%	0.70 [0.39, 1.25]	
Mauri 2014 (DAPT)	99	5020	198	4941	70.4%	0.49 [0.39, 0.62]	
Total (95% CI)		**11474**		**11373**	**100.0%**	**0.55 [0.45, 0.67]**	
Total events	148		266				

Heterogeneity: Tau² = 0.00; Chi² = 4.40, df = 5 (P = 0.49); I² = 0%
Test for overall effect: Z = 5.84 (P < 0.00001)



CI = confidence interval; DES = drug-eluting stent; mo = months.

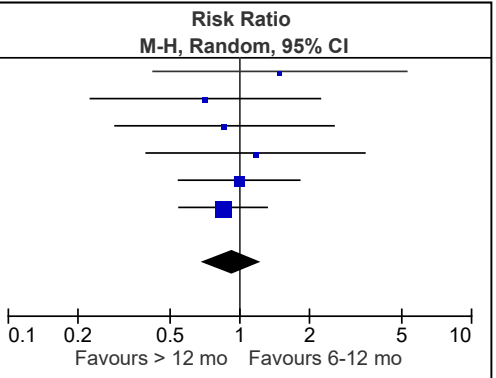
Stroke

Six RCTs[22,23,26,29,30,33] 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

	> 12 mo		6-12 mo			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Collet 2014 (ARCTIC-INT)	6	645	4	641	5.7%	1.49 [0.42, 5.26]	
Helft 2016 (OPTIDUAL)	5	701	7	697	6.9%	0.71 [0.23, 2.23]	
Nakamura 2017 (NIPPON)	6	1653	7	1654	7.6%	0.86 [0.29, 2.55]	
Gilard 2015 (ITALIC)	7	924	6	926	7.7%	1.17 [0.39, 3.47]	
Lee 2014 (DES-LATE)	21	2531	21	2514	24.9%	0.99 [0.54, 1.81]	
Mauri 2014 (DAPT)	37	5020	43	4941	47.2%	0.85 [0.55, 1.31]	
Total (95% CI)		**11474**		**11373**	**100.0%**	**0.92 [0.68, 1.25]**	
Total events	82		88				

Heterogeneity: Tau² = 0.00; Chi² = 1.16, df = 5 (P = 0.95); I² = 0%
Test for overall effect: Z = 0.53 (P = 0.60)



CI = confidence interval; DES = drug-eluting stent; mo = months.

Stent Thrombosis

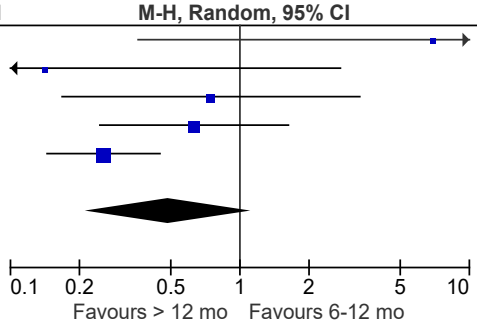
Definite Stent Thrombosis

Five RCT[23,24,26,29,33] 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 DAPT 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

Study or Subgroup	> 12 mo Events	> 12 mo Total	6-12 mo Events	6-12 mo Total	Weight	Risk Ratio M-H, Random, 95% CI
Helft 2016 (OPTIDUAL)	3	701	0	697	6.8%	6.96 [0.36, 134.50]
Collet 2014 (ARCTIC-INT)	0	645	3	641	6.8%	0.14 [0.01, 2.74]
Valgimigli 2015 (PRODIGY)	3	725	4	723	18.7%	0.75 [0.17, 3.33]
Lee 2014 (DES-LATE)	7	2531	11	2514	29.2%	0.63 [0.25, 1.63]
Mauri 2014 (DAPT)	15	5020	58	4941	38.4%	0.25 [0.14, 0.45]
Total (95% CI)		**9622**		**9516**	**100.0%**	**0.49 [0.21, 1.13]**
Total events	28		76			

Heterogeneity: Tau² = 0.39; Chi² = 7.93, df = 4 (P = 0.09); I² = 50%
Test for overall effect: Z = 1.68 (P = 0.09)

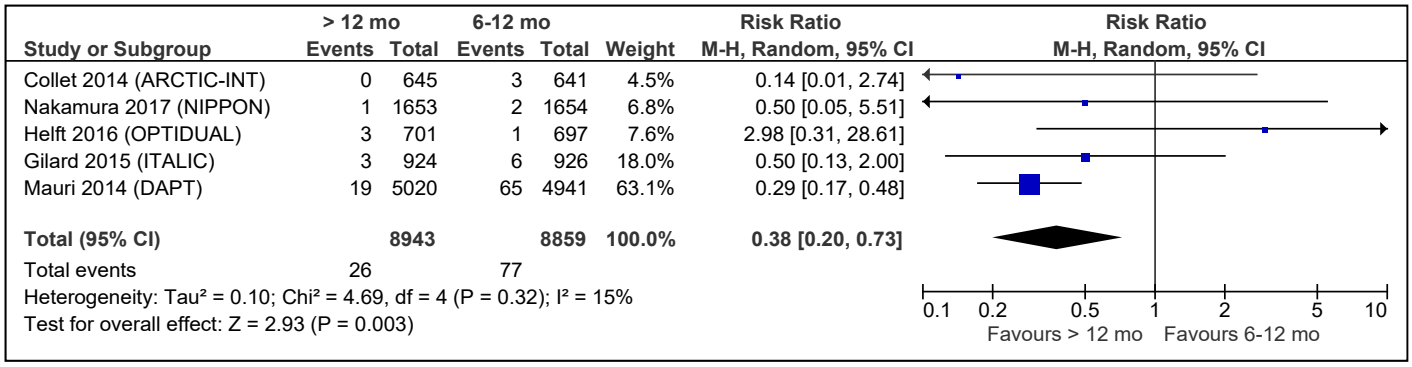


CI = confidence interval; DES = drug-eluting stent; mo = months.

Definite or Probable Stent Thrombosis

Five RCTs[22,23,29,30,33] involving 17,802 participants with a DES assessed definite or probable stent thrombosis. Among those with an implanted DES, DAPT for more than 12 months was associated with a lower risk of definite or probable stent thrombosis compared with DAPT for six to 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

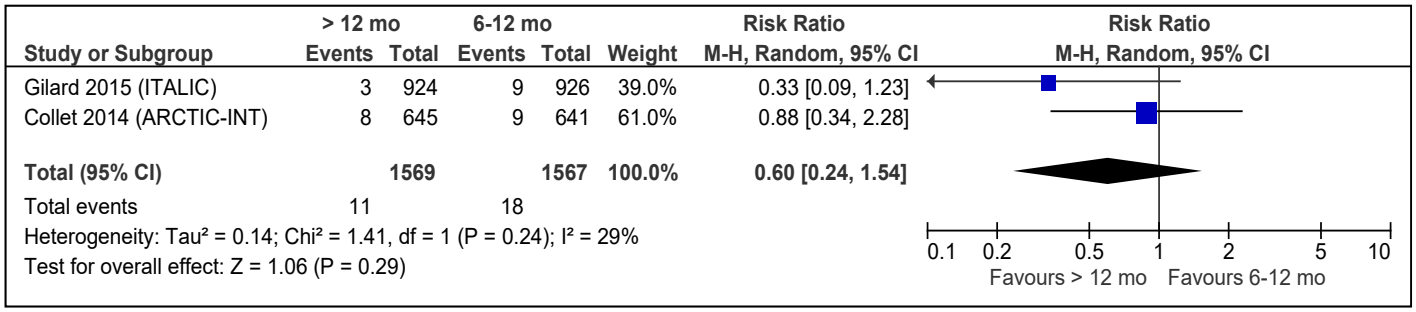


CI = confidence interval; DES = drug-eluting stent; mo = months.

Urgent Revascularization

Two RCTs[30,33] 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



CI = confidence interval; DES = drug-eluting stent; mo = months.

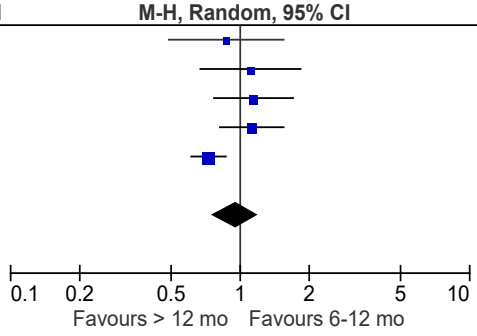
MACCE

Five RCTs[23,24,26,30,33] 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

Study or Subgroup	> 12 mo Events	> 12 mo Total	6-12 mo Events	6-12 mo Total	Weight	Risk Ratio M-H, Random, 95% CI
Collet 2014 (ARCTIC-INT)	21	645	24	641	12.0%	0.87 [0.49, 1.55]
Gilard 2015 (ITALIC)	31	924	28	926	14.3%	1.11 [0.67, 1.83]
Valgimigli 2015 (PRODIGY)	49	723	43	725	18.8%	1.14 [0.77, 1.70]
Lee 2014 (DES-LATE)	78	2531	69	2514	22.9%	1.12 [0.82, 1.55]
Mauri 2014 (DAPT)	211	5020	285	4941	31.9%	0.73 [0.61, 0.87]
Total (95% CI)		**9843**		**9747**	**100.0%**	**0.95 [0.75, 1.21]**
Total events	390		449			

Heterogeneity: Tau² = 0.04; Chi² = 9.14, df = 4 (P = 0.06); I² = 56%
Test for overall effect: Z = 0.42 (P = 0.68)



CI = confidence interval; DES = drug-eluting stent; mo = months.

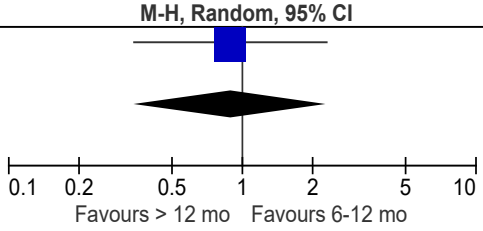
Gastrointestinal Bleeding

Gastrointestinal bleeding was reported by one RCT[22] involving 3,773 participants with a DES, with no significant difference in risk between participants who received DAPT for six or 18 months (Figure 30).

Figure 30: Relative Risk of Gastrointestinal Bleeding Among Participants With an Implanted DES

Study or Subgroup	> 12 mo Events	> 12 mo Total	6-12 mo Events	6-12 mo Total	Weight	Risk Ratio M-H, Random, 95% CI
Nakamura 2017 (NIPPON)	8	1887	9	1886	100.0%	0.89 [0.34, 2.30]
Total (95% CI)		**1887**		**1886**	**100.0%**	**0.89 [0.34, 2.30]**
Total events	8		9			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.24 (P = 0.81)



CI = confidence interval; DES = drug-eluting stent; mo = months.

Major and Minor Bleeding

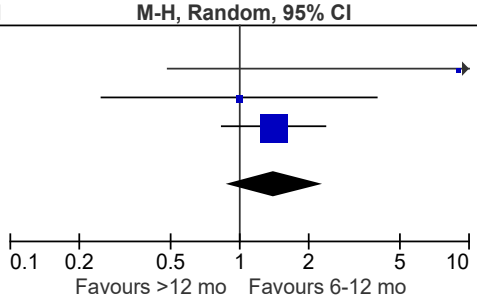
TIMI Major Bleeding

TIMI major bleeds were assessed in four RCTs[26,29,30,33] involving 9,579 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

Study or Subgroup	> 12 mo Events	> 12 mo Total	6-12 mo Events	6-12 mo Total	Weight	Risk Ratio M-H, Random, 95% CI
Collet 2014 (ARCTIC-INT)	0	645	0	641		Not estimable
Gilard 2015 (ITALIC)	4	924	0	926	2.7%	9.02 [0.49, 167.29]
Helft 2016 (OPTIDUAL)	4	701	4	697	12.1%	0.99 [0.25, 3.96]
Lee 2014 (DES-LATE)	34	2531	24	2514	85.2%	1.41 [0.84, 2.37]
Total (95% CI)		**4801**		**4778**	**100.0%**	**1.42 [0.88, 2.29]**
Total events	42		28			

Heterogeneity: Tau² = 0.00; Chi² = 1.83, df = 2 (P = 0.40); I² = 0%
Test for overall effect: Z = 1.43 (P = 0.15)



CI = confidence interval; DES = drug-eluting stent; mo = months.

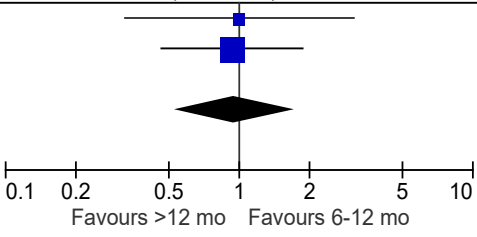
TIMI Minor Bleeding

TIMI minor bleeds were assessed in two RCTs[29,30] 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 32).

Figure 32: Relative Risk of TIMI Minor Bleeding Among Participants With an Implanted DES

Study or Subgroup	> 12 mo Events	> 12 mo Total	6-12 mo Events	6-12 mo Total	Weight	Risk Ratio M-H, Random, 95% CI
Gilard 2015 (ITALIC)	6	924	6	926	27.6%	1.00 [0.32, 3.10]
Helft 2016 (OPTIDUAL)	15	701	16	697	72.4%	0.93 [0.46, 1.87]
Total (95% CI)		**1625**		**1623**	**100.0%**	**0.95 [0.53, 1.72]**
Total events	21		22			

Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.91); I² = 0%
Test for overall effect: Z = 0.17 (P = 0.87)



CI = confidence interval; DES = drug-eluting stent; mo = months.

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 15). There was no statistically significant difference in risk between DAPT for more than 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 15: Relative Risk of Bleeding, Assessed by Use of Alternative Bleeding Classification Systems, Among Participants With an Implanted DES

Bleeding Classification System[a]	Trial	Number of Events/ Number Randomized	RR (95% CI); I^2
BARC			
Type 2	DAPT[23]	12 mo: 72/4,941 30 mo: 145/5020	1.39 (0.53, 3.62); 66%
	OPTIDUAL[29]	12 mo: 7/697 48 mo: 5/701	
Type 3	DAPT[23]	12 mo: 68/4,941 30 mo: 122/5,020	1.29 (0.78, 2.12); 51%
	OPTIDUAL[29]	12 mo: 14/697 48 mo: 13/701	
	NIPPON[22]	6 mo: 11/1,654[b] 18 mo: 10/1,653[b]	
Type 5	DAPT[23]	12 mo: 4/4,941 30 mo: 7/5,020	2.08 (0.71, 6.07); 0%
	OPTIDUAL[29]	12 mo: 0/697 48 mo: 1/701	
	NIPPON[22]	6 mo: 0/1,654[b] 18 mo: 2/1,653[b]	
Type 2,3,5	DAPT[23]	12 mo: 137/4,941 30 mo: 263/5,020	1.38 (0.67,2.85); 80%
	OPTIDUAL[29]	12 mo: 20/697 48 mo: 18/701	
GUSTO			
Moderate	DAPT[23]	12 mo: 48/4,941 30 mo: 81/5,020	**1.62 (1.16, 2.25); 0%**
	OPTIDUAL[29]	12 mo: 8/697 48 mo: 11/701	
Severe	DAPT[23]	12 mo: 26/4,941 30 mo: 38/5,020	1.35 (0.84, 2.16); 0%
	OPTIDUAL[29]	12 mo: 4/697 48 mo: 3/701	
Moderate or severe	DAPT[23]	12 mo: 73/4941 30 mo: 119/5020	**1.53 (1.17, 2.00); 0%**
	OPTIDUAL[29]	12 mo: 12/697 48 mo: 13/701	
Replace			
Major	NIPPON[22]	6 mo: 11/1,654[b] 18 mo: 22/1,653[b]	2.00 (0.97, 4.11); NA
ISTH			
Major	OPTIDUAL[29]	12 mo: 14/697 48 mo: 14/701	0.99 (0.48, 2.07); NA
Minor	OPTIDUAL[29]	12 mo: 7/697 48 mo: 6/701	0.85 (0.29, 2.52); NA

Bleeding Classification System[a]	Trial	Number of Events/ Number Randomized	RR (95% CI); I^2
STEEPLE			
Major	ARCTIC-INT[33]	12 mo: 1/641 18-30 mo: 7/645	6.96 (0.86, 56.38); NA
Minor	ARCTIC-INT[33]	12 mo: 2/641 18–30 mo: 5/645	2.48 (0.48, 12.76); NA

CI = confidence interval; DES = drug-eluting stent; mo = months; NA = not applicable; RR = relative risk.
[a] Definitions for each bleeding classification system are available in Appendix 10.
[b] The number randomized who reached the six-month landmark without experiencing the primary outcome.

Participants With a Prior MI

Two RCTs[23,30] reported outcomes data among participants with a prior MI. The DAPT trial[23] 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.

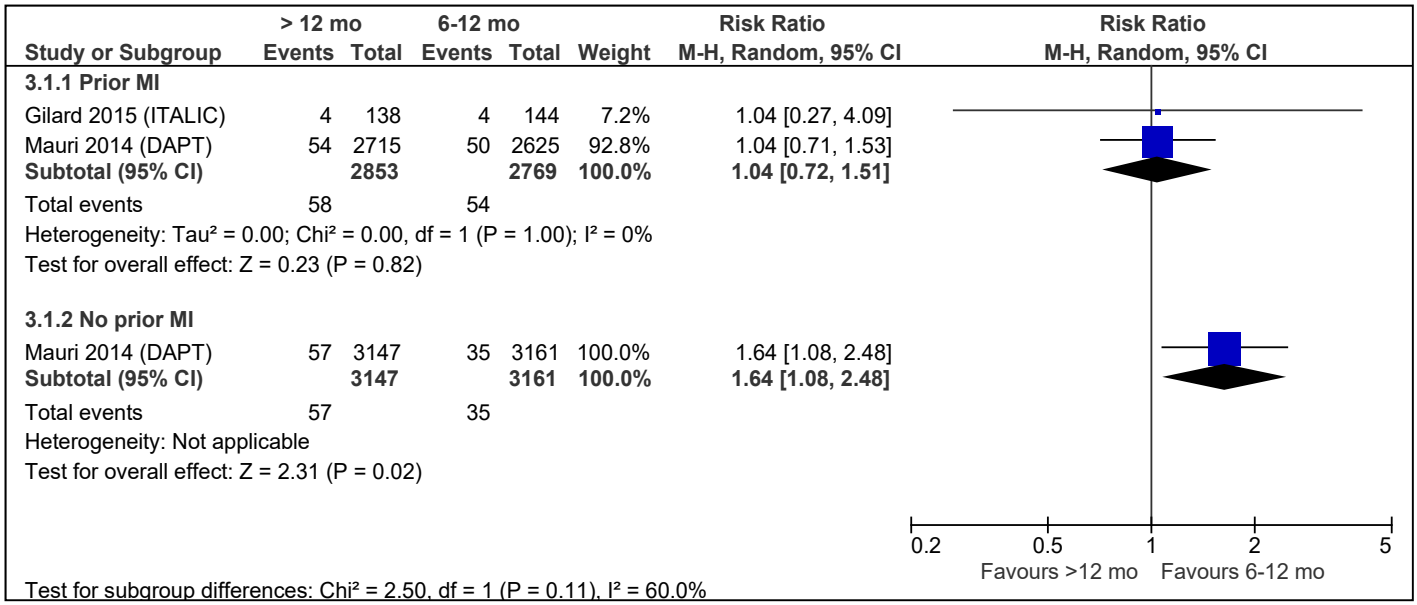
All-Cause Death

Two RCTs[23,30] involving 5,622 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 more than12 months (RR 1.04, 95% CI, 0.72 to 1.51) (Figure 33).

One RCT[23] involving 6,308 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).

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

Figure 33: Relative Risk of All-Cause Death Among Participants With or Without a History of Myocardial Infarction

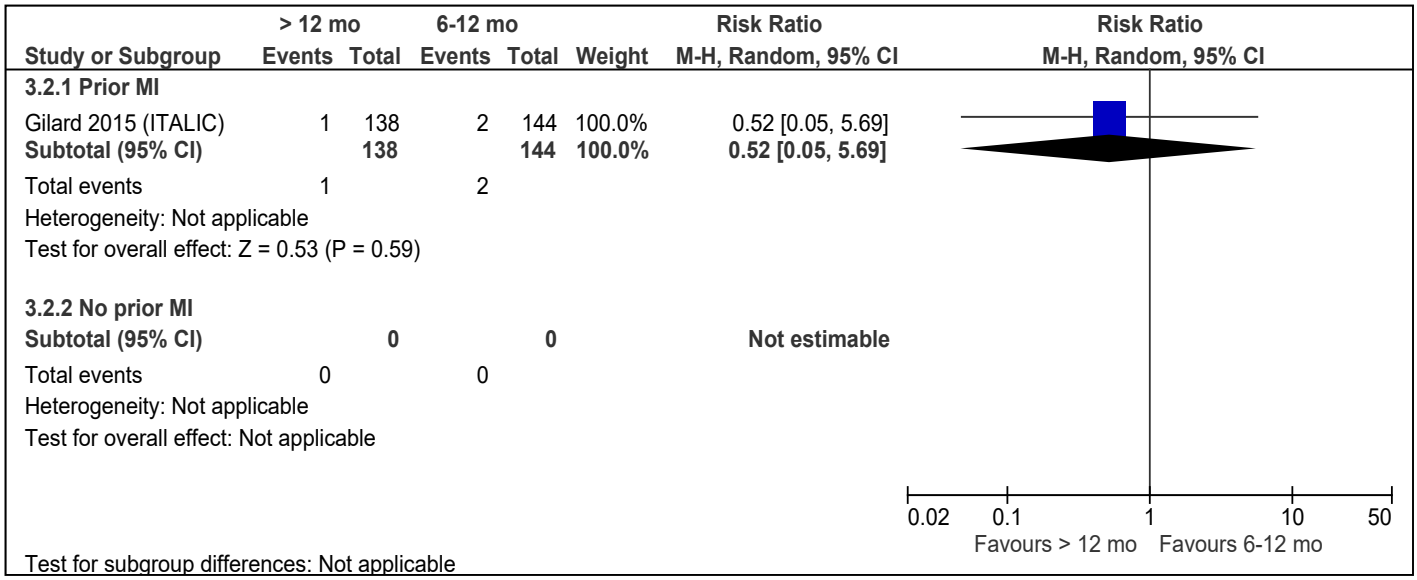


CI = confidence interval; mo = months.

Cardiovascular Death

One RCT[30] involving 282 participants with a history of MI reported no significant difference in the risk of cardiovascular death between six to 12 months and more than 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



CI = confidence interval; mo = months.

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

Non-cardiovascular Death

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

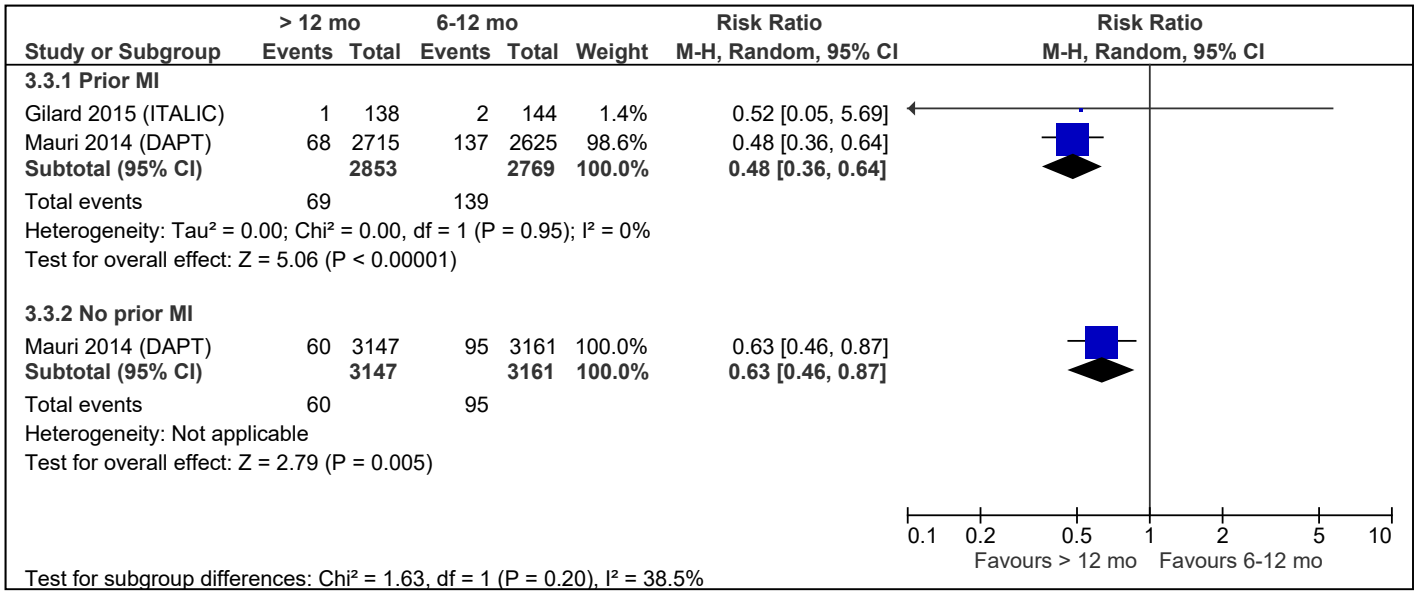
Myocardial Infarction

Two RCTs[23,30] involving 5,622 participants reported the new occurrence of MI. Among participants with a prior MI, participants who received DAPT for more than 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[23] involving 6,308 participants with no history of MI reported a significantly 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



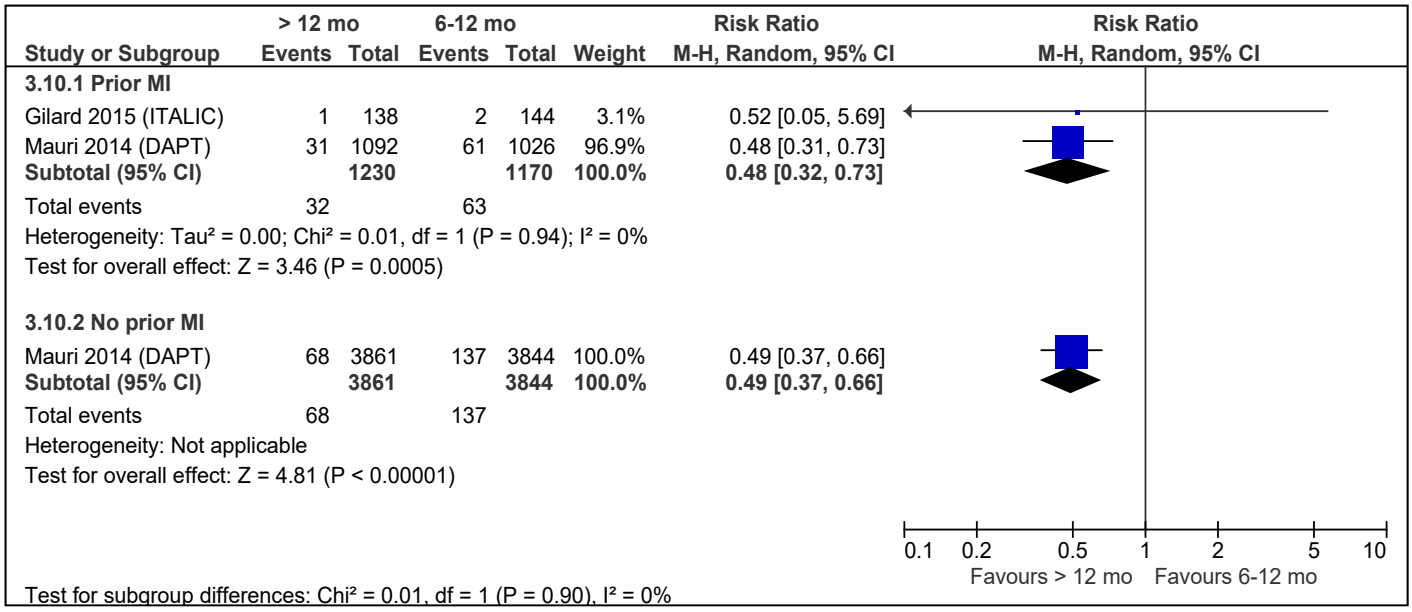
CI = confidence interval; mo = months.

Drug-Eluting Stents

Two RCTs[23,30] assessed MI 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 new 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



CI = confidence interval; mo = months.

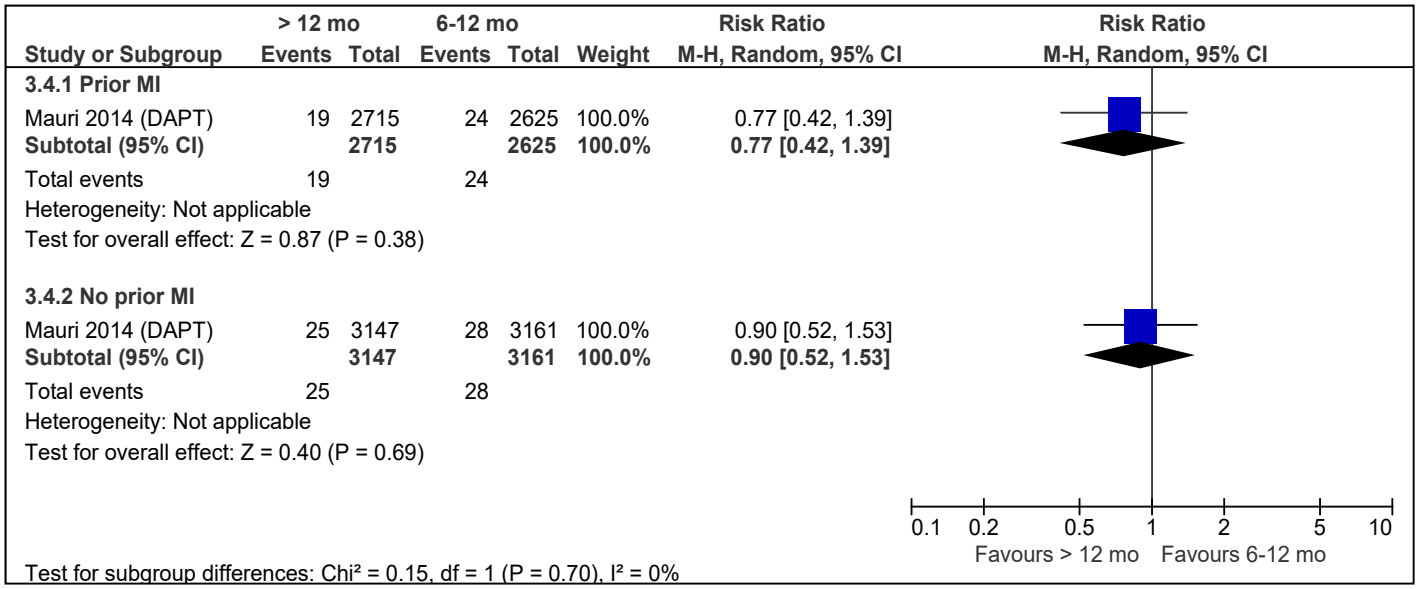
Bare-Metal Stents

No studies assessed MI among participants with or without a history of MI with an implanted bare-metal stent (BMS).

Stroke

One RCT[23] 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



CI = confidence interval; mo = months.

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

Stent Thrombosis

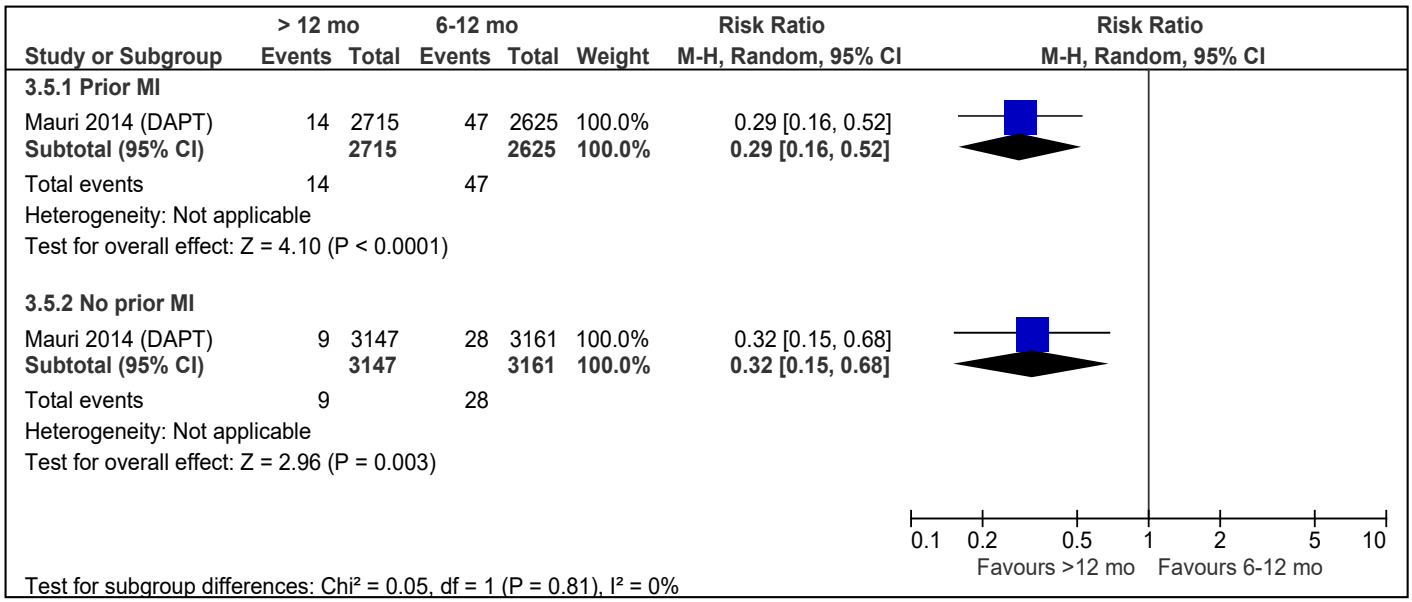
Definite

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

Definite or Probable Stent Thrombosis

One RCT[23] 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



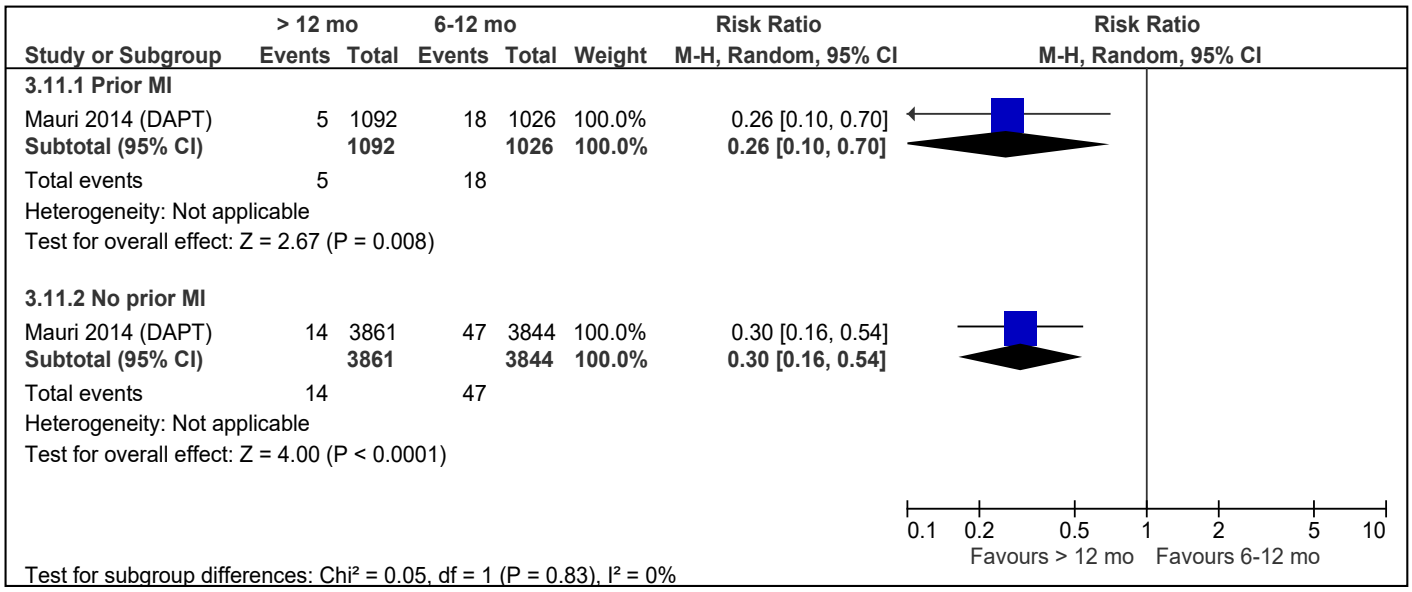
CI = confidence interval; mo = months.

Drug-Eluting Stents

One RCT[23] 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



CI = confidence interval; mo = months.

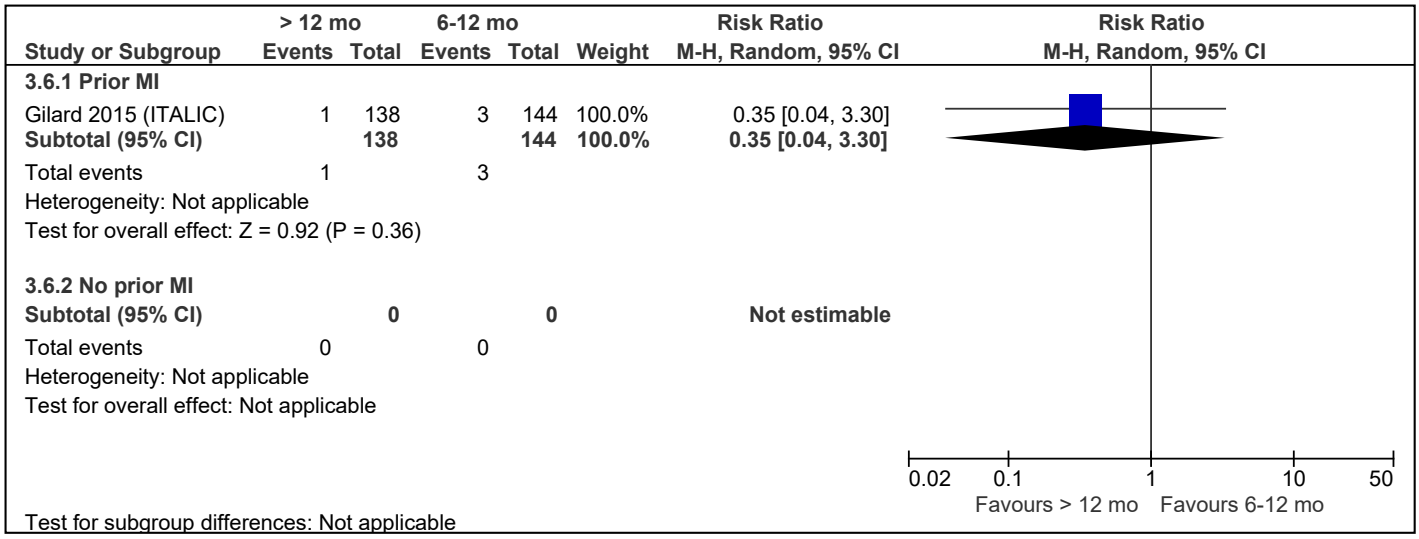
Bare-Metal Stents

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

Urgent Revascularization

One RCT[30] involving 282 participants with a history of MI reported no significant difference in the risk of urgent revascularization between six to 12 months and more than 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. As well, no studies assessed urgent revascularization among participants with or without a history of MI by stent type (BMS or DES).

Figure 40: Relative Risk of Urgent Revascularization Among Participants With or Without a History of Myocardial Infarction

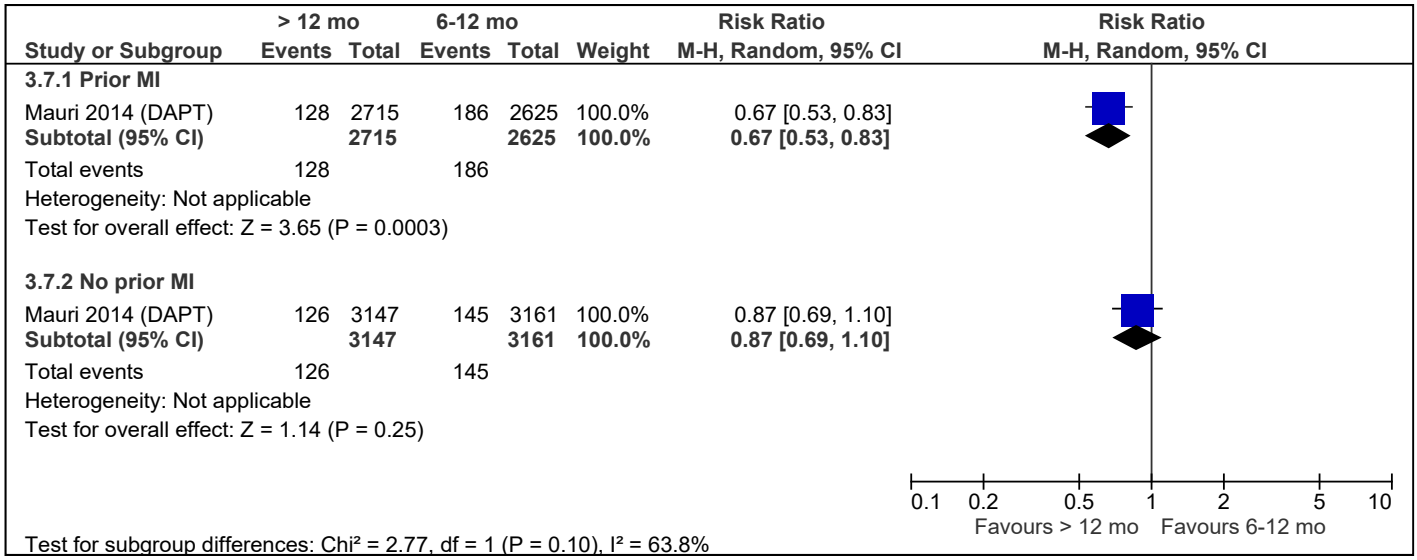


CI = confidence interval; mo = months.

MACCE

One RCT[23] 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



CI = confidence interval; mo = months.

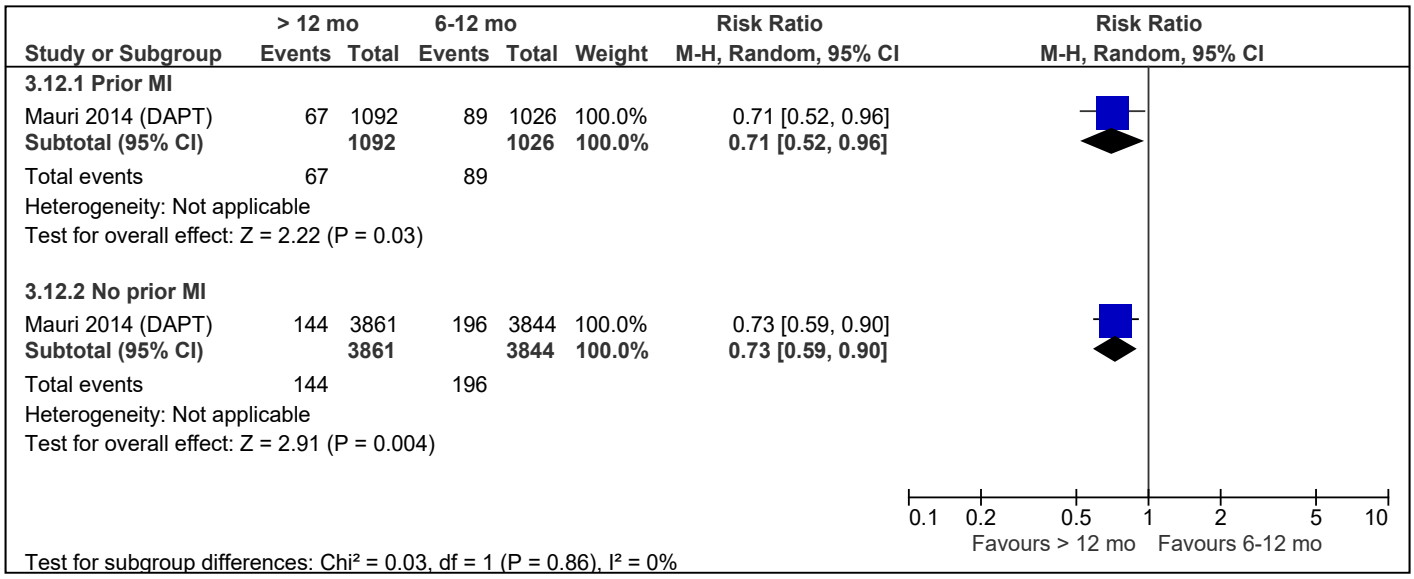
Using an alternative definition of MACCE (all-cause death, MI, stroke, urgent revascularization, major bleeding), one RCT (ITALIC[30]) reported a non-significant difference in risk between DAPT for six to 12 months or DAPT for more than 12 months (RR 0.38, 95% CI, 0.12 to 1.16) among those with a history of MI. No data were reported for participants without a history of MI.

Drug-Eluting Stents

One RCT[23] 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



CI = confidence interval; mo = months.

Bare-Metal Stents

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

Gastrointestinal Bleeding

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

Major and Minor Bleeding

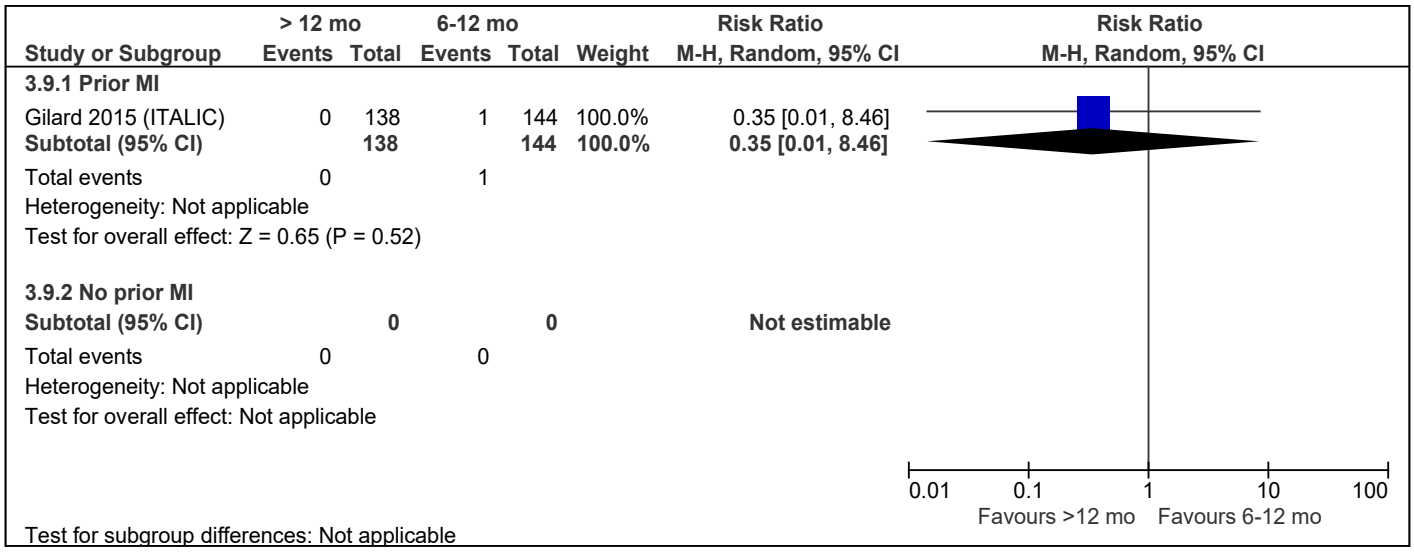
TIMI Major Bleeding

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

TIMI Minor Bleeding

One RCT[30] 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[30]) 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



CI = confidence interval; mo = months.

Other Bleeding

Among participants with either a DES or a 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 either with or without a history of MI (Table 16). There was no difference in GUSTO severe bleeding between DAPT durations for either those with or those 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 16).

Table 16: 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[a]**	**Number of Events/ Number of Participants**	**RR (95% CI)**	**Number of Events/ Number of Participants**	**RR (95% CI)**
Mauri et al., 2014 (DAPT)[23b]	GUSTO moderate or severe	12 mo: 29/2,625 30 mo: 57/2,715	**1.89 (1.21, 2.95)**	12 mo: 54/3,161 30 mo: 85/3,147	**1.58 (1.13, 2.22)**
	GUSTO moderate	12 mo: 16/2,625 30 mo: 38/2,715	**2.30 (1.28, 4.11)**	12 mo: 38/3,161 30 mo: 57/3,147	**1.51 (1.00, 2.26)**
	GUSTO severe	12 mo: 13/2,625 30 mo: 16/2,715	1.19 (0.57, 2.47)	12 mo: 19/3,161 30 mo: 28/3,147	1.48 (0.83, 2.64)
	BARC type 2, 3 or 5	12 mo: 55/2,625 30 mo: 117/2,715	**2.06 (1.50, 2.82)**	12 mo: 101/3,161 30 mo: 192/ 3,147	**1.91 (1.51, 2.42)**
Mauri et al., 2014 (DAPT) [23c]	GUSTO moderate or severe	12 mo: 18/1,026 30 mo: 24/1092	1.25 (0.68, 2.29)	12 mo: 55/3,844 30 mo: 95/3861	**1.72 (1.24, 2.39)**

BARC = Bleeding Academic Research Consortium; CI = confidence interval; DAPT = dual antiplatelet therapy; MI = myocardial infarction; mo = months; RR = relative risk.
[a] Definitions for each bleeding classification system are available in Appendix 10.
[b] Participants with either an implanted drug-eluting stent or a bare-metal stent.
[c] Participants with an implanted drug-eluting stent.

Participants With ACS at Presentation

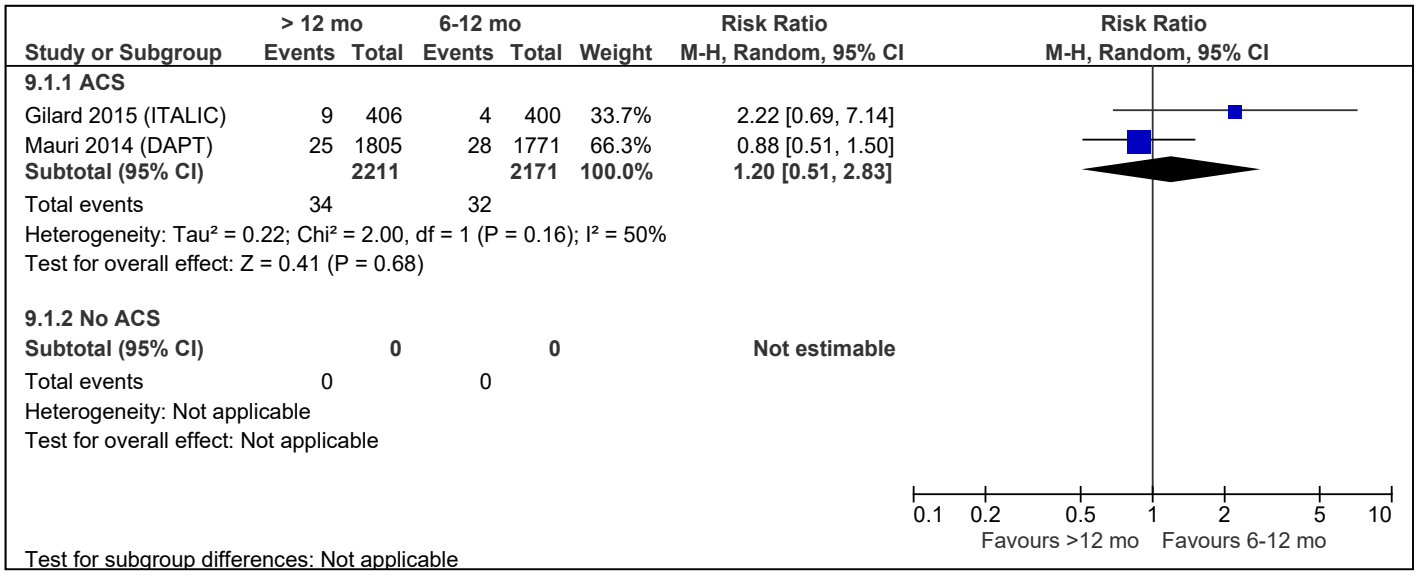
In total, six RCTs[22-24,26,30,33] reported data for participants with ACS. Of these, five trials[22,24,26,30,33] categorized participants as having "ACS" or "No ACS," while one RCT (DAPT) reported data for participants with an index MI (occurring within 72 hours before the index PCI).[23]

Although the PRODIGY trial[24] 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 six to 12 months after PCI). We therefore did not pool data from PRODIGY with data from the other trials because of differences in the reporting period.

All-Cause Death

Two RCTs[23,30] involving 4,382 participants with ACS reported all-cause death, with no significant difference in the risk of all-cause death between DAPT more than12 months or six to 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

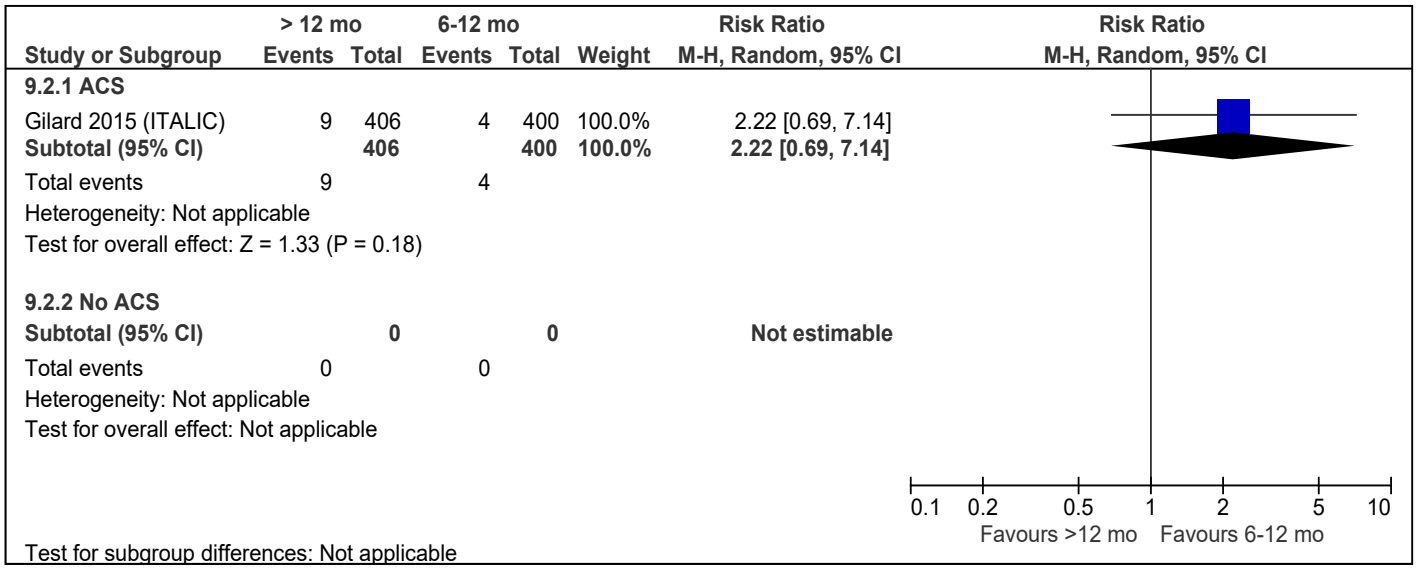


ACS = acute coronary syndrome; CI = confidence interval; mo = months.

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 more than 12 months and six to 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 Drug-Eluting Stent, by Acute Coronary Syndrome Status



ACS = acute coronary syndrome; CI = confidence interval; mo = months.

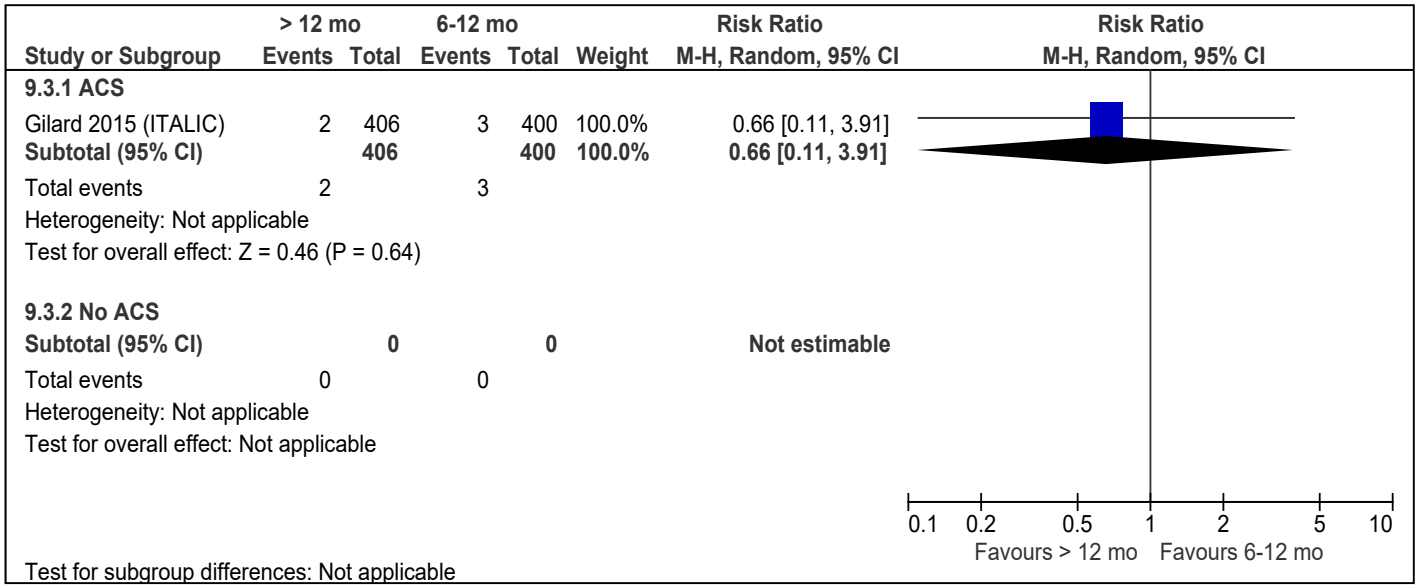
Bare-Metal Stents

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

Cardiovascular Death

One RCT[30] involving 806 participants with ACS assessed cardiovascular death, with no significant difference in risk between DAPT for more than12 months or six to 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 Acute Coronary Syndrome Status



ACS = acute coronary syndrome; CI = confidence interval; mo = months.

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.

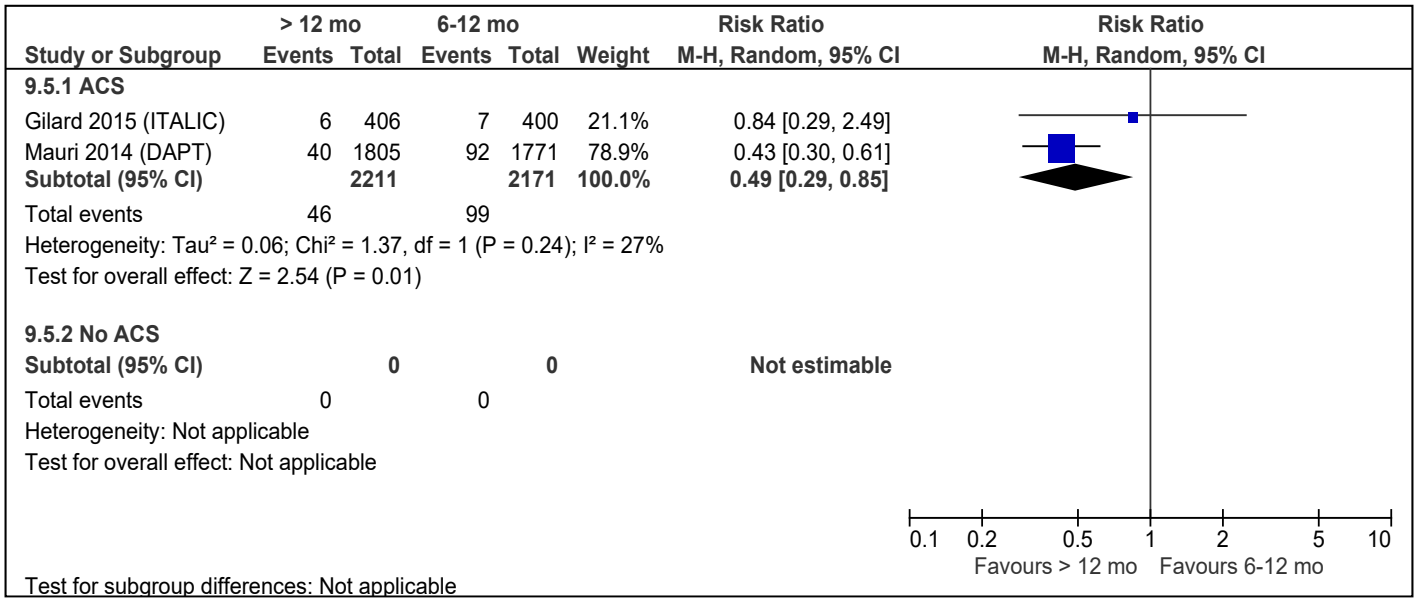
Non-cardiovascular Death

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

Myocardial Infarction

Two RCTs[23,30] 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 Acute Coronary Syndrome Status

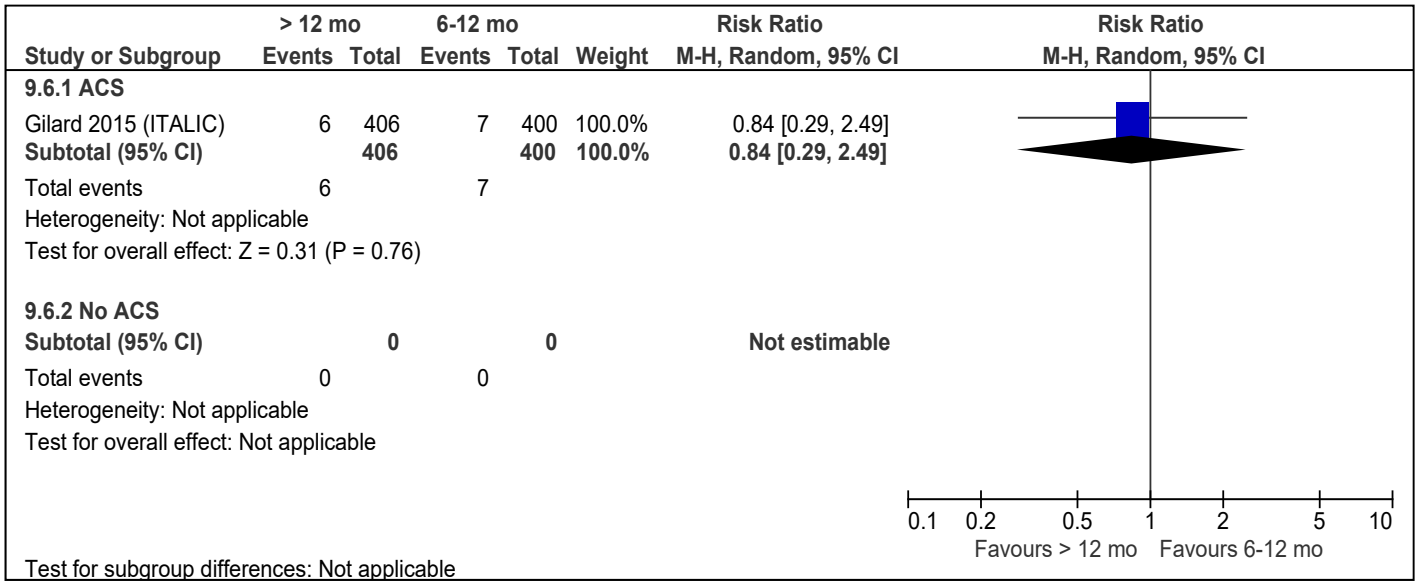


ACS = acute coronary syndrome; CI = confidence interval; mo = months.

Drug-Eluting Stents

Among participants with ACS and with a DES, there was no difference in the risk of MI 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 Drug-Eluting Stent by Acute Coronary Syndrome Status



ACS = acute coronary syndrome; CI = confidence interval; mo = months.

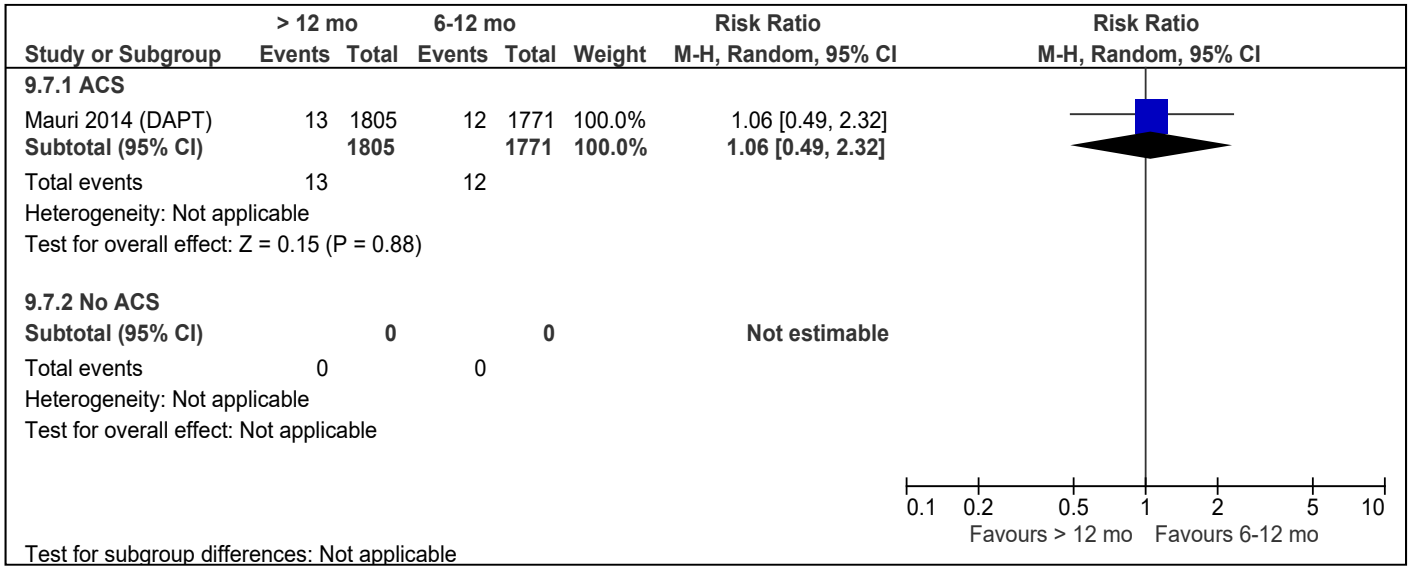
Bare-Metal Stents

No studies assessed MI among participants with an implanted BMS by ACS status.

Stroke

One RCT[23] 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 more than 12 months or six to 12 months (RR 1.06, 95% CI, 0.49 to 2.32) (Figure 49). No data were reported for participants without ACS. As well, no studies assessed stroke among participants with or without ACS by stent type (BMS or DES).

Figure 49: Relative Risk of Stroke by Acute Coronary Syndrome Status



ACS = acute coronary syndrome; CI = confidence interval; mo = months.

Stent Thrombosis

Definite Stent Thrombosis

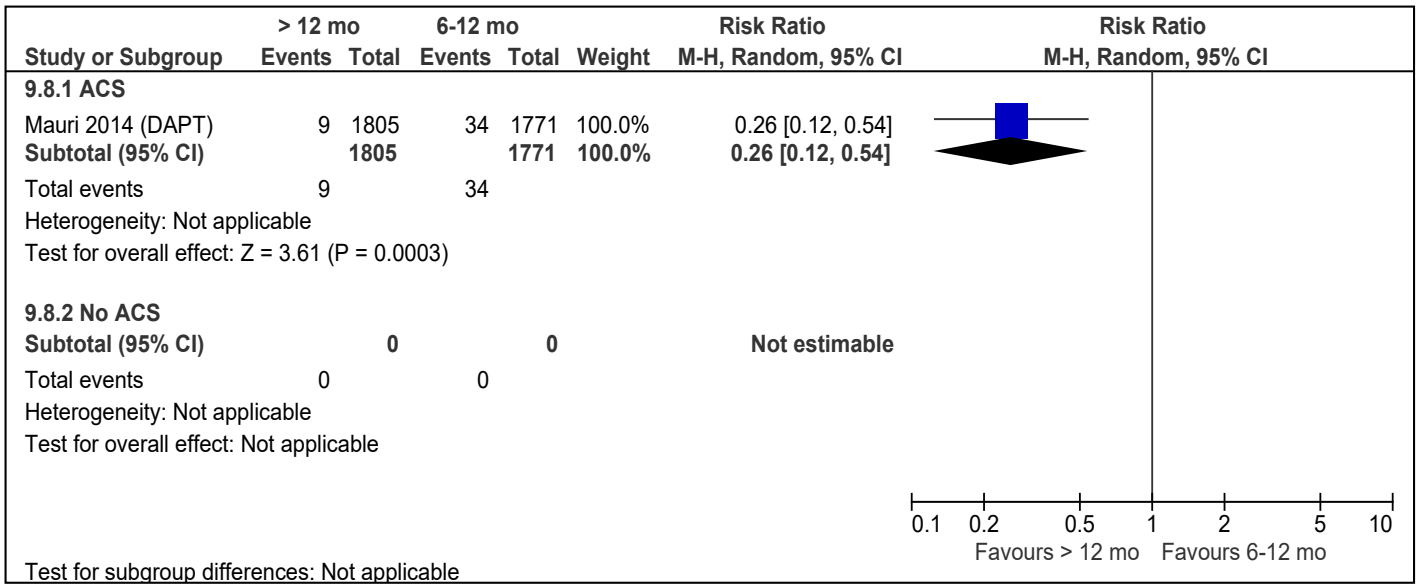
No studies assessed definite stent thrombosis by ACS status.

Definite or Probable Stent Thrombosis

One RCT[23] involving 3,576 participants with ACS assessed definite or probable stent thrombosis. Among those with ACS at presentation, those who received DAPT for more than 12 months were at 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, 0.12 to 0.54) (

Figure 50). No data were reported for participants without ACS. As well, no studies assessed stroke among participants with or without ACS by stent type (BMS or DES).

Figure 50: Relative Risk of Definite or Probable Stent Thrombosis by Acute Coronary Syndrome Status



ACS = acute coronary syndrome; CI = confidence interval; mo = months.

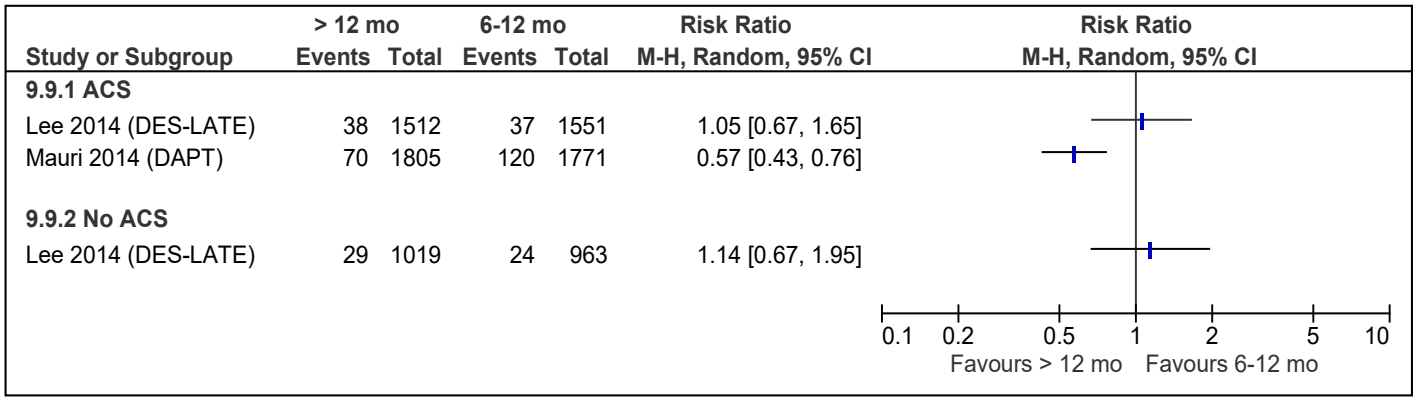
Urgent Revascularization

One RCT[30] 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 (six months, n = 400) (RR 0.08, 95% CI, 0.00 to 1.34). No data were available for participants without ACS.

MACCE

Two RCTs[23,26] 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 to 1.95) (Figure 51).

Figure 51: Relative Risk of MACCE by Acute Coronary Syndrome Status



ACS = acute coronary syndrome; CI = confidence interval; mo = months.

An additional three RCTs[22,30,33] assessed MACCE using 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 17).

Table 17: MACCE Reported by Use of Alternative Definitions by Acute Coronary Syndrome Status

Trial		Acute Coronary Syndrome		No Acute Coronary Syndrome	
Author, Date,Trial	**MACCE Definition**	**Number of Events/ Number of Participants**	**RR (95% CI)**	**Number of Events/ Number of Participants**	**RR (95%,CI)**
Nakamura et al., 2017 (NIPPON) [22]	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: 20/1,128 18 mo: 17/1104	0.87 (0.46, 1.65)
Gilard et al., 2015 (ITALIC)[30]	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 et al., 2014 (ARCTIC-INT)[33]	All-cause death, myocardial infarction, stent thrombosis, stroke, urgent revascularization	12 mo: 8/167 18 to 30 mo: 6/156	0.80 (0.28, 2.26)	12 mo: 19/457 18 mo: 18/479	0.90 (0.48, 1.70)

CI = confidence interval; MACCE = major adverse cardiac and cerebrovascular event; MI = myocardial infarction; mo = months; NR = not reported; RR = relative risk.

Gastrointestinal Bleeding

No studies assessed gastrointestinal bleeding by ACS status.

Major and Minor Bleeding

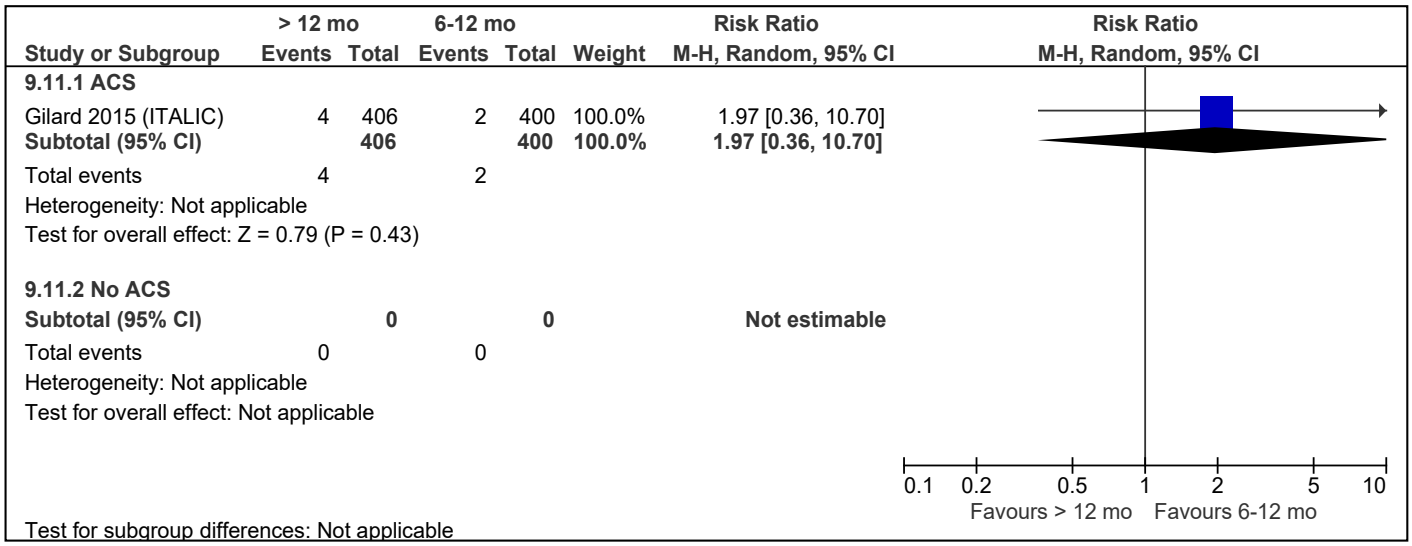
TIMI Major Bleeding

No studies assessed TIMI major bleeding by ACS status.

TIMI Minor Bleeding

One RCT[30] 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 more than 12 months or six to 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 Acute Coronary Syndrome Status



ACS = acute coronary syndrome; CI = confidence interval; mo = months.

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 18). No data were available for participants without ACS.

Table 18: Bleeding Reported by Use of Alternative Classification Systems by Acute Coronary Syndrome Status

		ACS		No ACS	
Trial	**Bleeding Classification System[a]**	**Number of Events/ Number of Participants**	**RR (95%CI)**	**Number of Events/ Number of Participants**	**RR (95%CI)**
Mauri et al., 2014 (DAPT)[23b]	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 type 2,3,5	12 mo: 37/1771 30 mo: 78/1805	**2.07 (1.41, 3.04)**	NR	—

ACS = acute coronary syndrome; CI = confidence interval; mo = months; NR = not reported; RR = relative risk.
[a] Definitions for each bleeding classification system are available in Appendix 10.
[b] Participants with either an implanted drug-eluting stent or bare-metal stent.

Participants With Diabetes

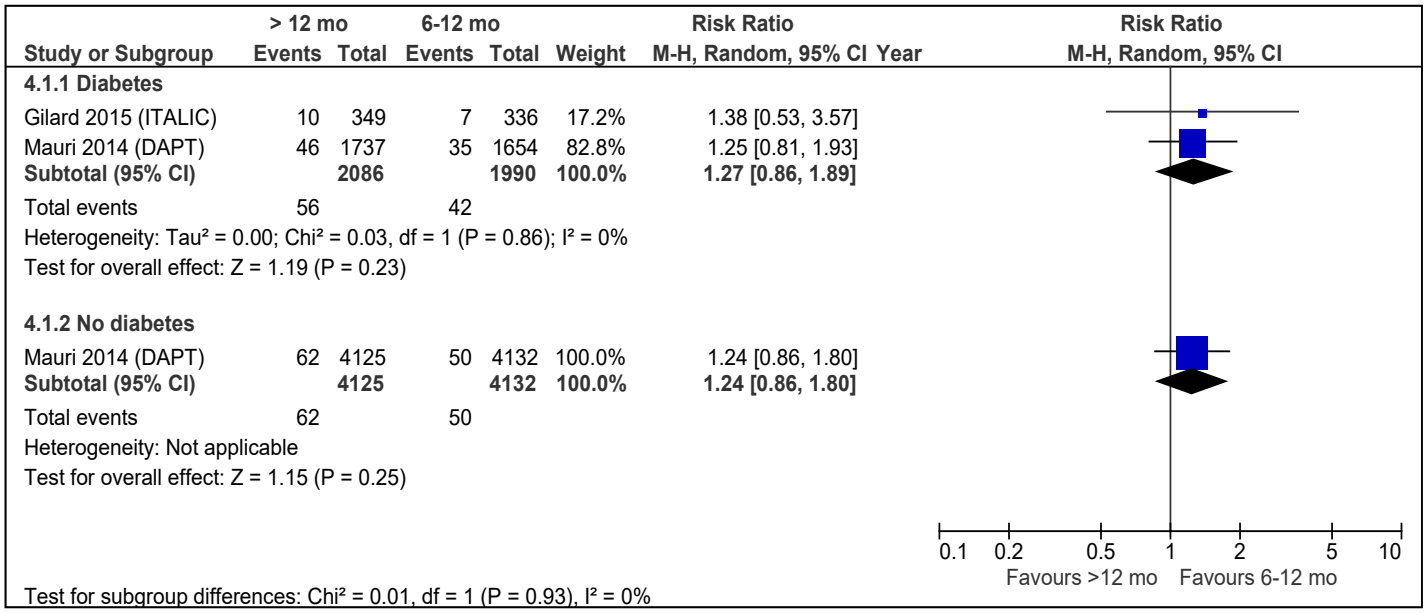
In total, two RCTs[23,30] reported outcomes data among participants with diabetes. Both enrolled participants with either implanted DES or BMS. Neither study differentiated between type 1 and type 2 diabetes.

All-Cause Death

Two RCTs[23,30] reported all-cause death among 4,076 participants with diabetes, with no significant difference in the risk between DAPT for more than 12 months or DAPT for six to 12 months (RR 1.27, 95% CI, 0.86 to 1.89) (Figure 53).

One RCT[23] 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



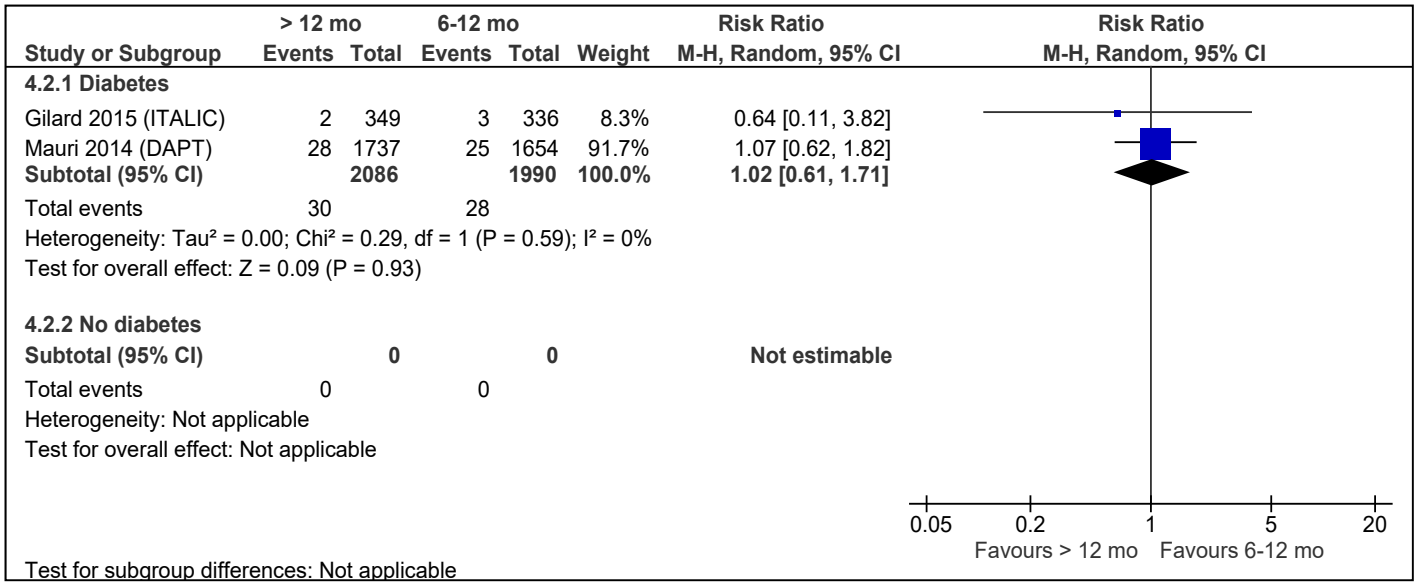
CI = confidence interval; mo = months.

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

Cardiovascular Death

Two RCTs[23,30] 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



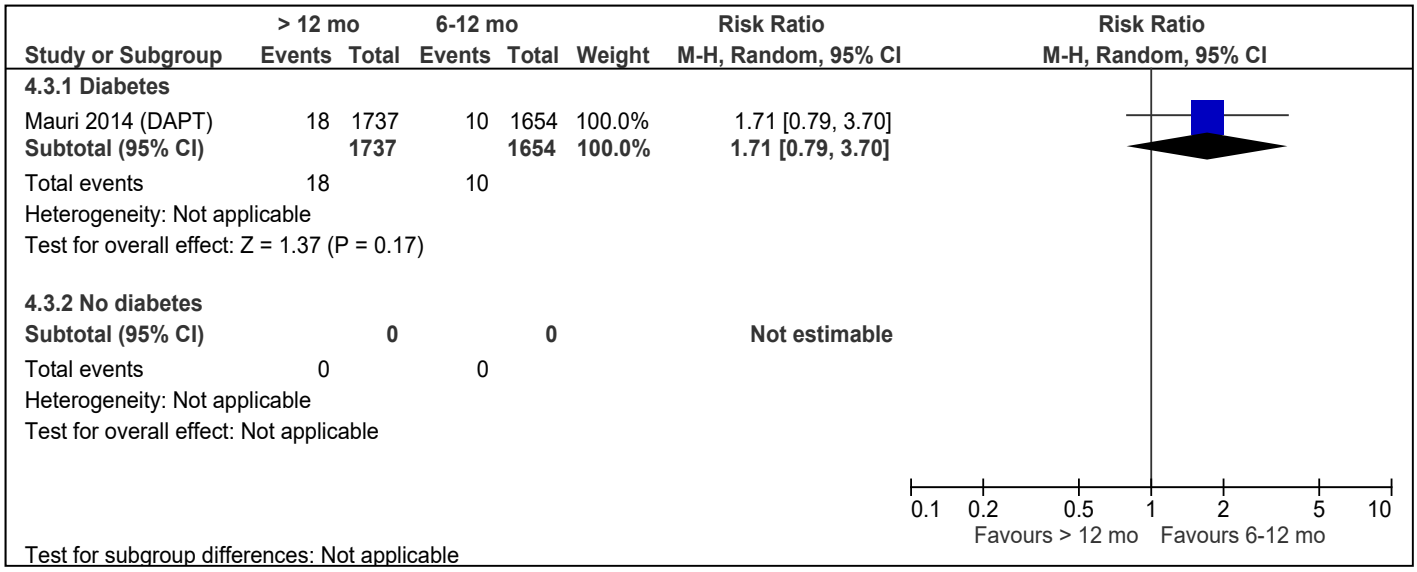
CI = confidence interval; mo = months.

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

Non-cardiovascular Death

One RCT[23] reported non-cardiovascular death among 3,391 participants with diabetes, with no significant difference in the risk between DAPT for more than 12 months or DAPT for six to 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



CI = confidence interval; mo = months.

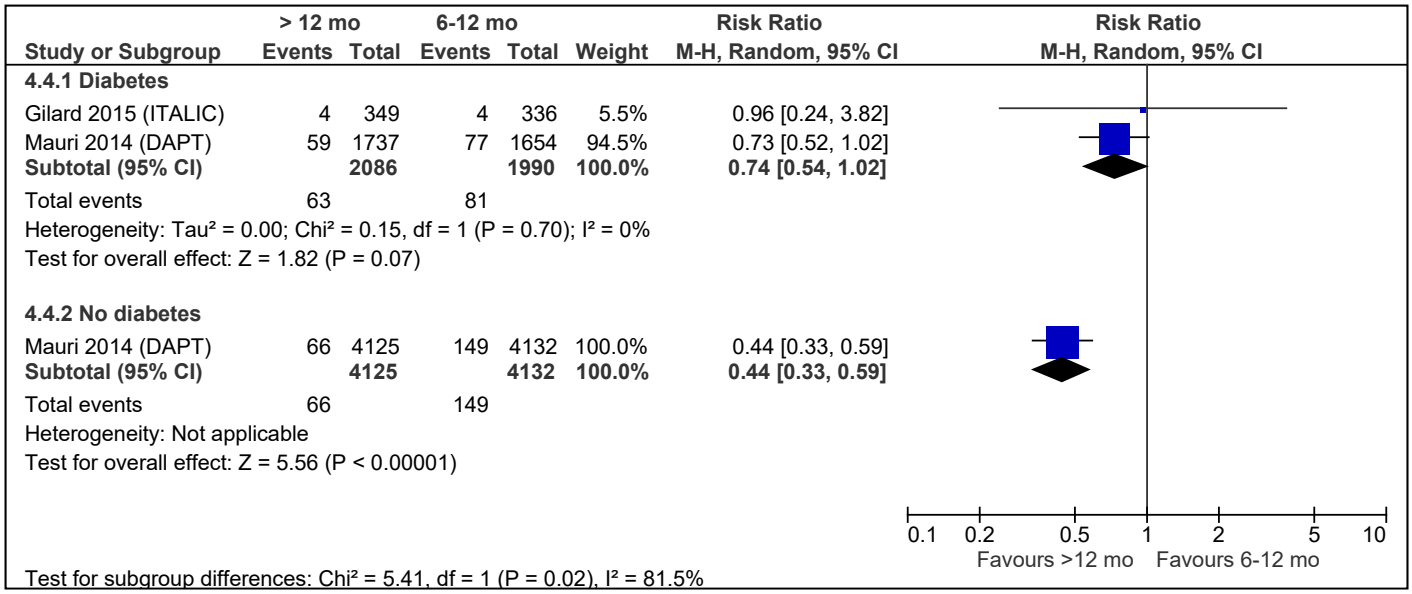
No studies assessed non-cardiovascular death among participants with or without diabetes by stent type (BMS or DES).

Myocardial Infarction

Two RCTs[23,30] reported MI among 4,076 participants with diabetes, with no significant difference in the risk between DAPT for more than 12 months or DAPT for six to 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[23] involving 8,257 participants without diabetes reported a significantly lower risk of MI among participants who received DAPT for more than 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



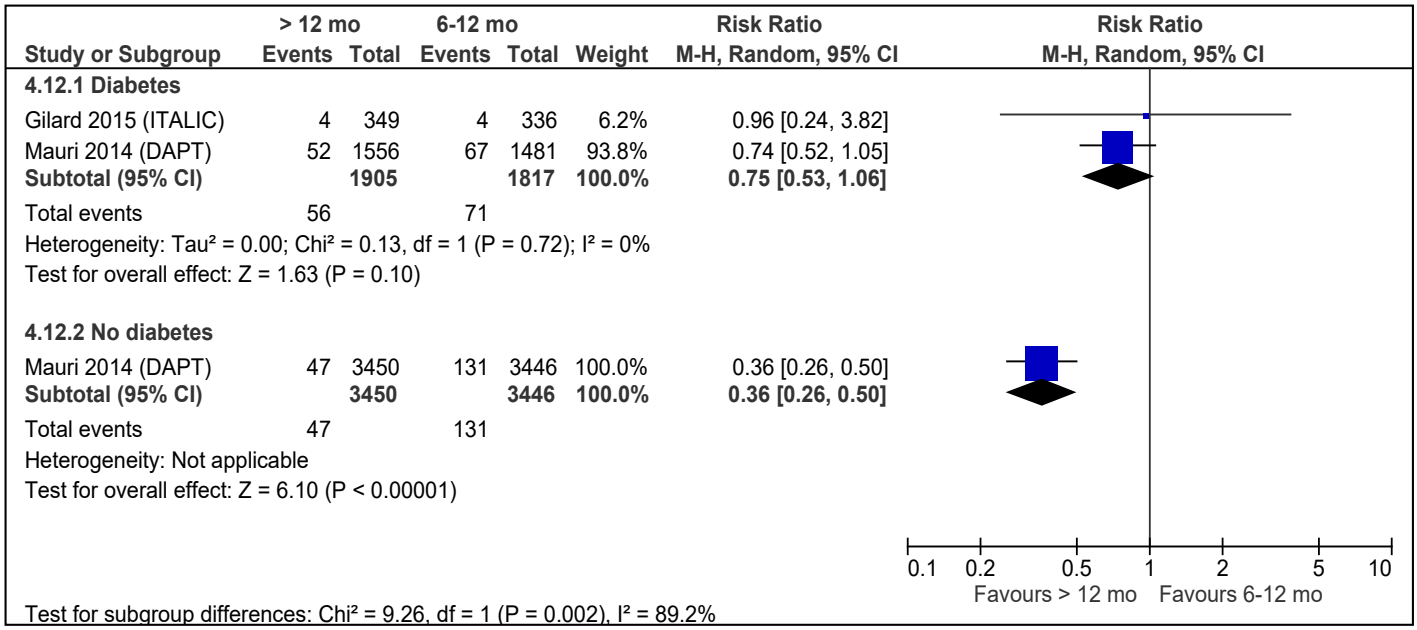
CI = confidence interval; mo = months.

Drug-Eluting Stents

Two RCTs[23,30] 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 for more than12 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 more than 12 months compared with six to 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



CI = confidence interval; mo = months.

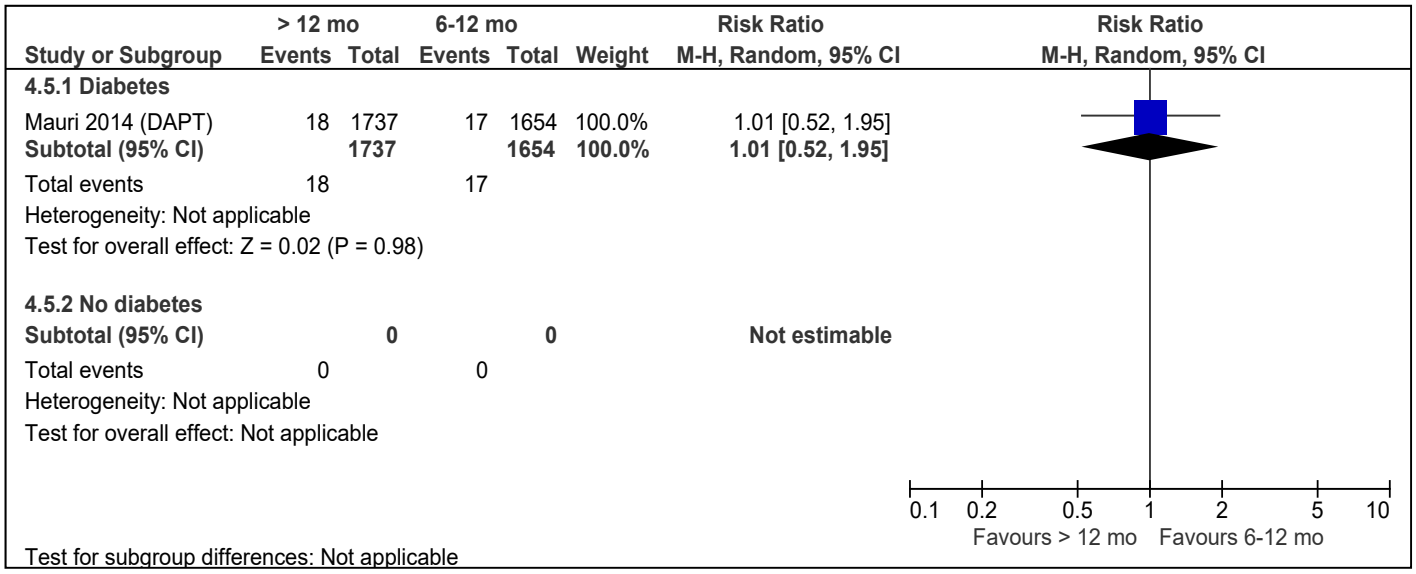
Bare-Metal Stents

No studies assessed MI among participants with or without diabetes with an implanted BMS.

Stroke

One RCT[23] reported stroke among 3,391 participants with diabetes, with no significant difference in the risk of stroke between DAPT for more than 12 months or DAPT for six to 12 months (RR 1.01, 95% CI, 0.52 to 1.95) (Figure 58). No studies reported stroke among participants without diabetes. In addition, no studies assessed stroke among participants with or without diabetes by stent type (BMS or DES).

Figure 58: Relative Risk of Stroke Among Participants With or Without Diabetes



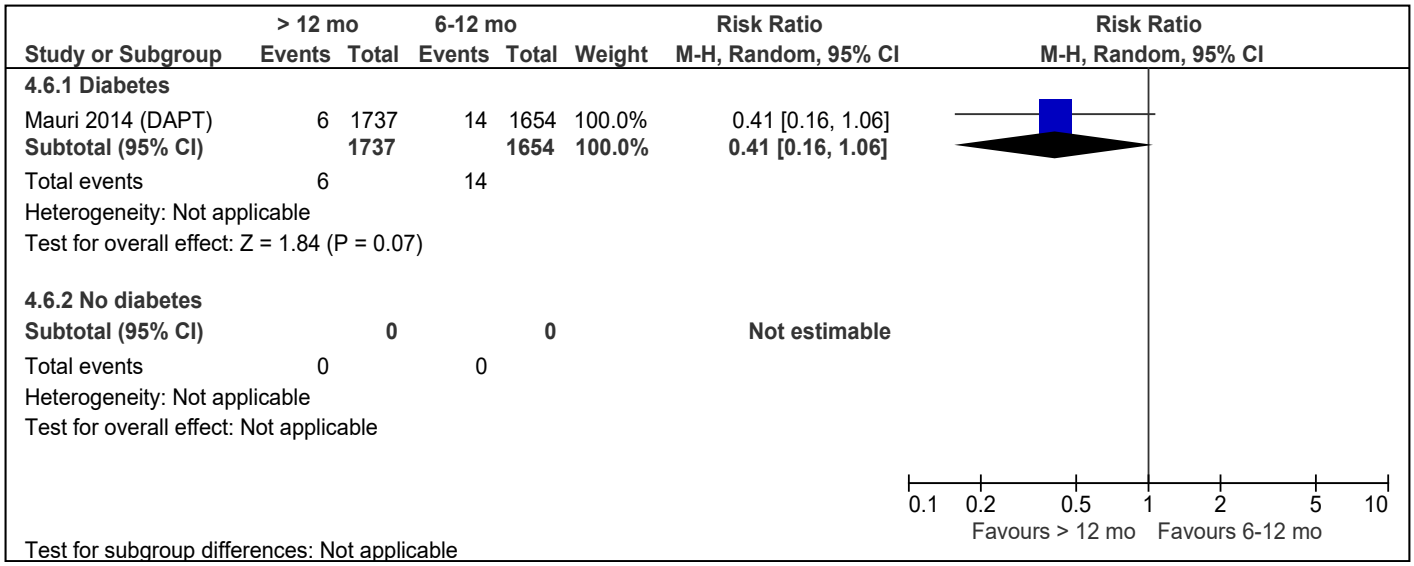
CI = confidence interval; mo = months.

Stent Thrombosis

Definite Stent Thrombosis

One RCT[23] reported definite stent thrombosis among 3,391 participants with diabetes, with no significant difference in the risk of definite stent thrombosis between DAPT for more than 12 months or for six to 12 months (RR 0.41, 95% CI, 0.16 to 1.06) (Figure 59). No studies reported definite stent thrombosis among participants without diabetes. Also, no studies assessed definite stent thrombosis among participants with or without diabetes by stent type (BMS or DES).

Figure 59: Relative Risk of Definite Stent Thrombosis Among Participants With or Without Diabetes



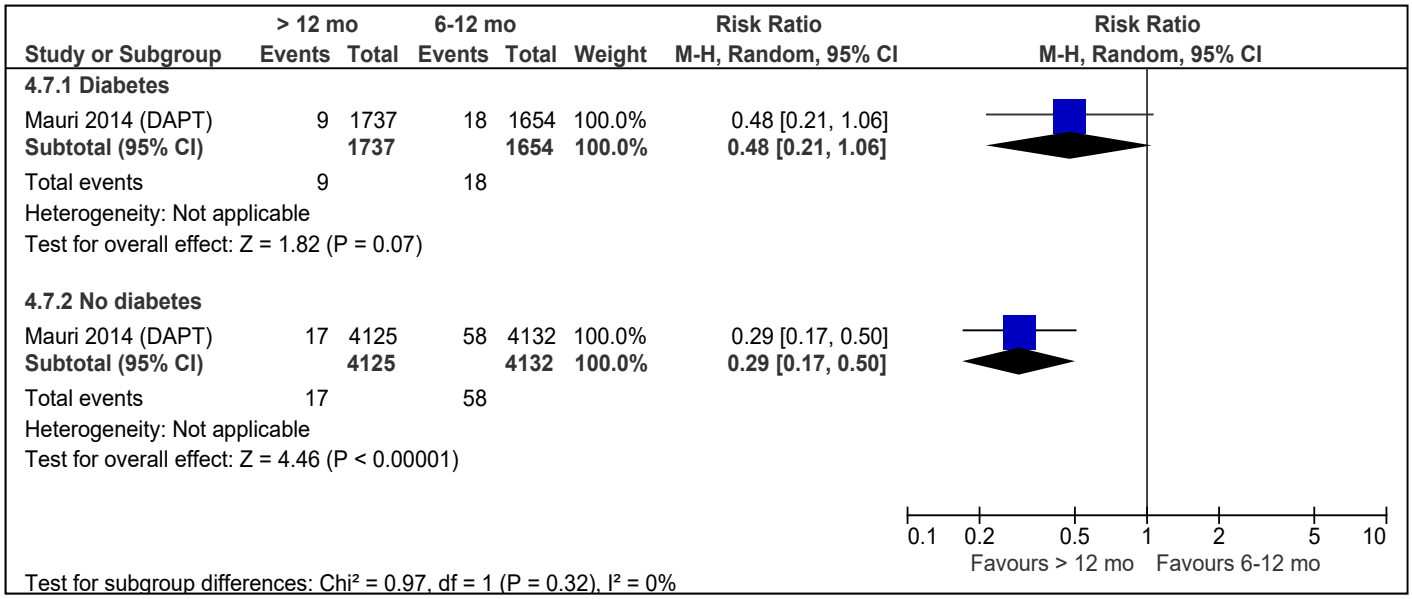
CI = confidence interval; mo = months.

Definite or Probable Stent Thrombosis

One RCT[23] reported no significant difference between DAPT durations 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[23] reported a significantly lower risk of definite or probable stent thrombosis among participants who received DAPT for more than 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



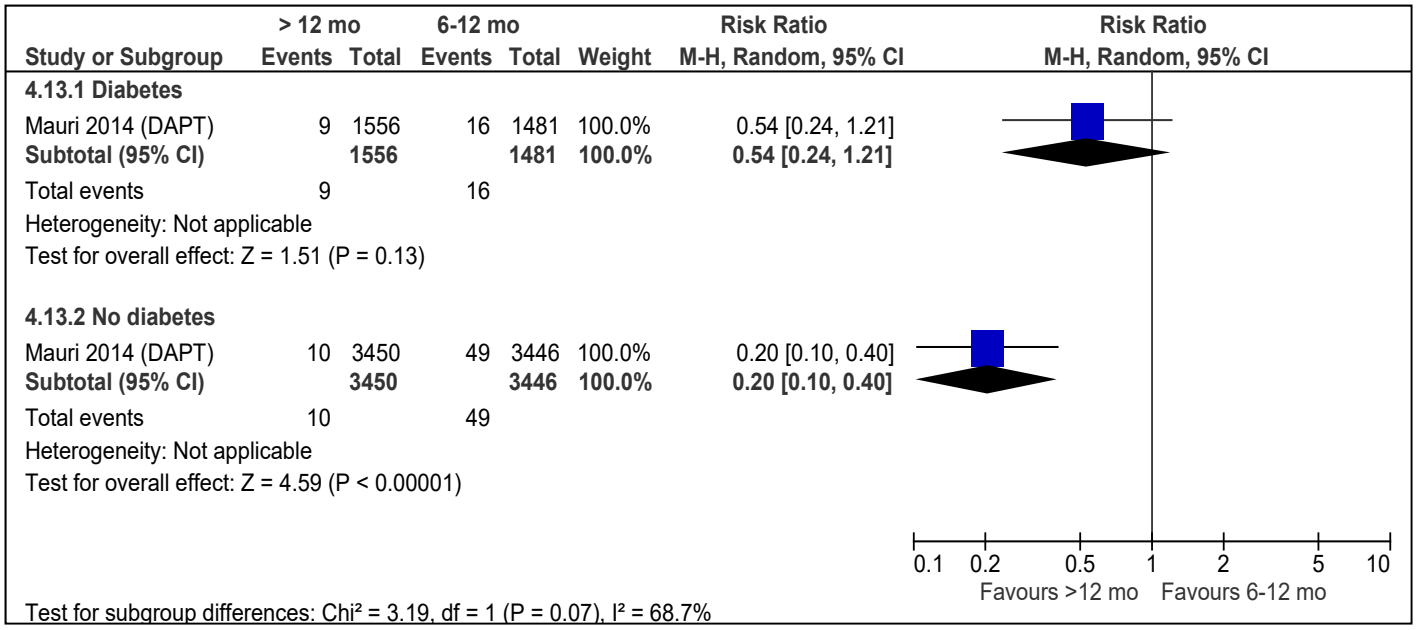
CI = confidence interval; mo = months.

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 six to 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 more than 12 months compared with six to 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



CI = confidence interval; mo = months.

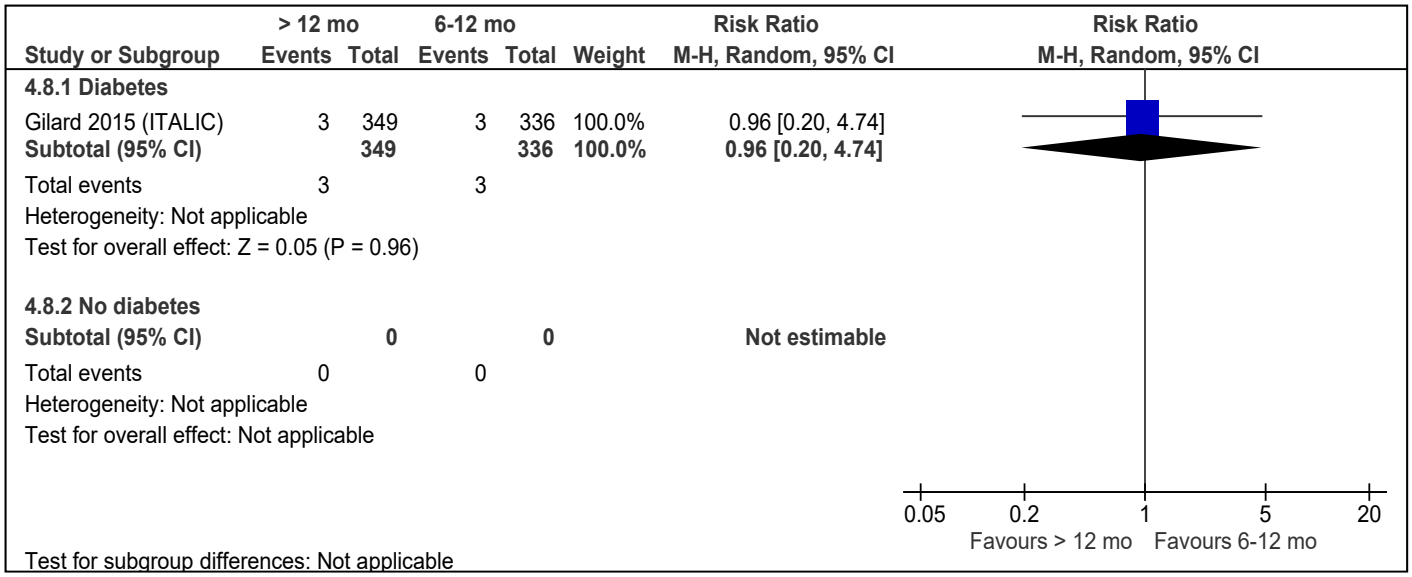
Bare-Metal Stents

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

Urgent Revascularization

One RCT[30] involving 685 participants with diabetes reported no significant difference in the risk of urgent revascularization between more than 12 months of DAPT and six to 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. In addition, no studies assessed urgent revascularization among participants with or without diabetes by stent type (BMS or DES).

Figure 62: Relative Risk of Urgent Revascularization Among Participants With or Without Diabetes

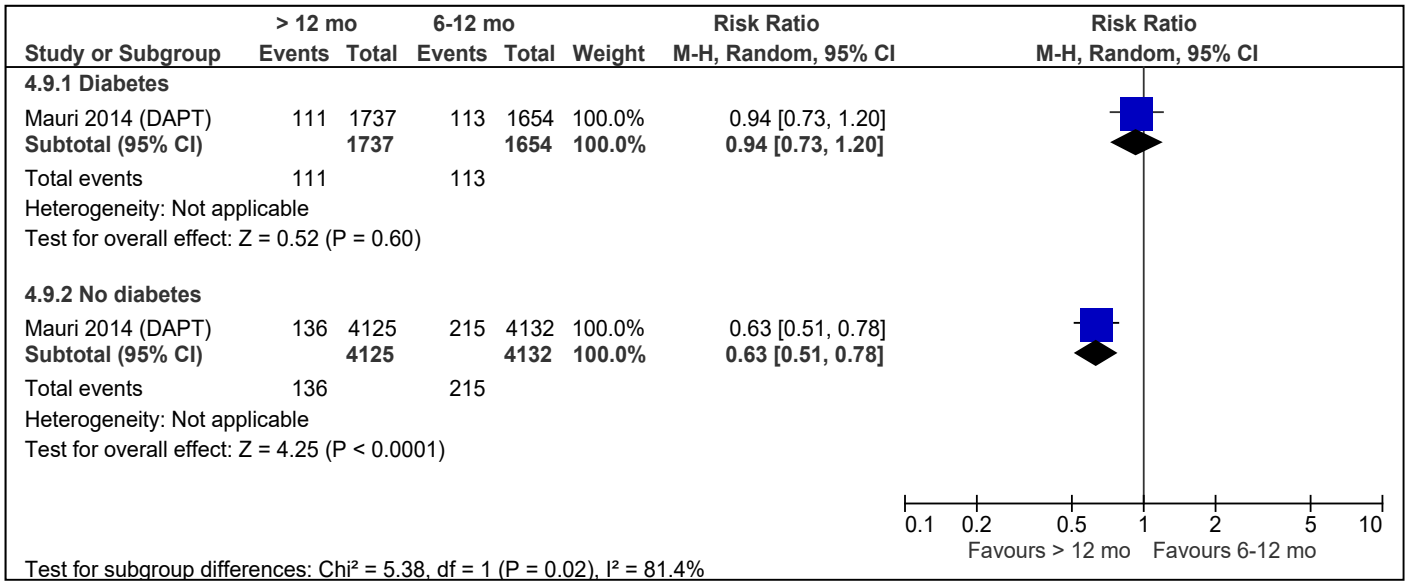


CI = confidence interval; mo = months.

MACCE

Two RCTs[23,24] reported MACCE using a consistent definition (all-cause death, MI, stroke) and are subsequently described. Valgimigli et al. (PRODIGY)[24] reported that there was no significant difference in the HR 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 et al. (DAPT)[23] 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 et al.[23] found a significantly lower risk of MACCE with participants who received more than 12 months of DAPT compared with six to12 months of DAPT (RR 0.63, 95% CI, 0.51 to 0.78) (Figure 63).

Figure 63: Relative Risk of MACCE Among Participants With or Without Diabetes



CI = confidence interval; mo = months.

An additional three RCTs[22,30,33] reported MACCE using alternative definitions. The outcomes definitions and data are summarized in Table 19. 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 19).

Table 19: MACCE Reported by Use of Alternative Definitions by Diabetes Status

		Diabetes		No Diabetes	
Author, Date, Trial	**MACCE Definition**	**Number of Events/ Number of Participants**	**RR (95% CI)**	**Number of Events/ Number of Participants**	**RR (95% CI)**
Nakamura et al., 2017 (NIPPON)[22]	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: 17/1,035 18 mo: 14/1,018	0.84 (0.41, 1.69)
Gilard et al., 2015 (ITALIC)[30]	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 et al., 2014 (ARCTIC-INT)[33]	All-cause death, MI, stent thrombosis, stroke, urgent revascularization	12 mo: 10/222 18 to 30 mo: 11/198	1.23 (0.54, 2.84)	12 mo: 17/402 18 to 30 mo: 13/437	0.70 (0.35, 1.43)

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

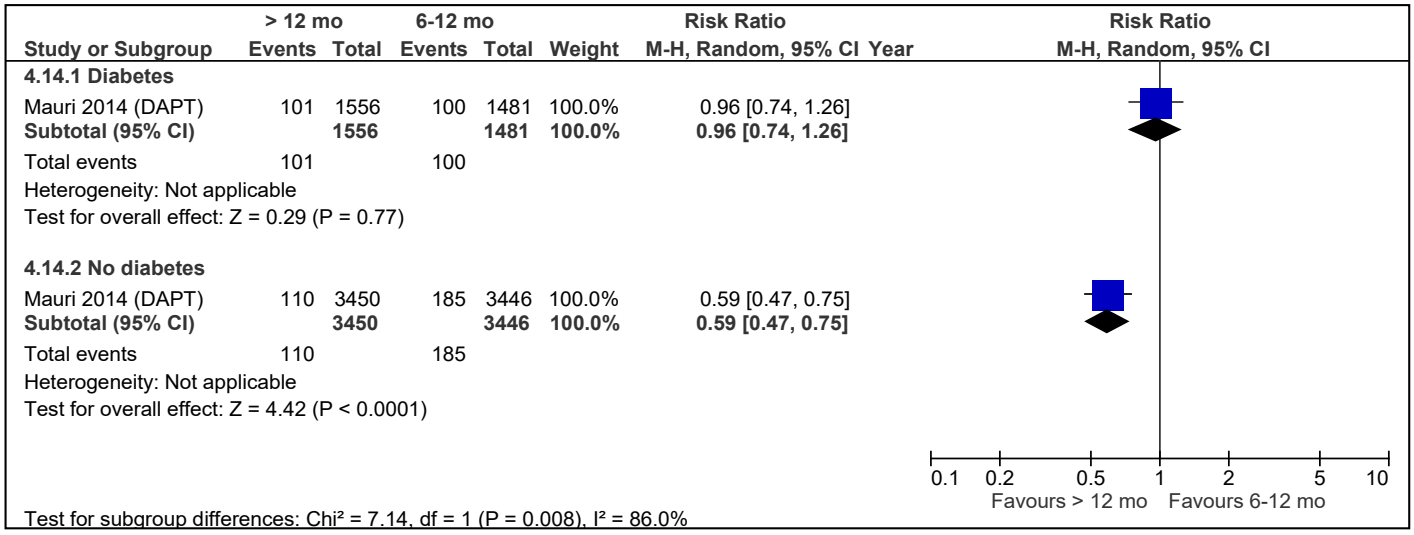
Drug-Eluting Stents

One RCT[23] 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 19, three additional RCTs involving participants with diabetes found no significant difference in the risk of MACCE assessed using alternative definitions.

Among those without diabetes, the risk of MACCE was significantly lower among participants who received more than 12 months of DAPT compared with six to 12 months of DAPT (RR 0.59, 95% CI, 0.47 to 0.75) (Figure 64). As noted in Table 19, two additional RCTs involving participants without diabetes reported no significant difference in the risk of MACCE assessed using alternative definitions.

Figure 64: Relative Risk of MACCE Among Participants With an Implanted DES, With or Without Diabetes



CI = confidence interval; mo = months.

Bare-Metal Stents

No studies assessed MACCE among participants with or without diabetes with an implanted BMS.

Gastrointestinal Bleeding

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

Major and Minor Bleeding

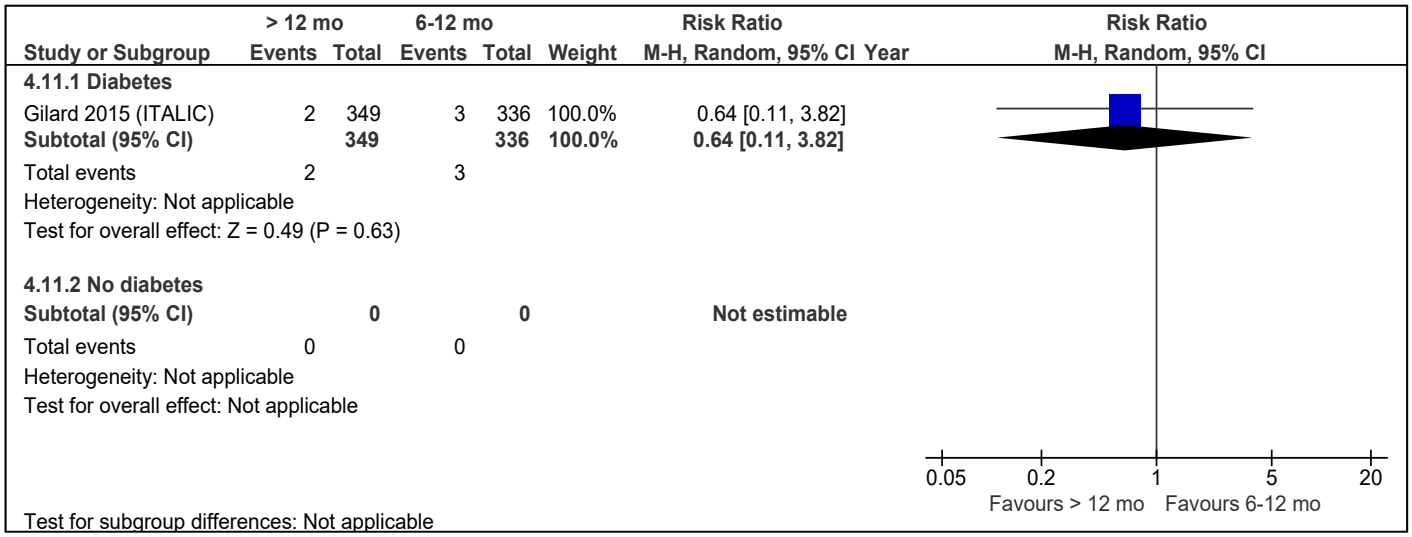
TIMI Major Bleeding

No studies reported TIMI major bleeding among participants with or without diabetes.

TIMI Minor Bleeding

One RCT[30] 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



CI = confidence interval; mo = months.

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 20).

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 20).

Table 20: Bleeding Reported Using Alternative Classification Systems, Among Participants With or Without Diabetes

		Diabetes		No Diabetes	
Author, Date, Trial	**Bleeding Classification System[a]**	**Number of Events/ Number of Participants**	**RR (95% CI)**	**Number of Events/ Number of Participants**	**RR (95% CI)**
Mauri et al., 2014 (DAPT)[23b]	GUSTO moderate or severe	12 mo: 26/1,654 30 mo: 41/1,737	1.50 (0.92, 2.44)	12 mo: 58/4,132 30 mo: 99/4,125	**1.71** **(1.24, 2.36)**
	GUSTO moderate	12 mo: 20/1,654 30 mo: 32/1,737	1.52 (0.87, 2.65)	NR	—
	GUSTO severe	12 mo: 6/1,654 30 mo: 9/1,737	1.43 (0.51, 4.00)	NR	—
	BARC type 2, 3, 5	12 mo: 57/1,654 30 mo: 95/1,737	**1.59** **(1.15, 2.19)**	NR	—
	BARC type 3	12 mo: 24/1,654 30 mo: 44/1,737	**1.75** **(1.07, 2.86)**	NR	—
	BARC type 5	12 mo: 2/1,654 30 mo: 1/1,737	0.48 (0.04, 5.25)	NR	—
Mauri et al., 2014 (DAPT)[23c]	GUSTO moderate or severe	12 mo: 24/1,481 30 mo: 39/1,556	1.55 (0.93, 2.56)	12 mo: 49/3,446 30 mo: 80/3,450	**1.63** **(1.15, 2.32)**

CI = confidence interval; MI = myocardial infarction; mo = months; NR = not reported; RR = relative risk.
[a] Definitions for each bleeding classification system are available in Appendix 10.
[b] Participants with either an implanted DES or BMS.
[c] Participants with an implanted DES.

Age

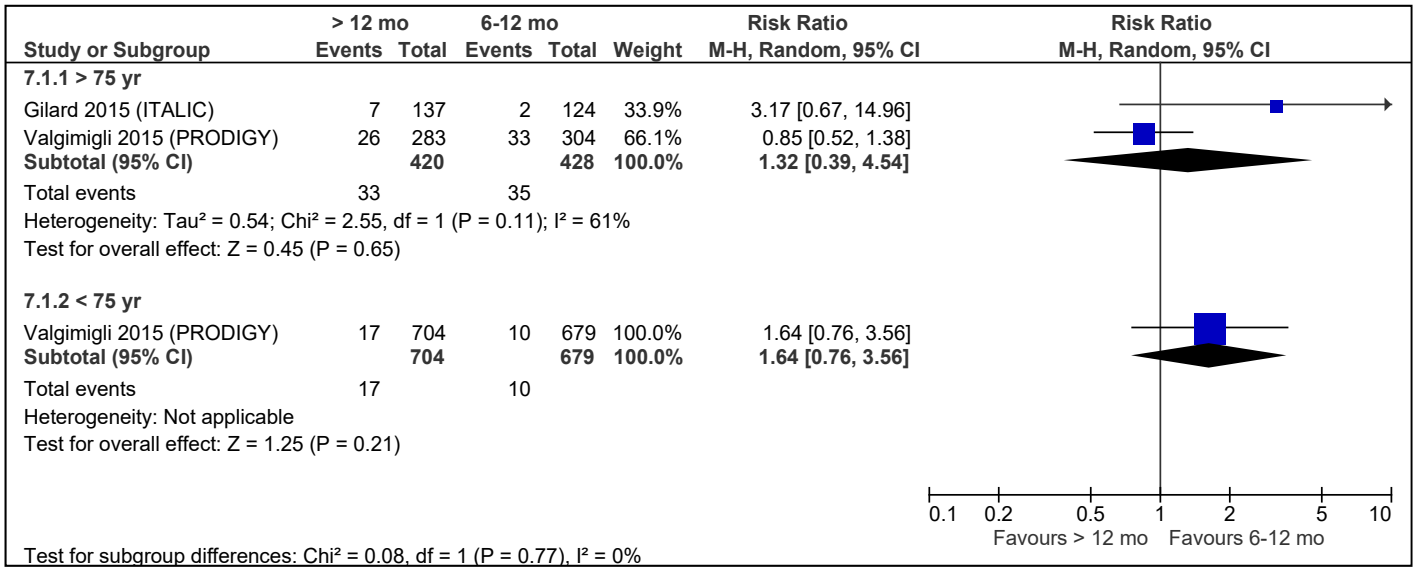
In total, five RCTs[22-24,30,33] reported outcomes data based on age, i.e. participants aged less than 75 years or those older than 75 years. One additional RCT[26] provided risk outcomes data among those aged less than 65 years or those older than 65 years. Outcomes data were available for all-cause death, cardiovascular death, MI, stroke, stent thrombosis, urgent revascularization, MACCE, and bleeding.

All-Cause Death

Two RCTs[24,30] assessed all-cause death among 848 participants aged at least 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[24] involving 1,383 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



CI = confidence interval; mo = months.

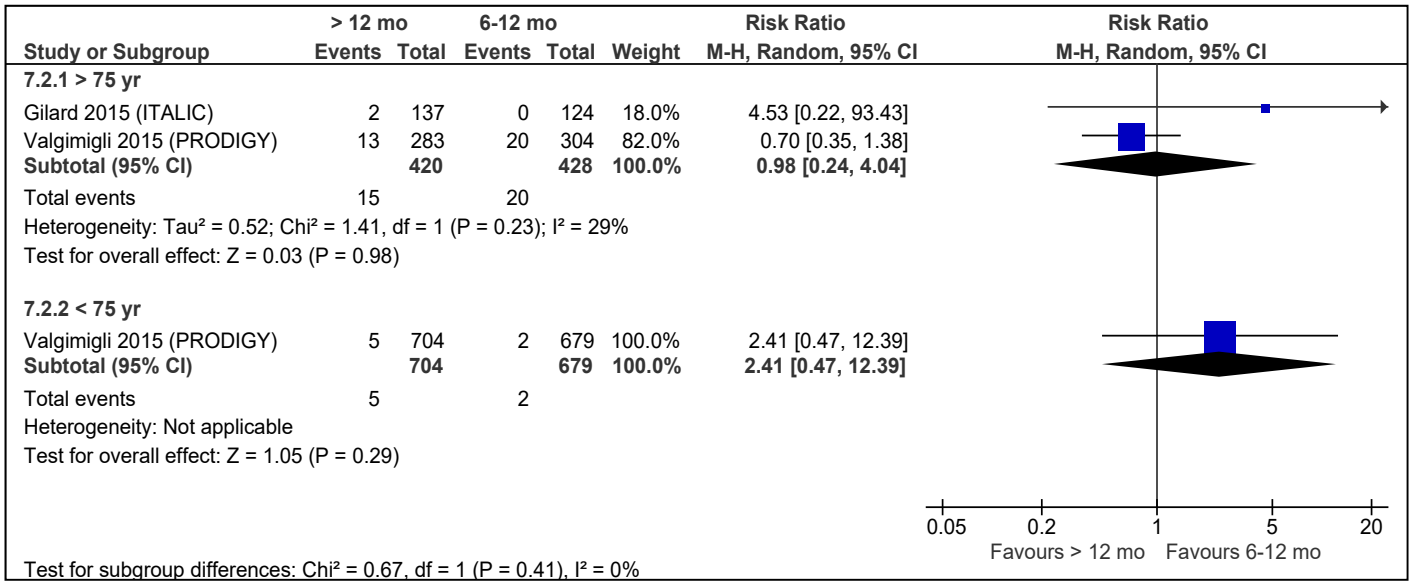
No studies assessed all-cause death among participants aged less than 75 years or older than 75 years by stent type (BMS or DES).

Cardiovascular Death

Two RCTs[24,30] assessed cardiovascular death among 848 participants aged at least 75 years. There was no significant difference in the risk of cardiovascular death between DAPT for more than 12 months and six to 12 months (RR 0.98, 95% CI, 0.24 to 4.04), with moderate heterogeneity between trials (I^2 = 29%) (Figure 67).

One RCT[24] involving 1,383 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



CI = confidence interval; mo = months.

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

Non-cardiovascular Death

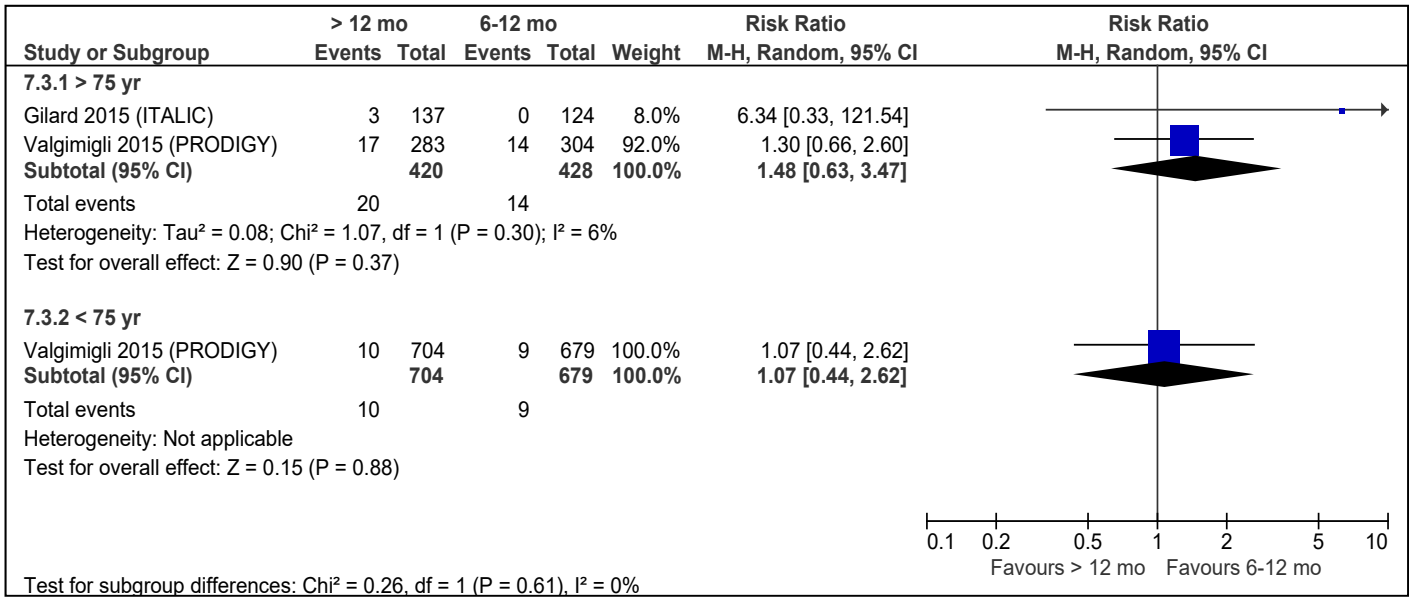
No studies assessed non-cardiovascular death among participants aged more or less than 75 years.

Myocardial Infarction

Two RCTs[24,30] assessed MI among 848 participants aged at least 75 years. There was no significant difference in the risk of MI between DAPT for more than 12 months and six to 12 months (RR 1.48, 95% CI, 0.63 to 3.47) (Figure 68).

One RCT[24] involving 1,383 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



CI = confidence interval; mo = months.

One additional RCT (DAPT[23]) reported that there was a significantly lower risk of MI with extended DAPT 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 21); the number of participants in each group was not reported, precluding pooling.

Table 21: Risk of Myocardial Infarction by Age Group

		≥ 75 Years		< 75 Years	
Author, Date, Trial	**DAPT Duration**	**%**	**Reported HR (95% CI)**	**%**	**Reported HR (95% CI)**
Mauri et al., 2014 (DAPT)[23a]	12 mo	3.6%	0.76 (0.38, 1.54)	4.2%	**0.46 (0.36, 0.60)**
	30 mo	2.7%		2.0%	

CI = confidence interval; DAPT = dual antiplatelet therapy; HR = hazard ratio; mo = months.
[a] Participants with a drug-eluting stent.

Drug-Eluting Stents

Two RCTs[23,30] assessed the risk of MI among participants aged at least 75 years with a DES. As shown in Figure 68, in the ITALIC trial,[30] there was no significant difference in the risk of MI between extended DAPT and DAPT for six to 12 months among participants aged more than 75 years.

Mauri et al. (2014) (DAPT[23]) 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 MI by age group among participants with an implanted BMS.

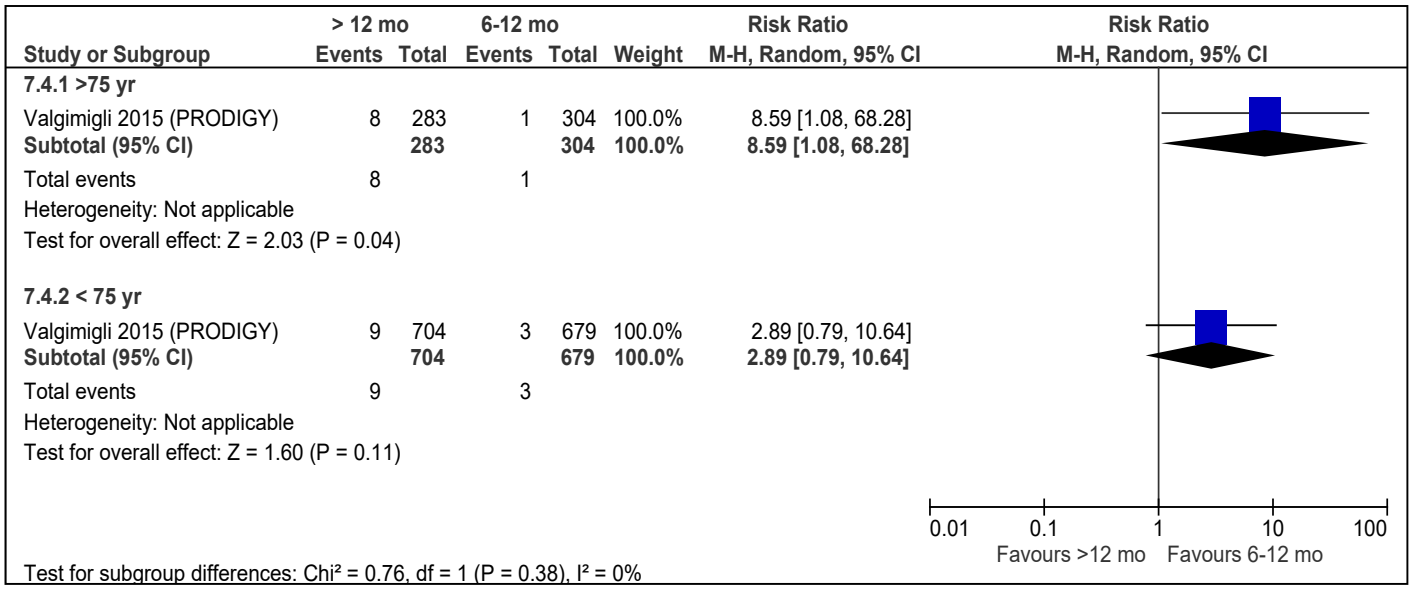
Stroke

One RCT[24] assessed the risk of stroke among 587 participants aged at least 75 years and 1,383 participants aged less than 75 years.

Among participants aged at least 75 years, the risk of stroke was significantly higher in those who received DAPT for more than 12 months compared with six to 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 six to 12 months (RR 2.89, 95% CI, 0.79 to 10.64) (Figure 69).

Figure 69: Relative Risk of Stroke by Age Group



CI = confidence interval; mo = months.

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

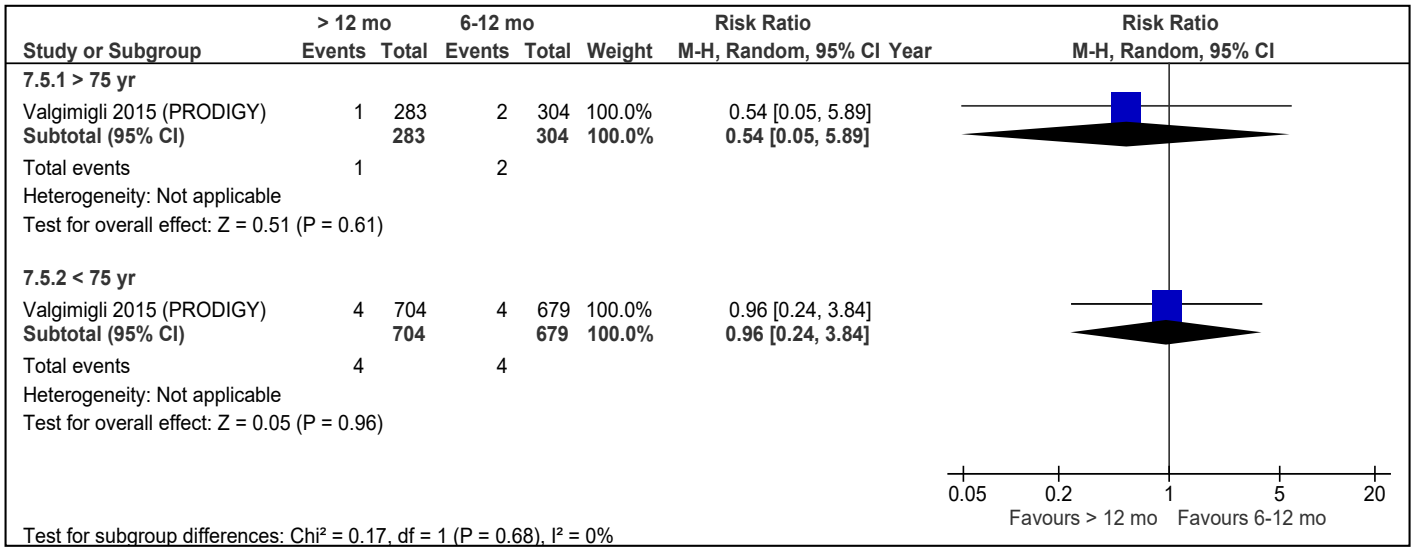
Stent Thrombosis

Definite Stent Thrombosis

One RCT[24] assessed the risk of definite stent thrombosis among 587 participants aged at least 75 years and 1,383 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 at least 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



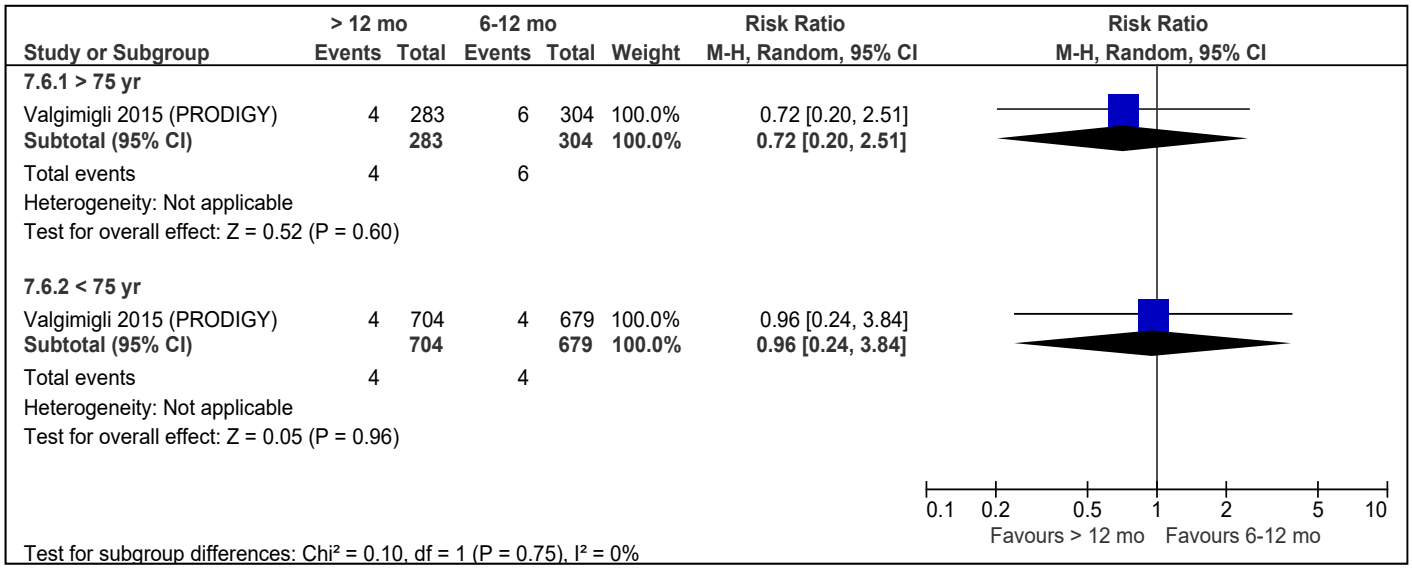
CI = confidence interval; mo = months.

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[24] assessed the risk of definite or probable stent thrombosis among 587 participants aged at least 75 years and 1,383 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 at least 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



CI = confidence interval; mo = months.

One additional RCT (DAPT[23]) 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 22); the number of participants in each group was not reported, precluding pooling.

Table 22: Risk Definite or Probable Stent Thrombosis by Age Group

		≥ 75 Years		< 75 Years	
Trial	**DAPT Duration**	**%**	**Reported HR (95% CI)**	**%**	**Reported HR (95% CI)**
Mauri et al., 2014 (DAPT)[23a]	12 mo	0.8%	0.23 (0.03, 2.06)	1.4%	**0.29 (0.17, 0.49)**
	30 mo	0.2%		0.4%	

CI = confidence interval; DAPT = dual antiplatelet therapy; HR = hazard ratio; mo = months.
[a] Participants with a drug-eluting stent.

Drug-Eluting Stents

Mauri et al. (2014)[23] 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 22).

Bare-Metal Stents

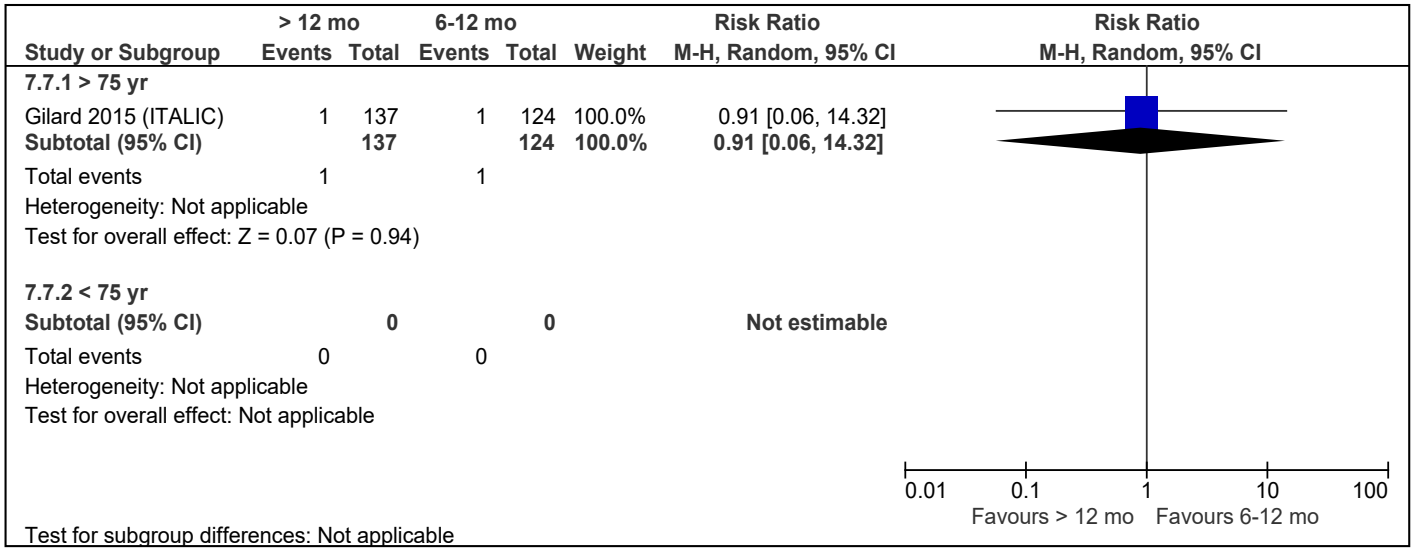
No studies assessed definite or probable stent thrombosis by age group among participants with an implanted BMS.

Urgent Revascularization

One RCT[30] involving 261 participants aged at least 75 years assessed urgent revascularization. No data were reported for participants aged less than 75 years.

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

Figure 72: Relative Risk of Urgent Revascularization by Age Group



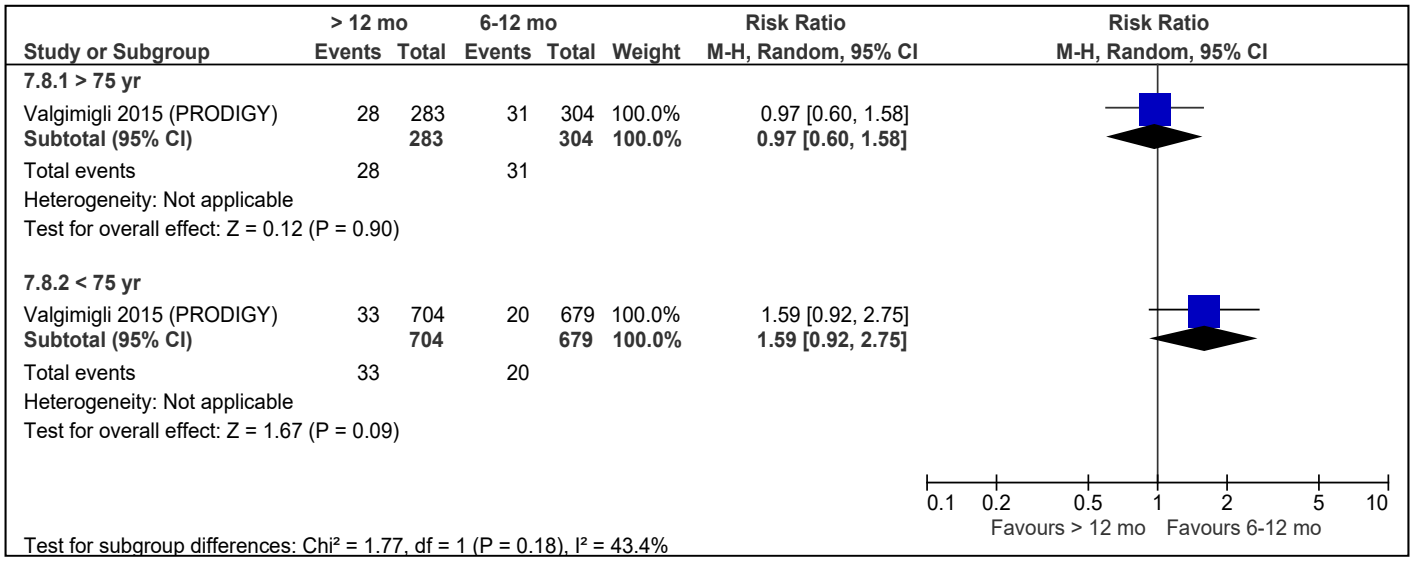
CI = confidence interval; mo = months.

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

MACCE

Two RCTs[23,24] 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,[23] precluding pooling of study data. In the PRODIGY trial,[24] there was no significant difference in the risk of MACCE between DAPT for more than 12 months or six to 12 months in either those aged at least 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



CI = confidence interval; MACCE = major adverse cardiac and cerebrovascular event; mo = months.

Mauri et al. (DAPT)[23] reported that there was no significant difference in the risk of MACCE between DAPT durations among those aged at least 75 years (HR 0.95, 95% CI, 0.59, 1.52).

Among those aged less than 75 years, Mauri et al.[23] reported a significantly lower risk of MACCE among participants who received more than 12 months of DAPT compared with six to 12 months of DAPT (HR 0.69, 95% CI, 0.57, 0.83).

An additional four RCTs[22,26,30,33] reported MACCE using alternative definitions. The outcomes definitions and data are summarized in Table 23. Despite differences in definitions across trials, each of the RCTs reported no significant difference in the risk of MACCE between DAPT durations in participants aged more or less than 75 years (Table 23).

Table 23: MACCE Reported Using Alternative Definitions by Age Group

Trial		> 75 Years		< 75 Years	
	MACCE Definition	Number of Events/ Number of Participants	RR (95% CI)[a]	Number of Events/ Number of Participants	RR (95% CI)[a]
Nakamura et al., 2017 (NIPPON)[b22]	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: 19/1,296	0.95 (0.51, 1.78)
Gilard et al., 2015 (ITALIC)[30b]	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 et al., 2014 (ARCTIC-INT)[33b]	All-cause death, MI, stent thrombosis, stroke, urgent revascularization	12 mo: 9/103 18 to 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 Years		< 65 Years	
Lee et al., 2014 (DES-LATE)[26b]	Cardiac death, MI, or stroke	12 mo: 2.9%[c] 36 mo: 3.7%[c]	HR 0.81 (0.51, 1.30)	12 mo: 2.0%[c] 36 mo: 1.7%[c]	HR 1.18 (0.67, 2.08)

CI = confidence interval; HR = hazard ratio; MACCE = major adverse cardiac and cerebrovascular events; MI = myocardial infarction; mo = months; NR = not reported; RR = relative risk.

[a] Unless reported otherwise.

[b] Involved participants with an implanted drug-eluting stent.

[c] Percentage of participants with an event; denominator not reported.

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

Gastrointestinal Bleeding

No studies assessed gastrointestinal bleeding by age group.

Major and Minor Bleeding

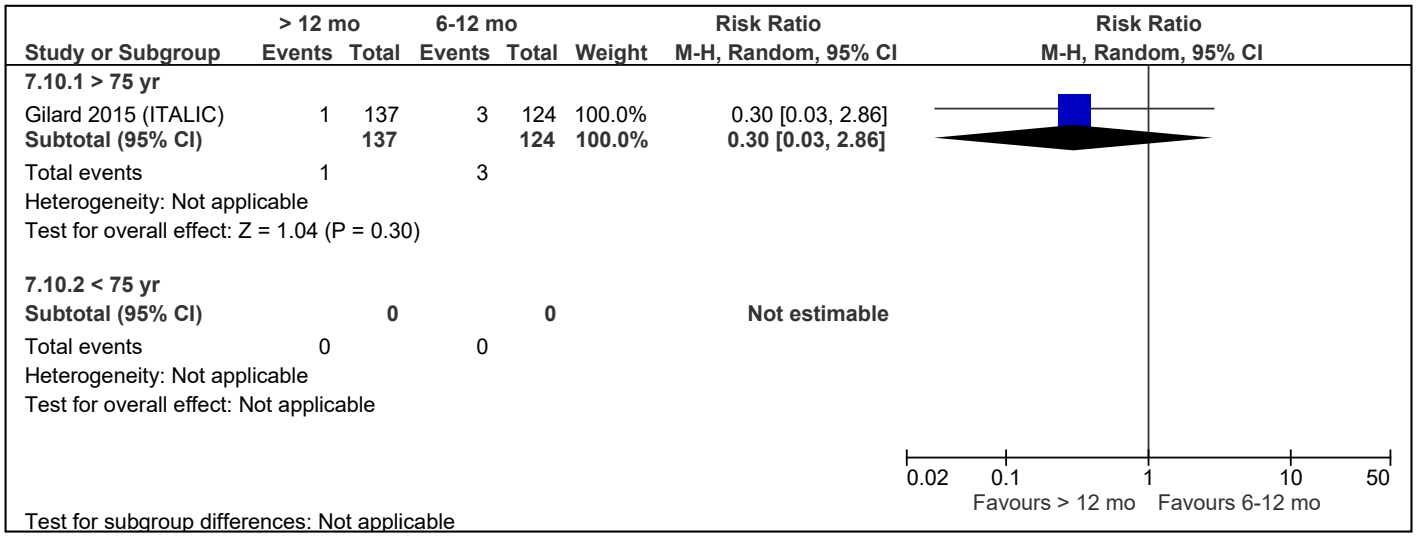
TIMI Major Bleeding

No studies assessed TIMI major bleeding by age group.

TIMI Minor Bleeding

One RCT[30] 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 at least 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



CI = confidence interval; mo = months; TIMI = thrombolysis in myocardial infarction.

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

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, and 5 bleeding; BARC type 3 and 5 bleeding; and GUSTO moderate and severe bleeding (Table 24). 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 (HR 1.78, 95% CI, 1.29 to 2.47) but not among those aged more than 75 years (HR 1.03, 95% CI, 0.54 to 1.98) (Table 24).

Bare-Metal Stent

No studies assessed bleeding by use of an alternative classification system in participants with a BMS by age group.

Table 24: Bleeding Reported Using Alternative Classification Systems by Age Group

		≥ 75 Years		< 75 Years	
Author, Year,Trial	**Bleeding Classification System[a]**	**Number of Events/ Number of Participants**	**RR (95% CI)[b]**	**Number of Events/ Number of Participants**	**RR (95% CI)[b]**
Valgimigli et al., 2012 (PRODIGY) [24c]	BARC type 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 type 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 type 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 or 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 et al., 2014 (DAPT[23d]	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)**

CI = confidence interval; HR = hazard ratio; mo = months; RR = relative risk.
[a] Definitions for each bleeding classification system are available in Appendix 10.
[b] Unless otherwise stated.
[c] Participants with an implanted drug-eluting stent or bare-metal stent.
[d] Participants with an implanted drug-eluting stent.

Participants Who Smoke

In total, three RCTs[23,24,33] reported outcomes data by smoking status. One RCT[24] categorized participants as "smokers" or "non-smokers," one RCT[23] categorized smoking status as "current tobacco use" and "no current tobacco use," and one RCT[33] 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[23] by smoking status were provided only for participants with an implanted DES.

All-Cause Death

One RCT[24] reported all-cause death among participants categorized as "smokers" (n = 469) or "non-smokers" (n = 1,493). There was no significant difference in the HR for all-cause death between DAPT for six 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).

Cardiovascular Death

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

Non-cardiovascular Death

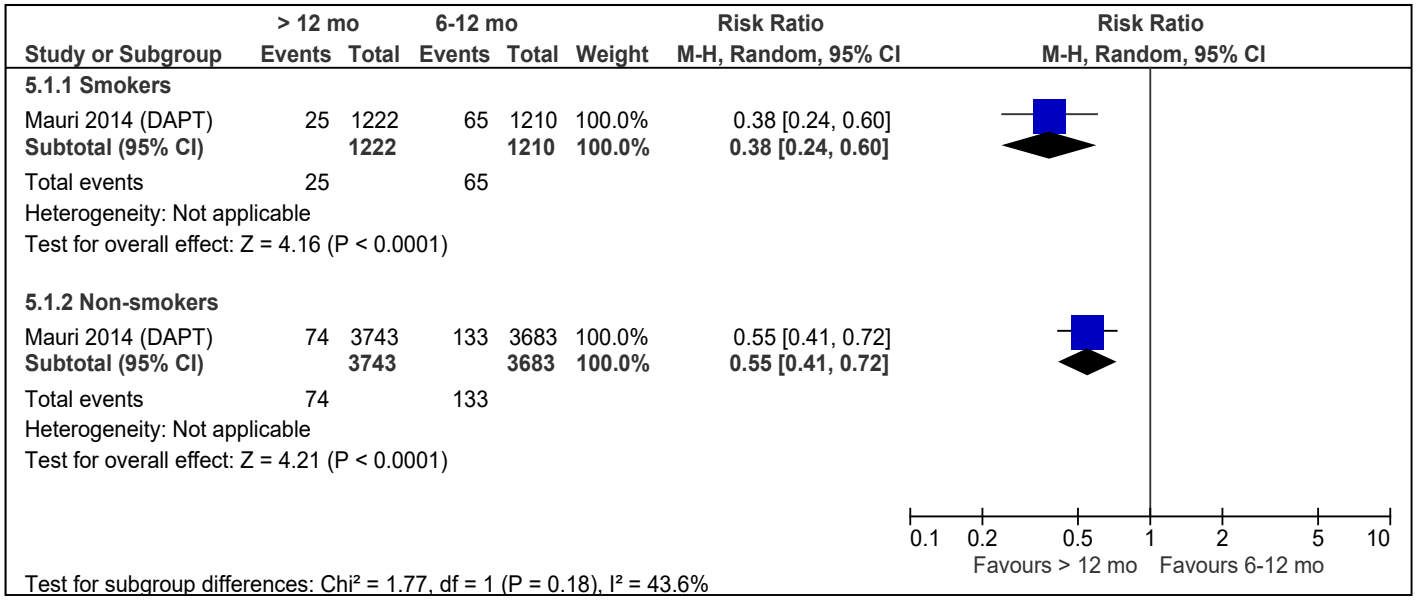
No studies reported non-cardiovascular death among smokers or non-smokers.

Myocardial Infarction

One RCT[23] reported a significantly lower risk of MI with DAPT for more than 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[23] included participants with either a DES or a 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



CI = confidence interval; mo = months.

Stroke

No studies reported stroke among smokers or non-smokers.

Stent Thrombosis

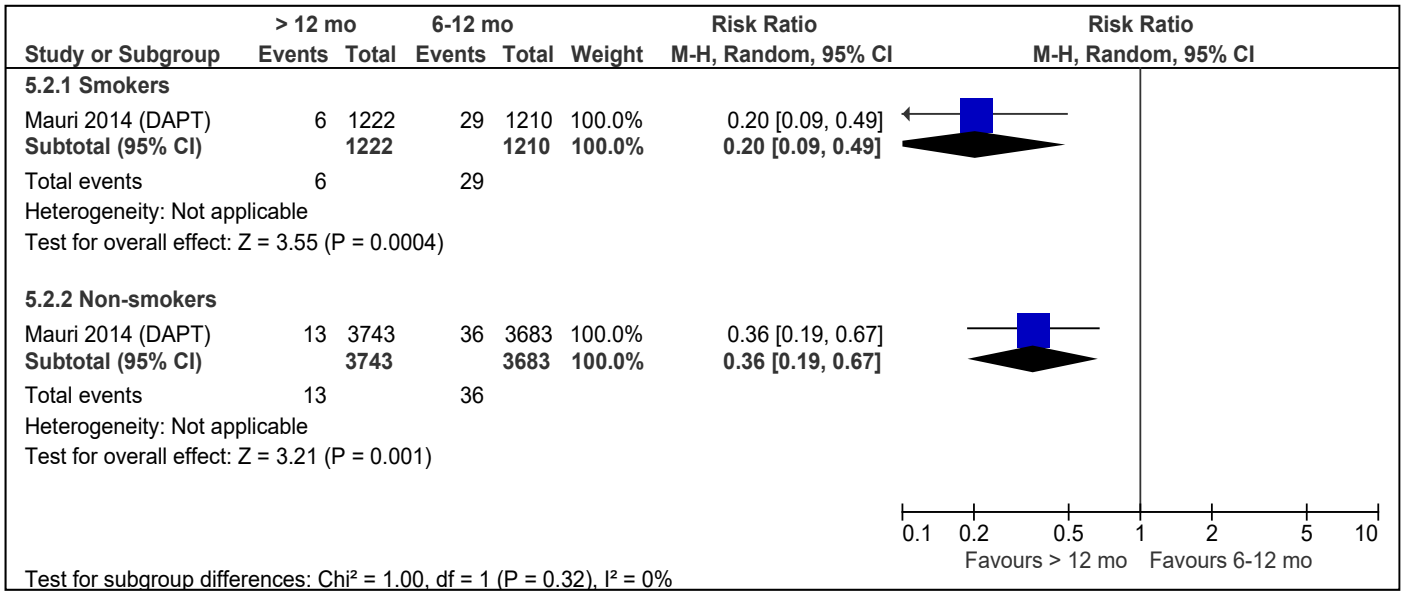
Definite Stent Thrombosis

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

Definite or Probable Stent Thrombosis

One RCT[23] reported a significantly lower risk of definite or probable stent thrombosis with DAPT for more than 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[23] 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



CI = confidence interval; mo = months.

Urgent Revascularization

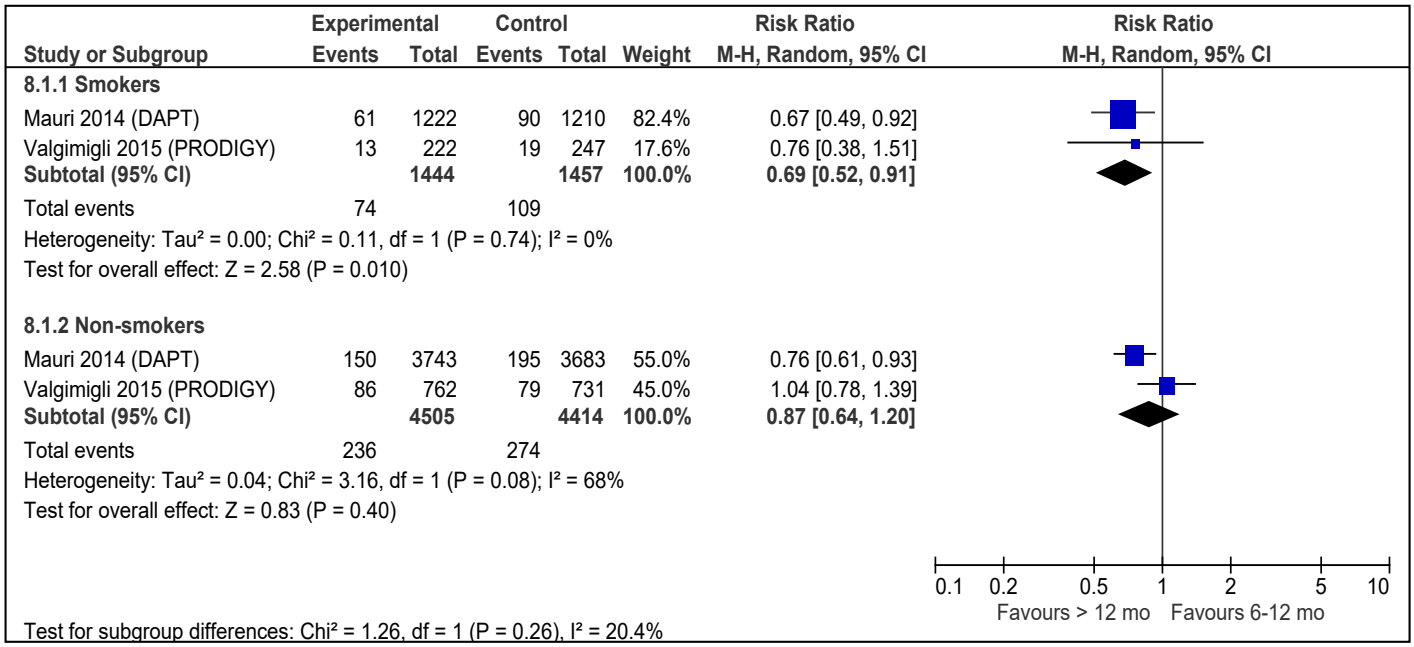
No studies reported urgent revascularization among smokers or non-smokers.

MACCE

In total, three RCTs[23,24,33] reported MACCE among smokers and non-smokers, with variation in definition of the composite outcome.

Two RCTs[23,24] reported MACCE using a consistent definition (all-cause death, MI, stroke). Among smokers, DAPT for more than 12 months was associated with a lower risk of MACCE (RR 0.69, 95% CI, 0.52 to 0.91) compared with DAPT for six to 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[33] assessed MACCE among smokers and non-smokers using 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, 95% CI, 0.48 to 1.61).

Figure 77: Relative Risk of MACCE by Smoking Status

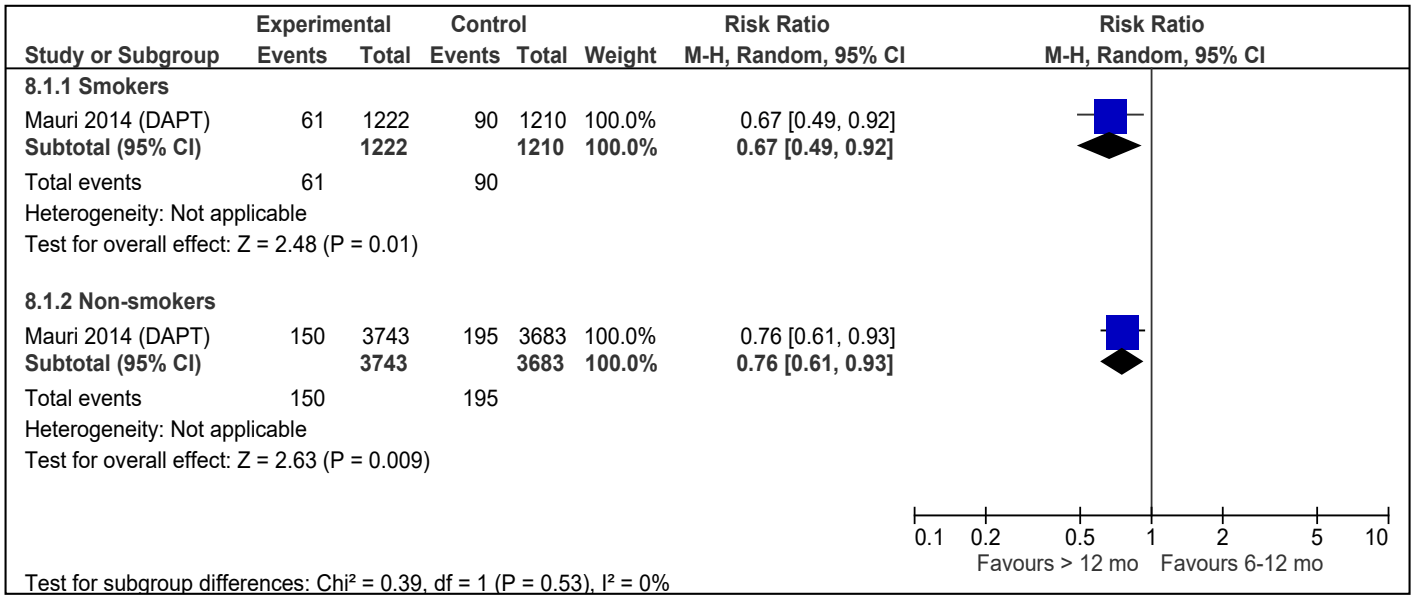


CI = confidence interval; mo = months.

Drug-Eluting Stents

One RCT[23] 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 six to 12 months (Figure 78).

Figure 78: Relative Risk of MACCE Among Participants With a DES by Smoking Status



CI = confidence interval; mo = months.

Bare-Metal Stents

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

Gastrointestinal Bleeding

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

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[23,24] assessed bleeding by use of an alternative classification system (Table 25). By use of either the GUSTO (moderate or severe) or BARC (type 2, 3, and 5), the risk of bleeding was increased among non-smokers who received DAPT for more than 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 25).

Table 25: Bleeding Reported by Use of Alternative Classification Systems by Smoking Status

		Smoking		No Smoking	
Trial	**Bleeding Classification System[a]**	**Number of Events/ Number of Participants**	**RR (95% CI)**	**Number of Events/ Number of Participants**	**RR (95% CI)**
Valgimigli et al., 2012 (PRODIGY) [24b]	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)[23c]	GUSTO moderate or severe	12 mo: 17/1,210 30 mo: 15/1,222	0.87 (0.44 to 1.74)	12 mo: 56/3,683 30 mo: 104/3,743	**1.83** **(1.32 to 2.52)**

CI = confidence interval, mo = months, RR = relative risk.
[a] Definitions for each bleeding classification system are available in Appendix 10.
[b] Participants with an implanted drug-eluting stent or bare-metal stent.
[c] Participants with an implanted drug-eluting stent.

Research Question 3: Compared with shorter treatment duration (six to 12 months), what is the comparative clinical efficacy and safety of ASA plus clopidogrel, prasugrel or ticagrelor when DAPT is used for longer (i.e., more than 12 months) duration of DAPT following PCI with BMS or DES insertion:

- all post-PCI patients
- those with a prior myocardial infarction
- those presenting with ACS at the time of PCI
- those with diabetes
- different age subgroups
- those who smoke?

As with Research Question 1, the evidence base for this research question included data from seven RCTs,[22-24,26,29,30,33] representing the treatment period starting six months following PCI.

Clopidogrel was the most commonly used P2Y12 inhibitor in the included RCTs (Table 10). Three RCTs (OPTIDUAL,[29] DES-LATE,[26] and PRODIGY[24]) 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 predominant 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 subsequently summarized for each P2Y12 inhibitor.

Clopidogrel

The RCTs that were used to address Research Question 1 primarily involved the use of clopidogrel, with between 65% and 100% of participants receiving this antiplatelet drug. 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 in preceding sections of this report.

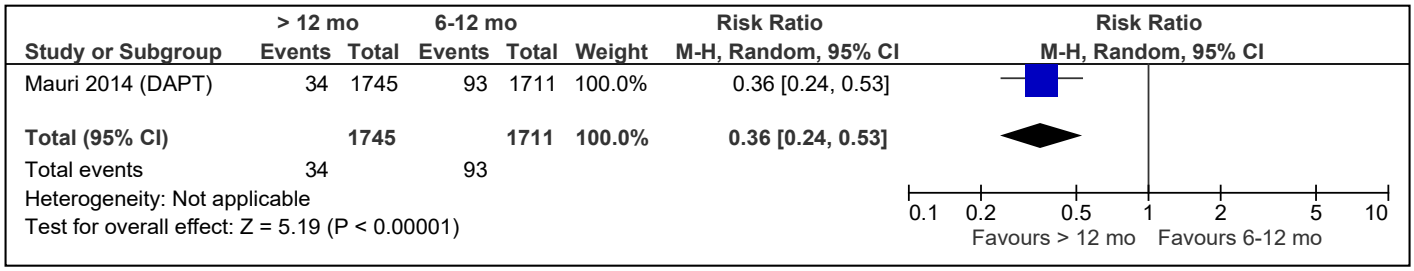
Prasugrel

Four of the included RCTs involved the use of prasugrel (ITALIC,[30] DAPT,[23] ARCTIC-Interruption,[33] and NIPPON[22]), with use by 0.1% to 35% of participants. Of these, one RCT (DAPT[23]) 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 or severe bleeding and are subsequently summarized. No data were reported for all-cause death, cardiovascular death, non-cardiovascular death, stroke, urgent revascularization, or TIMI bleeding.

Myocardial Infarction

Among participants who received prasugrel, DAPT for more than 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



CI = confidence interval, mo = months.

Stent Thrombosis

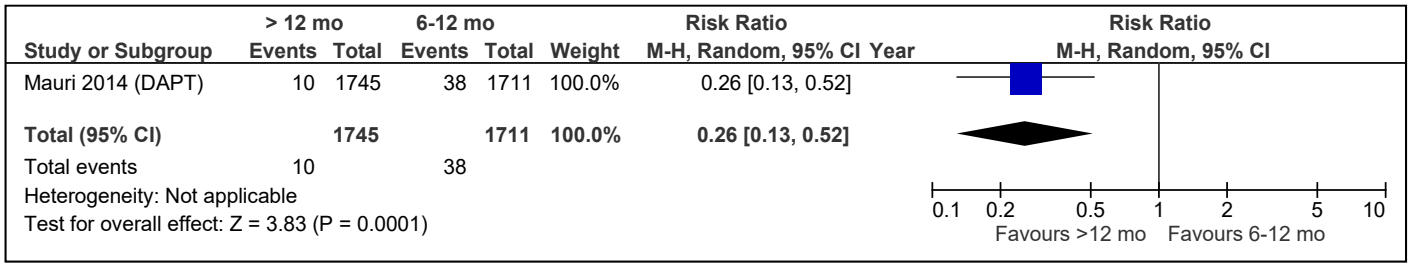
Definite Thrombosis

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

Definite or Probable Stent Thrombosis

Among participants who received prasugrel, DAPT for more than 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

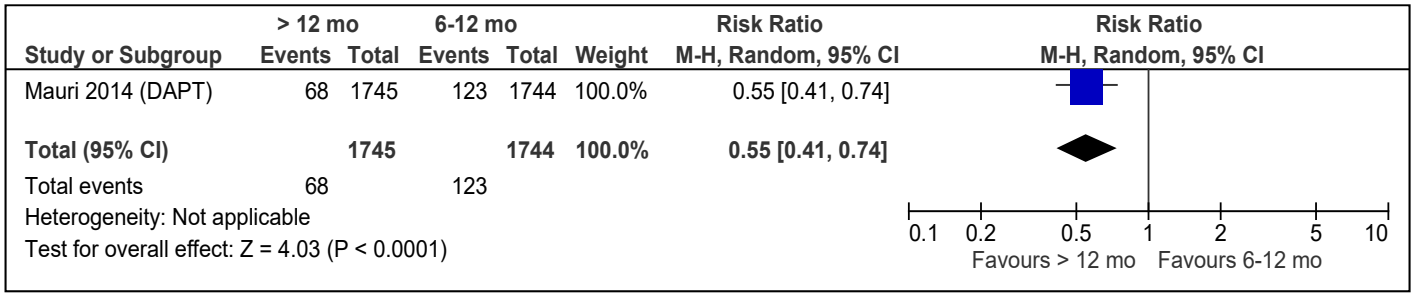


CI = confidence interval, mo = months.

MACCE

Among participants who received prasugrel, DAPT for more than 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

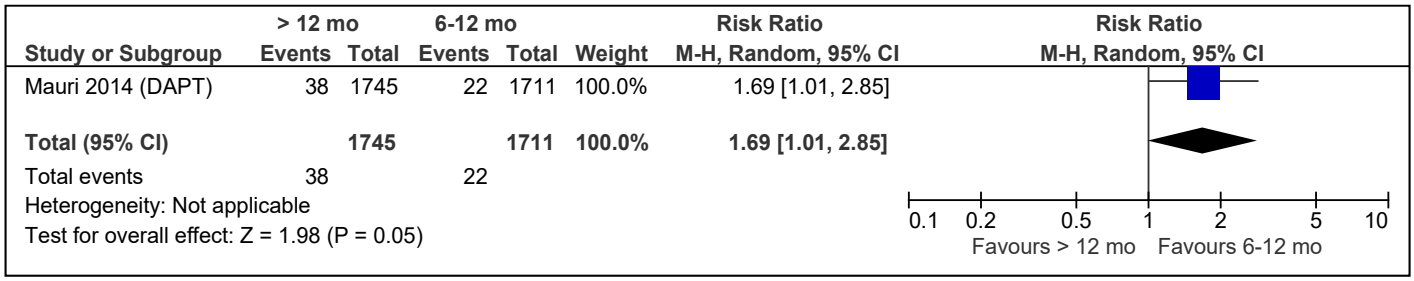


CI = confidence interval, mo = months.

GUSTO Moderate or Severe Bleeding

Among participants who received prasugrel, DAPT for more than 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



CI = confidence interval, mo = months.

Ticagrelor

Of the included RCTs, ticagrelor was an eligible P2Y12 inhibitor in one RCT (ITALIC[30]); however, no participants in the 24-month DAPT group and 0.1% of participants in the six-month DAPT group received ticagrelor (Table 10). There was therefore insufficient data available to assess the benefits and harms of extended DAPT involving ticagrelor.

One large RCT (PEGASUS-TIMI 54[34]) involving participants with a prior MI was identified during the review but not included. Participants were randomized to ticagrelor 60 mg or 90 mg twice daily, or placebo, one to three years after an 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[34] 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; 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 to 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[34] 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.

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 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 at the time of PCI
- those with diabetes
- different age groups
- those who smoke?

Research Question 4

Compared with a shorter treatment duration (six 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 at the time of PCI
- those with diabetes
- different age groups
- those who smoke?

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

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.[35-53] Of these, only three compared DAPT of different durations — aligning with the research questions of interest.[35,38,42] One of these was an exploratory analysis of the effect size needed for 30 months of DAPT to be cost-effective.[38] 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.[42] 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 that compared DAPT three to six months to DAPT six to 12 months, and DAPT 30 to 36 months, post-PCI. This analysis found that DAPT three to six months was dominant over the two other strategies where DAPT was used over a longer period.[35] Both the analyses by Jiang et al. [42] and by Arbel et al. [35] 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 three to six months being the preferred option in only 55% of the iterations.[35] The US

analysis was very sensitive to the risk of non-fatal stroke and cardiovascular death. Further description of the identified analyses can be found in Appendix 13, Table 44.

Since the publication of these analyses, the results of two additional RCTs became available and were included in a CADTH meta-analysis, adding approximately 4,800 patients to previous meta-analyses.[22,29] 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.

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 the use of ASA alone (six- 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 CADTH 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 CADTH meta-analysis — in particular for long-term outcomes, utilities, and costs (when costs could not be found directly from Canadian sources).

Type of Economic Evaluation

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

Target Population

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

Treatments

Treatments considered in the analysis included:

- continuing DAPT beyond six 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 six to 12 months of DAPT (six- to 12-month DAPT group).

P2Y12 inhibitor-specific analyses were originally planned to address Research Question 4. However, too few data were available and thus these agent-specific analyses could not be performed.

Perspective

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

Time Horizon

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

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 CADTH meta-analysis and the end points from the included 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 six to 12 months of DAPT).

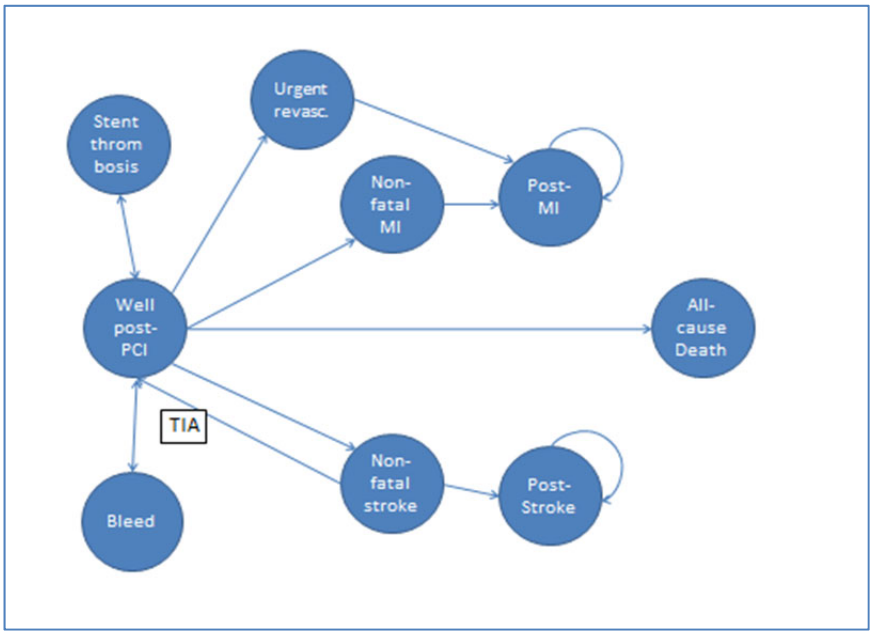
Once the cohort completes the extended DAPT phase, it moves into the second phase of the model (post-extended DAPT phase), which reflects the rest of their lives; i.e., up to 100 years of age. In the post-extended DAPT phase, additional health states were included to reflect the possibility of having subsequent cardiovascular 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 CADTH 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 (because of how data were reported in the studies included in CADTH meta-analysis), they were computed separately in the post-extended DAPT phase of the model.

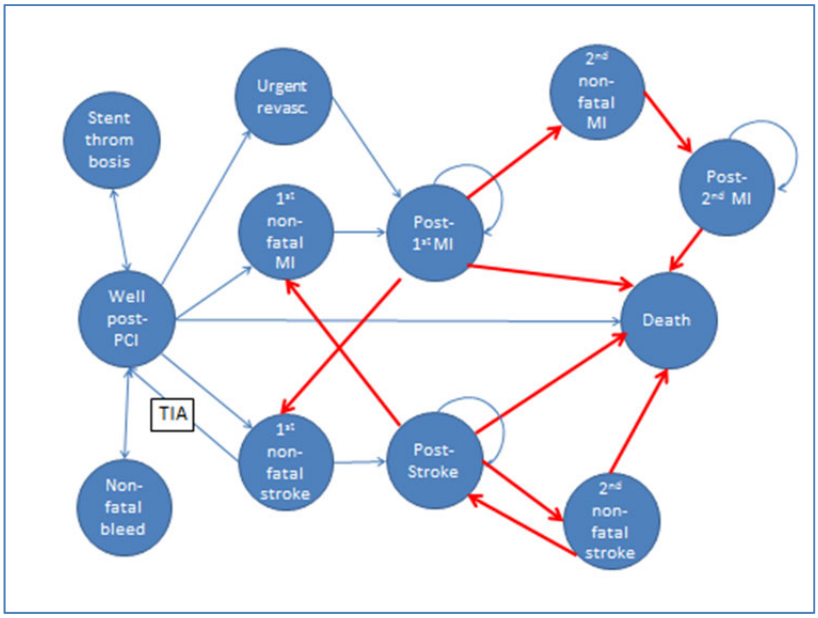
Outcomes of interest were costs, life-years, and QALYs derived from the presence or absence of clinical events such as all-cause death, non-fatal MI, non-fatal stroke, definite or probable stent thrombosis, urgent revascularization, and bleeds. It was originally planned to model strokes with major disabilities 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 were often not reported by the extent of disability remaining after the acute phase. A combined approach was thus adopted.

Figure 83: Model Structure — Extended DAPT Phase



DAPT = dual antiplatelet therapy; MI = myocardial infarction; PCI = percutaneous coronary Intervention; revasc.= revascularization; TIA = transient ischemic attack.

Figure 84: Model Structure — Post-Extended DAPT Phase



DAPT = dual antiplatelet therapy; MI = myocardial infarction; PCI = percutaneous coronary Intervention; revasc.= revascularization; TIA = transient ischemic attack.

Data Inputs

The results of the CADTH 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.

Cohort Demographics and Treatment Duration

The results from the CADTH meta-analysis were used to define the cohort age and gender. As studies of different duration were pooled in the CADTH 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 CADTH meta-analysis (i.e., from 12 to 36 months following the initial six-12 month DAPT treatment). Values for the cohort demographics and treatment duration can be seen in Table 26. Further information on patient demographics from each trial included in CADTH meta-analysis can be found in Appendix 5.

Table 26: 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		2,0579	6,897			Beta
Extended DAPT phase duration (months)	19.0				12.0	36.0	Normal

95%CI LL = 95% confidence interval lower limit; 95%CI UL = 95% confidence interval upper limit; DAPT = dual antiplatelet therapy; SE = standard error.

Treatment Efficacy and Safety (Extended DAPT Phase)

The results of CADTH 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 CADTH meta-analysis was computed and then transformed into a probability to be used in the Markov model using Equation 1, as follows:

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 27.

Table 27: 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[22]	1	1,653	12	0.000050
OPTIDUAL[29]	11	701	36	0.000436
ITALIC[30]	9	924	18	0.000541
ARCTIC-INT[33]	9	645	17	0.000821
DAPT[23]	121	5,862	18	0.001147
DES-LATE[26]	19	2,514	24	0.000313
Weighted average				0.000725

DAPT = dual antiplatelet therapy; MI = myocardial infarction.

These calculations were performed for the six- 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, probable 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.[26,30] 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 the CADTH meta-analysis base case. However, as this was likely to underestimate bleeding events, other approaches were considered in sensitivity analyses. These are described later in this report. An overview of the rates used in the extended DAPT phase of the model is provided in Table 28. Detailed data inputs can be found in Appendix 13, Table 45.

Table 28: 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 antiplatelet therapy; MI = myocardial infarction

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 in 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 extended DAPT is stopped has been observed in some studies.[23] 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-cardiovascular events). Preference was given to studies performed in Canada.

Probability of Subsequent Cardiovascular Events

A retrospective cohort study in individuals admitted for an MI (*International Classification of Diseases*, *Tenth 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.[54] The cohort had an average age of 67.7 years, with 65.7% being males, 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, year 2, and year 4 were used to generate an average monthly rate (later transformed into a probability) for the first four 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.[55] Cases were identified from the Ontario regional stroke centres, 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% versus 25%) and patients were also older (72 versus 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 second 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 six- to 12-month DAPT and the extended DAPT arms of the model.

An overview of the rates of subsequent cardiovascular events (later transformed into probabilities) used in the post-extended DAPT phase model is shown in Table 29, while more details can be found in Appendix 13, Table 46.

Table 29: Overview of Monthly Rates of Subsequent Cardiovascular Events

Parameter	6- to 12-month DAPT and Extended DAPT	Source
Second MI in an MI patient	0.004416	Tangri et al.[54]
Stroke in an MI patient	0.000912	Tangri et al.[54]
Second stroke in a stroke patient	0.001638	Edwards et al.[55]
MI in a stroke patient	0.000626	Edwards et al.[55]

DAPT= dual antiplatelet therapy; MI = myocardial infarction.

Probability of Death

There is a lack of long-term mortality data post-PCI. Most studies on coronary stents or antiplatelet 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 six 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

individuals at risk was less than 50% of the original cohort at six years and beyond.[56] 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.[35] 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 HRs of death post-cardiovascular 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 cardiovascular diseases; hence, using a HR of death post-cardiovascular events might overestimate death from cardiovascular events, unless the HR 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 life tables 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 four years post-MI was available from the retrospective study in Manitoba previously mentioned, no comparison to the general population was done in this study and hence this data could not be used for the analysis.[54] No other Canadian sources of data were identified from the medical literature. A Danish study was identified reporting HRs for cardiovascular death in incident MI patients diagnosed between 1997 and 2006.[57] In the late-period (2000 to 2006) cohort, 11,923 of the 43,769 MI patients died from cardiovascular disease over a five-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 four years) and an international study comparing ASA to clopidogrel in patients at risk of ischemic events reported a rate of 3.11% (annualized over three years). [54,58] The Danish data were used in the base case, but the difference with the Canadian data were further explored in sensitivity analyses.

Mortality Post-Stroke: The case-control study in stroke from Ontario (previously described) provided the estimated HR of death at year 1, year 3, and year 5 for stroke patients over a control cohort.[55] These HRs were averaged into a single HR, which was used to adjust mortality from the Canadian life tables.[59] This likely underestimated the risk of death from stroke for the same reasons as previously cited. An overview of the values used for death post cardiovascular events is shown in Table 30, while detailed inputs can be found in Appendix 13, Table 46.

Table 30: Overview of Hazards Ratios for Death Post-Cardiovascular Events

Parameter	6- to 12-month DAPT and Extended DAPT	Source
Post-MI (HR)	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[57]
Post-stroke (HR)	1.6333	Average of year 1, year 3, and year 5 from Edwards et al.[55]

DAPT = dual antiplatelet therapy; HR = hazard ratio; MI = myocardial infarction.

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 CADTH 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.

Comparative Effects of Antiplatelet Agents

P2Y12 inhibitor-specific analyses were planned to address Research Question 4. However, as noted in previous sections, the studies included in the base case of the CADTH meta-analysis consisted of participants receiving mainly (90% to 100%) clopidogrel; 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 CADTH meta-analysis. However, the available end points (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.

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.[60]

Medication Costs

The costs of medications (i.e., ASA, clopidogrel, prasugrel) were obtained from the Ontario Drug Benefit program formulary.[61] A ratio of 81:19 clopidogrel:prasugrel as per usage in the studies included in the meta-analysis was used to compute a weighted average cost for P2Y12 agents. As per the Ontario Benefit Drug Program requirements for chronic conditions, medications shall be dispensed every three months.[62] In the model, medication costs and dispensing fees were distributed over three months rather than being applied every three months.

Acute Event Costs

The Ontario Case Costing Initiative (OCCI) was used to obtain the costs for MI, stroke, and bleeding acute events.[63] This was supplemented with two Canadian publications estimating physician costs.[64,65] Both studies had a population that was older and included more women than the studies in the CADTH meta-analysis (72-years-old, 52.5% men in the Ewara et al. study[64], and 79.7-years-old and 51.9% men in the Cohen et al. study[65]). 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.[64] Similarly, in Cohen et al., each year of age was associated with a 0.7% decrease in acute MI overall health care costs.[65] 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.[64,65] 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 CADTH meta-analysis patient cohort is likely representative of MI patients. However, in general, stroke patients are older than those in the CADTH 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 (three from Canada, two from Denmark, one from Finland, and one from New Zealand) were identified.[66-72] Only one of these seven studies had validated its method by performing a medical chart review.[66] 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., more than four out of seven) 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 in-patient 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 47 of Appendix 13. The proportion of minor (TIMI) bleed as reported in the CADTH 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.[73]

Monthly Costs

Targeted literature searches were performed to identify monthly costs post-cardiovascular events. Health care 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 previously.[64] 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 (standard deviation: $14.39) for the care of patients in the post-MI period (physician fees, medications, hospitalization, etc.).[65] 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 31. More details can be found in Appendix 13, Table 48.

Table 31: Overview of Cost Inputs (Adjusted for Age and Gender When Applicable; All in 2018 Canadian Dollars)

Parameter	Value	Standard Error	Source and Details
Medications			
ASA (per month)	$0.42	Not applicable	ODB; 325 mg divided by 2[61]
Clopidogrel (per month)	$7.89	Not applicable	ODB[61]
Prasugrel (per month)	$57.48	Not applicable	ODB[61]
Pharmacist dispensing fee (per prescription, per month)	$2.94	Not applicable	ODB; 1 prescription per 3 months[61]
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[63]
Physician	$1,927	Age- and gender-adjusted value. PSA performed on unadjusted value and adjustment factors	Ewara et al.; physician costs during the first 30 days adjusted for age and gender[64]
MI	$10,763		Aggregate of hospital and physician costs
Hospitalization	$8,731	$87	OCCI IC-10 I21 and I22[63]
Physician	$2,891	Age- and gender-adjusted value. PSA performed on unadjusted value and adjustment factors	Cohen et al.; physician costs during acute event adjusted for age and gender[65]
Bleeding event	$1,195	Aggregate value	Weighted average of minor (84.62%) and major (15.38%) bleed
Major bleed	$6,541	$124	OCCI in-patient costs for bleeding events (see Appendix 13, Table 47 for full list of ICD-10 codes)[63]
Minor bleed	$223	$1	OCCI emergency costs from ambulatory care for bleeding events (see Appendix 13, Table 47 for full list of ICD-10 codes)[63]
PCI	$567.08	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)[73]
Monthly Costs			
Post-stroke	$2,245	Aggregate value. PSA performed on each component of cost	Ewara et al.; two-year costs minus hospital, emergency room, and physician costs during the first 30 days; adjusted for age and gender.[64]
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[65]

CMG = case mix group; ICD-10 = *International Classification of Diseases Tenth Revision*; MI = myocardial infarction; OCCI = Ontario Case Costing Initiative; ODB = Ontario Drug Benefit; PCI = percutaneous coronary intervention; PSA = probabilistic sensitivity analysis.

Utilities

Targeted literature searches were performed to identify utility or disutility values for the various health states of the model. Preference was given to EuroQol 5-Dimensions questionnaire (EQ-5D) values and Canadian sources. All utilities and disutilities used in the model are shown in Table 32 and Table 26.

Table 32: Overview of Utility and Disutility Inputs

Health State	Average	Standard Error	Applied For	Source and Details
Disutility				
Stroke (acute event)	–0.0524	0.0001	1 monthly cycle	Sullivan and Ghushchyan; acute cerebrovascular disease[74]
MI (acute event)	–0.0409	0.0002	1 monthly cycle	Sullivan and Ghushchyan; acute MI[74]
Bleed: major (event)	–0.0290	0.0077	1 monthly cycle	Wang et al.; average of major gastrointestinal and major non-gastrointestinal disutility[75]
Bleed: minor (event)	–0.0160	0.0041	1 monthly cycle	Wang et al.; relevant non-major bleeding[75]
Post-MI	–0.0120	0.0002	Until death	Sullivan and Ghushchyan; MI[76]
Post-stroke	–0.0400	0.0002	Until death	Sullivan and Ghushchyan; stroke [76]
Utility				
Baseline	0.7930	0.0100	Until death	Szende et al.; EQ-5D norms for Alberta 65- to 74-years-old given as an example (values for each age group displayed in Table 33).[77]

EQ-5D = EuroQol 5-Dimensions questionnaire; 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.[74] Although this data are now getting older and would probably have to be refreshed, this source is still used in several health technology assessments, likely because of the lack of more recent data.[78,79] The EQ-5D disutility value for MI (i.e., –0.0409) had been generated in 62-year-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.[80]

Bleeding Events: Data from the ENGAGE AF-TIMI 48 trial was used for the disutility of bleeding events.[75] 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 three months for up to four 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) than the CADTH meta-analysis patient cohort, 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.[77] 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 33.

Table 33: Baseline Utility Values Per Age Group

Age Group (Years)	Average	Standard Error	Source
18 to 24	0.8730	0.0090	Szende et al.[77]
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 Panel Survey mentioned earlier but from which chronic conditions (present for more than one year) were extracted.[76] 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.

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 34.

Table 34: Model Assumptions

Parameter	Assumption	Comment
All efficacy and safety parameters	There are no differences in the efficacy and safety between six and 12 months of DAPT and between 18 to 48 months of extended DAPT; hence, studies with different DAPT and extended DAPT durations can be pooled	This may or may not be true. Sensitivity analyses were performed by pooling studies of similar DAPT or similar extended DAPT duration.
All event rates	Risks of events at the end of the studies included in CADTH meta-analysis are representative of events throughout the study duration; i.e., there is no change in rates of events over the study period	Available cumulative incidence curves from studies included in the CADTH meta-analysis seem to show linear progression of the cumulative incidence. This is consistent with a stable rate of events throughout the study period.
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 CADTH meta-analysis reported non-fatal events. It was impossible to deduct how many MI, stroke, or bleeding events 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	As study patients were followed until the end of the follow-up period, subsequent events were

Parameter	Assumption	Comment
	studies included in the CADTH meta-analysis	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 CADTH 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 aging 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.[23] 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 or her lifetime.
Mortality in post-PCI patients free from cardiovascular events	Mortality was 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 cardiovascular event	Using a HR over general population mortality rates is an adequate representation of mortality post-cardiovascular events	The mortality in the general population is already including a certain proportion of individuals dying from cardiovascular disease, which may result in an overestimation of cardiovascular death. However, as the HR had been calculated over a general population, this is likely adequate. Nonetheless, alternative scenarios were tested in sensitivity analyses.
Weighted HR of death post-MI and post-stroke	A weighted average of HR values at one to five years is representative of the increased risk of death post-MI or post-stroke for the entire modelling period	This may be an overestimation, as it is possible that the increased risk of death observed within five 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.[57] For the HR of death post-stroke, there was overlap between the three- and five-year value 95% CI (indicating no statistical difference) but the one-year value was statistically lower (i.e., 1.4 versus 1.7 and 1.8) than the three- and five-year values.[55]Alternative scenarios were tested in the sensitivity analyses.
Minor bleed costs	Minor bleed events are managed as outpatient in the emergency room	As per the TIMI bleeding definition, a minor bleed requires medical attention to stop bleeding, including hospitalization and an unscheduled visit to a health care 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	There is no reason to believe that event rates would be different in the two treatment arms once

Parameter	Assumption	Comment
	assumed to be the same in the six- to 12-month DAPT and the extended DAPT arms of the model	extended DAPT is stopped, apart from the possible rebound effect in stent thrombosis as previously noted.
Stent thrombosis	Stent thrombosis is assumed to be diagnosed at hospital visits and is managed via an urgent PCI	As per a discussion with the clinical expert involved in this review (Dr. Robert C. Welsh, Mazankowski Alberta Heart Institute, University of Alberta, Edmonton, AB: personal communication, 2018 Oct 30). Alternative resource use has been tested in a scenario analysis.
Urgent revascularization	Urgent revascularization is an emergency situation equivalent to having an MI	As per a discussion with the clinical expert involved in this review (Dr. Robert C. Welsh: personal communication, 2018 Oct).

AB = Alberta; CI= confidence interval; DAPT = dual antiplatelet therapy; MI = myocardial infarction; PCI = percutaneous coronary intervention; HR = hazard ratio; TIMI = thrombolysis in myocardial infarction.

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 or more
  - patients less than 75-years-old.

Analyses planned for patients with no ACS, smokers, and non-smokers could not be conducted because of too few data available. For all subgroup analyses conducted, the rates of events in the extended DAPT phase of the model were taken from the CADTH meta-analyses. However, because of a 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 CADTH 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 49 to Table 56.

Additional sensitivity and scenario analyses were undertaken to address structural uncertainty or parameter uncertainty. For example, when reviewing the studies included in CADTH meta-analysis, it was clear that bleeding events were not reported in 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 CADTH 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:

- 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 type 2 bleeding events were equivalent to TIMI minor and that BARC type 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.
- 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 CADTH 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 six- 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.[23] Over three months, the HRs (extended DAPT over six to 12 months of 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, two scenarios were tested:

- The rates of stroke, MI, and stent thrombosis in the post-extended DAPT phase were multiplied by a calibration factor during the first three 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 three-month period after the discontinuation of extended DAPT.
- A similar approach was taken to bring the rates of events in the post-extended DAPT phase for the extended DAPT arm equal to those of the six- to 12-month DAPT arm after six monthly cycles.

Scenario and sensitivity analyses are described in Table 35 and detailed data inputs can be found in Appendix 13, Table 56.

Table 35: Description of Scenario and Sensitivity Analyses

Scenario/Sensitivity Analysis Description	Justification
Discounting at 0% and 3%	As per CADTH economic guidelines.[81]
Using the risk ratio from CADTH meta-analysis rather than rates in each group	There are small variations between the risk ratios estimated by CADTH 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 bleeds are managed at the emergency room and that some might be managed at the physician's office. This alternative scenario uses the cost of a medical visit (i.e., $77.20) as the cost for a minor bleeding event.[73]
Alternative proportions of antiplatelet drugs	Extreme value scenarios using 100% clopidogrel, 100% prasugrel, and 100% ticagrelor monthly costs.
Dispensing fees	Applied monthly rather than spread over three months.
Alternative resource use for stent thrombosis	Stent thrombosis might require more than an urgent PCI. This alternative scenario has stent thrombosis following the same path as urgent revascularization; i.e., equivalent to an MI.
Alternative utility values (using a 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 cardiovascular complications helps understand the importance of these utility values on the results of the analysis.
Shorter time horizon (19 months)	There is 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 follow-up of post-PCI patients is limited to three to four 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 analyzing 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 six months in three 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 three and five years post-stroke in a Canadian population. It is unknown how close these are to 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 who did not necessarily have a PCI and received DAPT. Furthermore, these rates were available for only up to four or five years post the initial MI or stroke. Removing the rate of secondary MI or stroke allows an estimation of the impact of these on the conclusions.
No CV event (i.e., MI, stroke, etc.) in the post-extended DAPT phase	It is unknown if the rate of CV events post-extended DAPT remains the same throughout the rest of life. This scenario assumes no additional CV events.

ACS = acute coronary syndrome; CV = cardiovascular; DAPT = dual antiplatelet therapy; EQ-5D = EuroQol 5 Dimensions questionnaire; HR = hazard ratio; MACCE = major adverse cardiovascular and cerebrovascular event; MI = myocardial infarction; PCI = percutaneous coronary intervention; TIMI = thrombolysis in myocardial infarction.

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.

Results of Economic Evaluation

Primary Analysis

Clinical Outcomes

The results of the model showed only marginal differences (i.e., ± 1% or 2%) in clinical outcomes between the six- to 12-month DAPT and the extended DAPT arms (Table 36). The largest difference was a 1.24% reduction in MI, which translated into a 0.85% reduction in death post-MI.

Table 36: 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	2.32%	36.94%	39.26%	1.34%	36.68%	38.01%	–1.24%
Stroke	0.73%	13.19%	13.93%	0.70%	13.07%	13.77%	–0.16%
Urgent revascularization	1.20%	11.73%	12.94%	0.73%	11.90%	12.63%	–0.31%
Stent thrombosis	0.91%	8.93%	9.84%	0.30%	9.04%	9.34%	-0.49%
Bleeding events	1.30%	12.05%	13.35%	1.52%	12.20%	13.73%	+0.37%
All-cause death	1.55%			1.74%			+0.18%
Death post-MI		34.64%			33.78%		-0.85%
Death post-stroke		9.41%			9.30%		-0.11%
Fatal bleeding events		0.69%			0.70%		+0.01%

DAPT = dual antiplatelet therapy; MI = myocardial infarction.

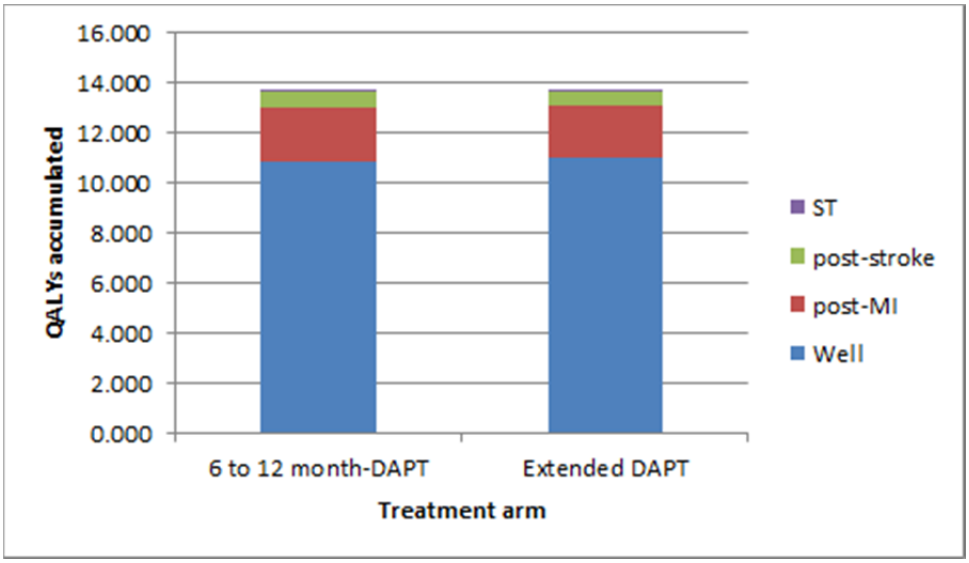
These modest differences in clinical outcomes resulted in small life-year and QALY gains for extended DAPT (Table 37). The QALY differences came from more patients in the “well post-PCI” state rather than post-MI or post-stroke (Figure 85) and less QALY loss because of MI (Figure 86). This offset any QALY loss due to more frequent bleeding events.

Table 37: Model Results — Life-Year and Quality-Adjusted Life-Year (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	1.54	16.18	17.72	1.54	16.19	17.73	0.0166
QALY	1.23	12.41	13.64	1.23	12.42	13.65	0.0160

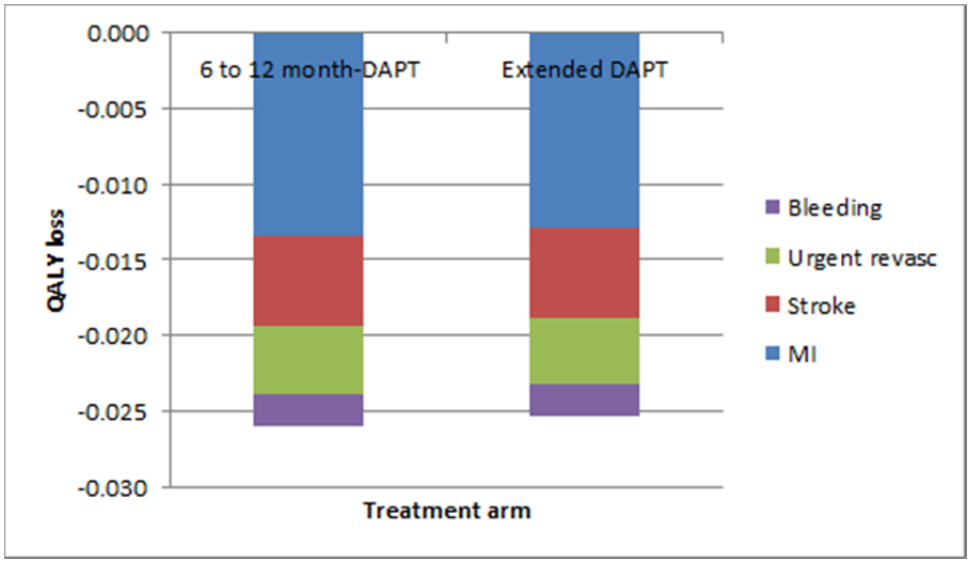
DAPT = dual antiplatelet therapy; LY= life-year; QALY = quality-adjusted life-year

Figure 85: Drivers of Accumulated Quality-Adjusted Life-Year



DAPT = dual antiplatelet therapy; MI = myocardial infarction; QALY = quality-adjusted life-year.

Figure 86: Drivers of Quality-Adjusted Life-Year Loss



DAPT = dual antiplatelet therapy; MI = myocardial infarction; QALY = quality-adjusted life-year.

Costs

The management of post-stroke patients was the largest (57%) contributor to lifetime costs in these patients, followed by post-MI patient management (25%) and acute MI events (9%).

Costs were slightly higher (+$160) with extended DAPT during the extended DAPT phase of the model, but slightly lower (–$1,654) in the post-extended DAPT phase of the model, resulting in overall savings of $707 versus the six- to 12-month DAPT (Table 38). Medication costs were higher (+$376) in the extended DAPT arm, but these were entirely offset by lower costs in acute MI, post-MI, and post-stroke states. Bleeding events had little impact on the overall cost difference.

Table 38: Model Results — Costs (1.5% Discounted)

	6- to 1-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	$787	$39,440	$40,227	$947	$38,573	$39,520	–$707
Medication	$61	$502	$563	$430	$509	$939	+$376
MI	$247	$3,276	$3,523	$142	$3,249	$3,391	–$132
Post-MI	$101	$10,476	$10,577	$59	$9,942	$10,001	–$576
Stroke	$93	$1,384	$1,477	$89	$1,371	$1,459	–$18
Post-stroke	$137	$22,583	$22,720	$130	$22,243	$22,373	–$347
Bleeding	$15	$120	$136	$18	$122	$140	+$4
Stent thrombosis	$5	$42	$47	$2	$43	$45	–$3
Urgent revascularization	$128	$1,055	$1,183	$78	$1,070	$1,148	–$36

DAPT = dual antiplatelet therapy; MI = myocardial infarction.

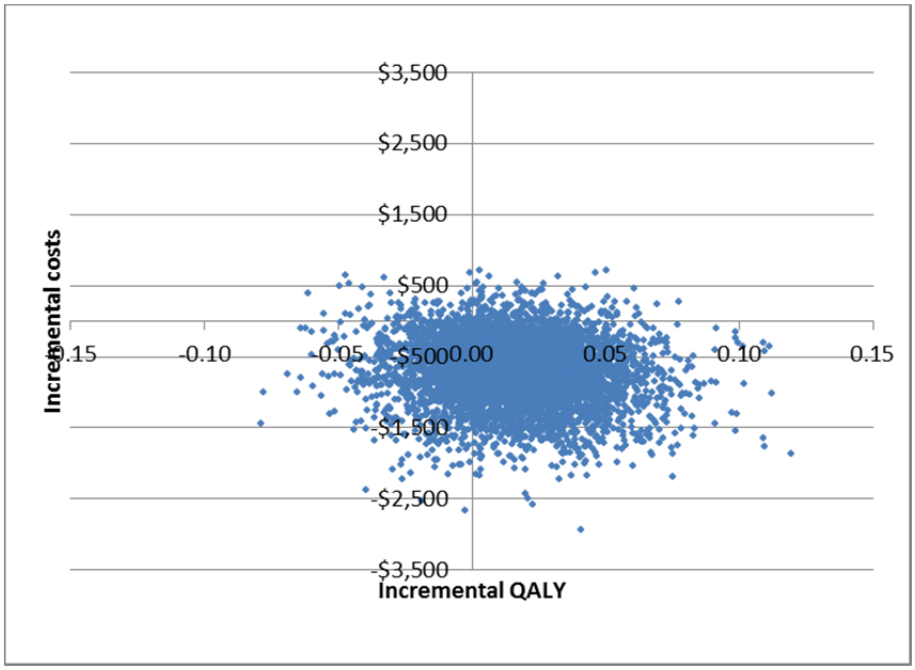
This resulted in the extended DAPT strategy being dominant (i.e., more effective and less costly) over the six- to 12-month DAPT strategy (Table 39). This dominance was observed in 71.6% of the 5,000 iterations, while extended DAPT was dominated (i.e., less effective and more expensive than the six- to 12-month DAPT) in only 1.5% of the iterations. However, 13.8% of the iterations resulted in an ICUR above $50,000 per QALY. The 5,000 iterations are graphically represented in Figure 87.

Table 39: Results From the Base Case

Analysis	6- to 12-month DAPT		Extended DAPT		Incremental		
	Costs	QALY	Costs	QALY	Δ Costs	Δ QALY	ICUR
All patients (base case)	$40,227	13.64	$39,520	13.65	-$707	0.0160	Extended DAPT dominant

Δ Costs = incremental costs; Δ QALY = incremental QALY; DAPT = dual antiplatelet therapy; ICUR: incremental cost-utility ratio; QALY= quality-adjusted life-year.

Figure 87: Cost-Effectiveness Plane



QALY= quality-adjusted life-year.

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 or older
  - patients less than 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 much 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.[23,30] For some of the end points (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.[23] Furthermore, the urgent revascularization end point 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. The exploratory analysis indicates that extended DAPT was less effective, but also less costly, than the six- to 12-month DAPT duration in patients without prior MI, with an ICUR of $18,706 per QALY (Table 40).

Patients With ACS

The inputs for this analysis came from two studies, ITALIC and DAPT, although for some end points only one of them had data.[23,30] Exploratory results in ACS patients indicate that extended DAPT was dominant (i.e., more effective and less costly) over six to 12 months of DAPT in these patients.

Patients With or Without Diabetes

The same ITALIC and DAPT studies provided input for the analysis in diabetes patients.[23,30] For the non- diabetes patients, only one study (DAPT) contributed to the analysis.[23] In these exploratory analyses, extended DAPT was less effective and also less costly than six to 12 months of DAPT in patients with diabetes (ICUR: $2,035 per QALY) and dominant (i.e., more effective and less costly) in patients without diabetes.

Patients Above and Below 75-Years-Old

The ITALIC and PRODIGY studies contributed to the analyses in patients older than 75 years.[24,30] Similar to the other subgroups analyses, some of the end points were populated by data from only one or the other study. For the less than 75-years-old patient population, only the PRODIGY study provided data.[24] These exploratory analyses indicate that extended DAPT is more expensive and less effective than six to 12 months of DAPT (i.e., six- to 12-month DAPT-dominant). In patients aged less than 75-years, the exploratory analysis indicates that extended DAPT is more expensive and more effective than six to 12 months of DAPT, with an ICUR of $37,901 per QALY.

Table 40: Model Results — Subgroup Analyses

Subgroup	6- to 12-month DAPT		Extended DAPT		Incremental		
	Costs	QALY	Costs	QALY	Δ Costs	Δ QALY	ICUR
All patients (base case)	$40,227	13.64	$39,520	13.65	–$707	0.0160	Extended DAPT dominant
Prior MI	$56,045	12.94	$53,936	13.00	–$2,109	0.0583	Extended DAPT dominant
No prior MI	$46,773	13.48	$45,697	13.42	–$1,076	–0.0575	$18,706
ACS	$48,826	13.17	$47,229	13.24	–$1,597	0.0685	Extended DAPT dominant
Diabetes	$51,880	13.14	$51,749	13.08	–$130	–0.0640	$2,035
No diabetes	$45,525	13.41	$44,239	13.43	–$1,286	0.0177	Extended DAPT dominant
More than 75-years-old	$9,596	6.51	$14,491	6.47	$4,895	–0.0394	6 to 12 months DAPT dominant
Less than 75-years-old	$33,016	14.10	$37,406	14.22	$4,390	0.1158	$37,901

Δ Costs = incremental costs; Δ QALY = incremental QALY; ACS = acute coronary syndrome; DAPT = dual antiplatelet therapy; ICUR: incremental cost-utility ratio; QALY= quality-adjusted life-year.

Sensitivity Analyses

The results of the sensitivity analyses are shown in Table 41. In most sensitivity analyses, extended DAPT remained dominant; i.e., more effective and less expensive than six to 12 months of DAPT. However, four sensitivity analyses stand out as having an ICUR greater than $25,000 per QALY. These are when ticagrelor is assumed to be the sole P2Y12 inhibitor used in the DAPT regimen (ICUR: $40,696 per QALY) when the analysis is performed on a shorter time horizon (i.e., 19 months; ICUR: $545,427 per QALY) and when using studies with an extended DAPT duration of 24 to 30 months (ICUR: $284,371 per QALY) and of 36 to 48 months (ICUR: $54,413 per QALY), only. As previously mentioned, P2Y12 inhibitor-specific analyses could not be performed because of 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 six 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 analyzing studies where the control arm had a six-month versus a12-month DAPT duration, it can be seen that the incremental benefit is greater in studies where the control arm had a six-month duration. Savings are seen in the studies where the control arm is of a 12-month duration, but not where it is when a six-month duration. Therefore, extended DAPT appears cost-effective compared with a six-month duration in the control arm and dominant (i.e., more effective and less expensive) compared with a 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 an increasing extended DAPT treatment duration, with the 18-month extended DAPT duration showing the largest incremental benefit of all sensitivity analyses (i.e., 0.1048). It is important to note that the 18-month extended DAPT duration analysis is based on only one study (NIPPON, with 1,600 patients in each group) where the control group received six months of DAPT. These sensitivity analyses also show that 24 months or more of extended DAPT duration might not be a cost-effective option with an ICUR more than $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 four years).[54,57] The second scenario used a similar calibration factor, this time applied to both the HR of death post-MI and the HR of death post-stroke in order to give an all-cause death proportion at six years similar to that reported by the US long-term, post-PCI study described previously (i.e., 11.8%).[56] 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 or all events had little impact on the results. Adding a rebound effect at discontinuation of extended DAPT reduced the benefit and even produced a QALY loss when the rates of MI, stroke, and stent thrombosis reached those of the control group six months after the discontinuation of extended DAPT.

In scenarios where extended DAPT was dominant, costs varied only minimally. The smallest saving ($20) was seen with the calibration of death post-MI, while the largest saving ($1,253) was seen with the 12-month DAPT duration in the control arm. QALY gains varied a little more with the smallest QALY gain (0.0092) seen with one of the alternative bleeding count methods and the largest QALY gain (0.1049) noted with the 18-month extended DAPT duration.

Table 41: Model Results — Scenario Analyses

Scenario	6- to 12-Month DAPT		Extended DAPT		Incremental		
	Costs	QALY	Costs	QALY	Δ Costs	Δ QALY	ICUR
Base case	$40,227	13.64	$39,520	13.65	–$707	0.0160	Extended DAPT dominant
Discounting: 0%	$50,759	16.23	$49,912	16.26	–$846	0.0167	Extended DAPT dominant
Discounting: 3%	$32,464	11.65	$31,877	11.66	–$587	0.0096	Extended DAPT dominant
Risk ratios versus rates	$40,187	13.63	$39,525	13.65	–$662	0.0223	Extended DAPT dominant
Alternative Bleeding Count							
a)	$40,254	13.60	$39,550	13.61	–$704	0.0140	Extended DAPT dominant
b)	$40,233	13.41	$39,557	13.42	–$676	0.0092	Extended DAPT dominant
Minor bleed costs	$40,164	13.63	$39,445	13.65	–$719	0.0158	Extended DAPT dominant
Alternative Proportion for Antiplatelet Agents							
a) 100% clopidogrel	$40,233	13.63	$39,340	13.65	–$893	0.0157	Extended DAPT dominant
b) 100% prasugrel	$40,319	13.64	$40,324	13.65	$5	0.0156	$322
c) 100% ticagrelor	$40,243	13.63	$40,895	13.65	$653	0.0160	$40,696
Dispensing fee (monthly)	$41,210	13.63	$40,600	13.65	–$609	0.0160	Extended DAPT dominant
Alternative resources use for stent thrombosis	$43,859	13.46	$42,827	13.48	–$1,032	0.0257	Extended DAPT dominant
Alternative utility values	$40,119	13.61	$39,398	13.63	–$720	0.0153	Extended DAPT dominant
Shorter time horizon (19 months)	$787	1.23	$947	1.23	$161	0.0003	$546,427
DAPT duration in control: 6 months	$29,562	14.06	$29,640	14.08	$78	0.0264	$2,958
DAPT duration in control: 12 months	$43,589	13.49	$42,336	13.51	–$1,253	0.0186	Extended DAPT dominant
Extended DAPT duration: 18 months	$29,033	14.11	$28,912	14.21	–$121	0.1048	Extended DAPT dominant
Extended DAPT duration: 24 months to 30 months	$45,840	13.42	$44,904	13.42	–$937	–0.0033	$284,371
Extended DAPT duration: 36 months to 48 months	$30,904	14.02	$30,448	14.01	–$456	–0.0084	$54,413
Alternative Values for Survival in the Post- Extended DAPT Phase							
a) Post-MI death calibration	$38,945	13.46	$38,280	13.48	–$666	0.0221	Extended DAPT dominant
b) All-cause death calibration	$13,899	11.57	$13,879	11.67	–$20	0.0986	Extended DAPT dominant
No secondary events	$34,182	13.63	$33,910	13.64	–$272	0.0163	Extended DAPT dominant
No events during the post-extended DAPT phase	$5,929	14.65	$5,225	14.69	–$704	0.0376	Extended DAPT dominant

Scenario	6- to 12-Month DAPT		Extended DAPT		Incremental		
	Costs	QALY	Costs	QALY	Δ Costs	Δ QALY	ICUR
Rebound effect							
a) Maximal rebound at 3 months	$40,157	13.64	$39,737	13.65	–$420	0.0078	Extended DAPT dominant
b) Rates reaching control rates at 6 months	$40,214	13.63	$40,171	13.62	–$43	–0.0070	$6,132

Δ Costs = incremental costs; Δ QALY = incremental QALY; DAPT = dual antiplatelet therapy; ICUR: incremental cost-utility ratio; MI = myocardial infarction; QALY= quality-adjusted life-year.

Validation

Results of the extended DAPT phase of the model compared with the results of the CADTH meta-analysis are shown in Table 42. In general, the model was able to reproduce the results of the CADTH 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 where 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 CADTH meta-analysis is on bleeding events. Although at first sight it seems that the model is underestimating the number of bleeding events, this is because of 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, and DES-LATE) reported bleeding events with the TIMI classification.[26,29,30,33] In two of these studies (OPTIDUAL and DES-LATE), extended DAPT was given for 24 months to 36 months beyond the initial six to 12 months, while the other two studies were 18 and 17 months. So, the risks calculated in the CADTH meta-analysis are for an average extended DAPT duration of 23 months beyond the initial six 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 CADTH meta-analysis results, which are reported for a longer extended DAPT duration.

Table 42: Comparison of the Model Results (Extended DAPT Phase) and CADTH Meta-Analysis

Clinical Outcome	Model Results			CADTH Meta-analysis Results		
	6 to 12 months DAPT	Extended DAPT	RR	6 to 12 months DAPT	Extended DAPT	RR
MI	2.32%	1.34%	0.5767	2.38%	1.38%	0.5790
Stroke	0.73%	0.70%	0.9513	0.76%	0.71%	0.9370
Urgent revascularization	1.20%	0.73%	0.6056	1.15%	0.70%	0.6050
Stent thrombosis	0.91%	0.30%	0.3333	0.89%	0.31%	0.3800
Bleeding	1.30%	1.52%	1.1709	1.94%	2.17%	1.1162
Bleeding (major)				1.36%	1.29%	0.9510
Bleeding (minor)				0.59%	0.87%	1.4190
Death	1.55%	1.74%	1.1188	1.58%	1.79%	1.0680

DAPT = dual antiplatelet therapy; MI = myocardial infarction; RR = relative risk.

Only two other analyses compared various DAPT durations and resulted in diverging conclusions for extended DAPT.[35,42] 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., the CADTH model estimates more MI and slightly less bleeding events, while stent thromboses are in the same range.[35] However, both costs and QALY are higher in CADTH analysis, likely because of a lower risk of death in post-stroke patients who are the largest contributor of costs in the CADTH analysis. Costs are slightly higher in the analysis by Jiang and You, while QALYs are lower.[42] This is likely because of higher unit costs.

Discussion

Summary of Clinical Evidence

Among all participants, extending DAPT beyond 12 months may reduce the risk of MI and stent thrombosis but may also increase the risk of bleeding. There were no significant differences in the risk of all-cause or cardiovascular death, stroke, urgent target revascularization, MACCE, or gastrointestinal bleeding between extended DAPT (more than 12 months) and standard-duration DAPT (six to 12 months). One large RCT (DAPT Trial) reported an increased risk of non-cardiovascular death among participants who received extended DAPT; however, this finding was not replicated in two smaller RCTs.

Most of the included studies enrolled participants who underwent PCI with DES insertion. The findings for this subgroup were therefore similar to the reference case involving all participants. Two RCTs (DAPT and PRODIGY) included a small proportion of participants with a BMS (15% to 25%), and data were not reported for all the outcomes of interest. The available data for participants with a BMS suggest an increased risk of BARC type 2 and type 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 BMS (n = 2,179) and should be interpreted with caution.

Data were limited for some subgroup analyses. We highlight the differences between groups, as follows:

Prior Myocardial Infarction

- Participants with a previous MI who received DAPT for more than 12 months had a reduced risk of MI, MACCE, and stent thrombosis but an increased risk of moderate bleeding. No significant differences were found in the risk of death (all-cause, cardiovascular), stroke, urgent revascularization, TIMI minor bleeding, GUSTO severe bleeding, or BARC type 3 or type 5 bleeding.
- Participants without a previous MI had an increased risk of all-cause death and moderate bleeding with extended DAPT but with a lower risk of MI 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 MI 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), MI, stroke, stent thrombosis, urgent revascularization, MACCE, and TIMI minor bleeding.
- Participants without diabetes had a lower risk of MI, stent thrombosis, and MACCE, but a 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 six to 12 months, as well as increased risk of GUSTO moderate or severe bleeding and BARC type 2, type 3, or type 5 bleeding. There were no significant differences between DAPT durations for the risk of death (all-cause, cardiovascular), MI, 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 MI but also had an increased risk of GUSTO moderate or severe bleeding and BARC type 2, type 3, or type 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 MI and stent thrombosis with extended DAPT, with no significant difference in the risk of GUSTO moderate or severe bleeding or BARC type 2, type 3, or type 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.

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 priori 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 MI; however, this benefit was accompanied by an increase of bleeding.

Patients with a prior MI, those with ACS at presentation, as well as patient with no diabetes, or aged less than 75 years, may derive the most benefit from extended DAPT; accordingly, individualized risk assessments should be made to determine the 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,[1] which found some patient subgroups, such as those with prior MI or aged less than 75 years, may receive the most benefit from extended 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 2014, the FDA issued a Safety Communication concerning the increased risk of death observed in the DAPT trial.[82] In this study, participants who received 30 months of DAPT were at higher risk of death compared to those who received 12 months of DAPT.[23] Specifically, the DAPT study reported 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 2015, the FDA issued an update to their 2014 Safety Communication stating that, in their meta-analysis involving the DAPT trial and “other long-term clinical

trials," they had found no increased risk of all-cause death with extended DAPT (more than 12 months) compared with short-term (six months or less) DAPT.[83] Also, a patient-level meta-analysis of cardiovascular trials assessing the impact of continued clopidogrel use on mortality and cancer was published in 2018. While results indicate that prolonged clopidogrel therapy has no overall effect on mortality or cancer, they also indicate that such therapy reduces ischemic events, including MI and stroke, but increases rates of bleeding, including a 0.12% absolute increase in fatal bleeding ($P = 0.03$). It should be noted, however, that this meta-analysis was interested in a more diverse cardiovascular population than ours. Indeed, while this meta-analysis included three trials that enrolled patients with coronary artery disease after PCI or ACS, including patients on clopidogrel from the DAPT trial, it also included one trial of patients with recent lacunar stroke, one trial of patients at high risk of atherothrombotic events and one trial of patients with atrial fibrillation. Of interest, while it is reassuring that no increase in mortality was observed, results of this meta-analysis do, however, raise potential questions on the net health impact of prolonged clopidogrel therapy when accounting for the competing effects of clopidogrel therapy on ischemic and bleeding events.[84]

In the present review, we compared extended DAPT to DAPT for six to 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.[22,29] 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 MI and an increased risk of stroke among those aged more than 75 years who received extended DAPT. Again, these findings highlight the importance of performing individualized assessments 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.

Strengths and Limitations of the Clinical Systematic Review

Strengths

We performed a comprehensive review of published RCTs that aimed to compare extended DAPT (more than 12 months) with standard DAPT; i.e., 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 also analyzed data for important subgroups of patients who may derive benefits or experience harms with prolonged DAPT, thus providing clinicians with considerations for patient characteristics that may change or influence decisions about the duration of DAPT following PCI.

Limitations

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

Most of the included trials involved the use of clopidogrel as the P2Y12 inhibitor associated with ASA; limited subgroup data were available for prasugrel and none for ticagrelor. As such, the findings of this review mainly apply to clopidogrel. Given that clopidogrel is still currently widely used after PCI, these findings are nonetheless important for clinicians looking to optimize the care of their patients who have undergone 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 after PCI should accommodate the 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 the findings of the PEGASUS-TIMI 54 trial,[34] 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 the results may be informative to clinical and policy decisions in practice.

Because of the current clinical use of ticagrelor, at a dose of 60 mg twice daily for patients with a previous MI (as opposed to the currently indicated 90 mg twice daily post-ACS prophylaxis), reimbursement of this drug is a policy issue related to the policy questions being considered in this report. Importantly, the 60 mg dose of ticagrelor in the PEGASUS-TIMI 54 trial reduced the rate of this trial's primary efficacy end point (i.e., a composite of cardiovascular death, MI, or stroke). This is reflected in the 2016 listing recommendation from the CADTH Canadian Drug Expert Committee which, among other criteria or condition, involves meeting the inclusion criteria of the PEGASUS-TIMI 54 trial in order to obtain reimbursement for this secondary prevention regimen for up to three years.[85] More specifically, patients must meet the following criteria:

- Patients who are between 12 and 24 months from their most recent MI, and less than 12 months since dual antiplatelet coverage with ASA and an adenosine diphosphate receptor inhibitor, with a high risk of subsequent cardiovascular events, defined as requiring at least one of:
  - age of 65 years or greater
  - diabetes requiring medication
  - second prior spontaneous MI (more than one year ago)
  - angiographic evidence of multi-vessel coronary artery disease
  - chronic renal dysfunction (defined as creatinine clearance of less than 60 mL/min).[85]

The 2018 Canadian Cardiovascular Society/Canadian Association of Interventional Cardiology Focused Update of Guidelines for the Use of Antiplatelet Therapy includes a DAPT regimen of ASA 81 mg daily and ticagrelor 60 mg twice daily up to three years as an option in patients with ACS who tolerate one year of DAPT without a major bleeding event and who are not at high risk of bleeding. Other P2Y12 options for extended therapy include clopidogrel 75 mg daily or prasugrel 10 mg once daily. In these recommendations, the first year of DAPT must involve the use of ASA 81 mg daily with either ticagrelor 90 mg twice daily or prasugrel 10 mg once daily or clopidogrel 75 mg daily.[6]

The RCTs included in this review 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 DES's were used in some of the participants in the DES-LATE,[26] ARCTIC-Interruption,[33] and DAPT[23] 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[22,24,30,31] randomized patients within the first 30 days after stenting. In contrast, in four trials (DAPT,[23] DES-LATE,[26] OPTIDUAL,[29] and ARCTIC-Interruption[33]), 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 using 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 durations. The majority of subgroup data were obtained from one RCT (the DAPT trial). 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.

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., 0.0160 QALY) and small savings (i.e., $707). However, 98% of this benefit was accrued in the post-extended DAPT phase of the model. In the extended DAPT phase of the model (i.e., the first 19 months following the initial 6- to 12-month DAPT treatment), the incremental benefit was only 0.0003 QALY; there were incremental costs ($161), and the ICUR was $546,427 per QALY.

In our economic analysis, it is unknown if the impact of extended DAPT will remain beyond three to four years, the latter time period being the duration of the studies included in CADTH 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 have to be confirmed in additional studies.[23] 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 the 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 sole P2Y12 inhibitor in the DAPT regimen (assuming that clinical impact is the same across agents), when extended DAPT duration was 24 to 30 or 36 to 48 months, and when the analysis was limited to the duration of the trials included in the 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 indicated that extended DAPT was more effective and less costly, and hence would be the preferred option in patients who had a prior MI and those presenting with ACS. Extended DAPT was less effective and also less

costly (ICUR below $18,706 per QALY) in patients with diabetes and patients with no prior MI. In patients older than 75 years of age, extended DAPT was less effective and more costly than six to 12 months of DAPT (i.e., six- to 12-month DAPT is dominant). In patients less than 75-years-old, extended DAPT was more effective and more costly, with an ICUR of $37,901 per QALY. However, more evidence would be required to provide more robust conclusions.

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 an increased risk of bleeding. Given that most study participants received clopidogrel, these findings mainly apply to clopidogrel-based DAPT regimens. Although data were limited, similar results were found for participants using prasugrel. Indeed, among participants who received prasugrel, using DAPT for at least 12 months was associated with a lower risk of MI, definite or probable stent thrombosis, and MACCE but a higher risk of moderate or severe bleeding, compared with those who received DAPT for six to 12 months. We were unable to assess the benefits and harms for the population of interest in this review (i.e., post-PCI patients) of extended DAPT involving ticagrelor compared with standard-duration, ticagrelor-based DAPT because of a lack of data.

Among those who received clopidogrel, an increased risk of death was observed among participants without prior MI, and an increased risk of stroke was observed among those aged more than 75 years. In general, patients with a prior MI, those with ACS at presentation, patients with no diabetes, or aged less than 75 years may derive the most benefit from extended DAPT provided that the risk of bleeding is 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 ACS. However, it may be less effective, and therefore not preferred, in patients with diabetes, patients with no prior MI, and in patients older than 75 years of age. As such, our economic findings are in line with our clinical findings and call for the careful selection of patients who may benefit most from extended DAPT to ensure that 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 pharmacoeconomic 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.

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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.

MULTI-DATABASE STRATEGY	
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/

MULTI-DATABASE STRATEGY	
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.

MULTI-DATABASE STRATEGY

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.

MULTI-DATABASE STRATEGY

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/

MULTI-DATABASE STRATEGY
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:	November 24 to 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.
29. Lee, C.W. Short-term dual antiplatelet and maintenance clopidogrel therapy after drug eluting stent implantation (STAMP-DES). NCT02494284. In: Clinical trials.gov. Bethesda (MD): U.S. National Library of Medicine. https://clinicaltrials.gov/ct2/show/NCT02494284
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.
31. Mauri L, Elmariah S, Yeh RW, Cutlip DE, Steg PG, Windecker S, et al. Causes of late mortality with dual antiplatelet therapy after coronary stents. *Eur Heart J*. 2016;37(4):378.
32. Mauri L, Kereiakes DJ, Normand SL, Wiviott SD, Cohen DJ, Holmes DR, et al. Rationale and design of the dual antiplatelet therapy study, a prospective, multicenter, randomized, double-blind trial to assess the effectiveness and safety of 12 versus 30 months of dual antiplatelet therapy in subjects undergoing percutaneous coronary intervention with either drug-eluting stent or bare metal stent placement for the treatment of coronary artery lesions. *Am Heart J*. 2010;160(6):1035.
33. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med*. 2014;371(23):2155-66
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.
35. Nakamura M, Iijima R, Ako J, Shinke T, Okada H, Ito Y, et al. Dual antiplatelet therapy for 6 versus 18 months after biodegradable polymer drug-eluting stent implantation. *JACC Cardiovasc Interv*. 2017;10(12):1189.
36. Piccolo R, Gargiulo G, Franzone A, Santucci A, Ariotti S, Baldo A, et al. Use of the Dual-Antiplatelet Therapy Score to guide treatment duration after percutaneous coronary intervention. *Ann Intern Med*. 2017;167(1):17.
37. Piccolo R, Magnani G, Ariotti S, Gargiulo G, Marino M, Santucci A, et al. Ischaemic and bleeding outcomes in elderly patients undergoing a prolonged versus shortened duration of dual antiplatelet therapy after percutaneous coronary intervention: insights from the PRODIGY randomised trial. *EuroIntervention*. 2017;13(1):78.
38. Resor CD, Nathan A, Kereiakes DJ, Yeh RW, Massaro JM, Cutlip DE, et al. Impact of optimal medical therapy in the Dual Antiplatelet Therapy Study. *Circulation*. 2016;134(14):989.
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

44. Valgimigli M, Campo G, Percoco G, Monti M, Ferrari F, Tumscitz C, et al. Randomized comparison of 6- versus 24-month clopidogrel therapy after balancing anti-intimal hyperplasia stent potency in all-comer patients undergoing percutaneous coronary intervention Design and rationale for the PROlonging Dual-antiplatelet treatment after Grading stent-induced Intimal hyperplasia study (PRODIGY). *Am Heart J*. 2010;160(5):804.

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.

47. Yeh RW, Kereiakes DJ, Steg PG, Cutlip DE, Croce KJ, Massaro JM, et al. Lesion complexity and outcomes of extended dual antiplatelet therapy after percutaneous coronary intervention. *J Am Coll Cardiol*. 2017;70(18):2213.

48. Yeh RW, Kereiakes DJ, Steg PG, Windecker S, Rinaldi MJ, Gershlick AH, et al. Benefits and risks of extended duration dual antiplatelet therapy after PCI in patients with and without acute myocardial infarction. *J Am Coll Cardiol*. 2015;65(20):2211.

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.
13. Erratum for Antiplatelet therapy duration following bare metal or drug-eluting coronary stents: The dual antiplatelet therapy randomized clinical trial. *JAMA.* 2016;316(1):105.
14. Erratum for Antiplatelet therapy duration following bare metal or drug-eluting coronary stents: The dual antiplatelet therapy randomized clinical trial. *JAMA.* 2015;313(21):2185.

15. Erratum for Diabetes mellitus and prevention of late myocardial infarction after coronary stenting in the randomized dual antiplatelet therapy study. *Circulation.* 2016; 133(22):e671.

16. Franchi F, Faz GT, Rollini F, Park Y, Cho JR, Thano E, et al. Pharmacodynamic Effects of Switching From Prasugrel to Ticagrelor: Results of the Prospective, Randomized SWAP-3 Study. *JACC Cardiovasc Interv.* 2016;9(11):1089-1098.

17. Genereux P, Giustino G, Witzenbichler B, Weisz G, Stuckey TD, Rinaldi MJ, et al. Incidence, Predictors, and Impact of Post-Discharge Bleeding After Percutaneous Coronary Intervention. *J Am Coll Cardiol.* 2015;66(9):1036-1045.

18. Genereux P, Rutledge DR, Palmerini T, Caixeta A, Kedhi E, Hermiller JB, et al. Stent Thrombosis and Dual Antiplatelet Therapy Interruption With Everolimus-Eluting Stents: Insights From the Xience V Coronary Stent System Trials. *Circ Cardiovasc Interv.* 2015;8(5). pii: e001362.

19. Gilard M, Morice MC. Double antiplatelet therapy duration: Standardize or personalize? *J Am Coll Cardiol.* 2015;65(20):2222-2224.

20. Giustino G, Chieffo A, Palmerini T, Valgimigli M, Feres F, Abizaid A, et al. Efficacy and Safety of Dual Antiplatelet Therapy After Complex PCI. *J Am Coll Cardiol.* 2016;68(17):1851-1864.

21. Grundeken MJ, Lansky A, Tanguay JF, Gershlick A, Baumbach A, Cuisset T. Will this trial change my practice? The Dual Antiplatelet Therapy (DAPT) study - 12 or 30 months of dual antiplatelet therapy after drug-eluting stents. *EuroIntervention.* 2015;11(3):364-365.

22. Helft G. Dual antiplatelet therapy duration after drug-eluting stents: How long? *J Thorac Dis.* 2016;8(8):E844-846.

23. Helft G. Optimal duration of dual antiplatelet therapy after drug-eluting stent implantation. *Arch Cardiovasc Dis.* 2013;106(5):271-273.

24. Helft G. Randomised controlled trial: Prolonged dual antiplatelet therapy after drug-eluting stent reduces the risk of stent thrombosis and major cardiovascular events but increases the rate of bleeding. *Evid Based Med.* 2015;20(3):99.

25. Hillegass WB, Brott BC. Optimal DAPT duration: Each in their own time. *Catheter Cardiovasc Interv.* 2015;85(1):41-2

26. Jeger RV, Pfisterer ME, Sorensen R, von Felten S, Alber H, Bonetti PO, et al. Tradeoff between bleeding and stent thrombosis in different dual antiplatelet therapy regimes: Importance of case fatality rates and effective treatment durations. *Am Heart J.* 2014;168(5):698-705.

27. Kandzari DE, Barker CS, Leon MB, Mauri L, Wijns W, Fajadet J, et al. Dual antiplatelet therapy duration and clinical outcomes following treatment with zotarolimus-eluting stents. *JACC Cardiovasc Interv.* 2011;4(10):1119-1128.

28. Kastrati A, Byrne RA, Schulz S. Will we ever know the optimal duration of dual antiplatelet therapy after drug-eluting stent implantation? *JACC Cardiovasc Interv.* 2011;4(10):1129-1132.

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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 et al., 2014, DAPT; NCT00977938)[23]	Multi-centre, placebo-controlled superiority RCT	≥ 18 years who had undergone PCI with a DES or BMS. 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 mg/d to 162 mg/d+ clopidogrel (75 mg/d) or prasugrel (10 mg/d) for 12 months, followed by continuation on DAPT or discontinuation of P2Y 12 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, MI, or stroke)	Multi-national	Abbott, Boston Scientific, Cordis, and Medtronic, Bristol-Myers Squibb–Sanofi Pharmaceuticals Partnership, Eli Lilly, Daiichi Sankyo, and the US Department of Health and Human Services
Valgimigli et al., 2012 (PRODIGY; NCT00611286)[24]	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 mg to 325 mg orally or 500 mg IV as a loading dose, 80 mg to 160 mg orally indefinitely) + clopidogrel (300 mg or 600 mg orally as a loading dose), then 75 mg/d for 6 or 24 months DAPT: 6 mo vs. 24 mo Mean/median treatment duration or follow-up not reported	30 d +/–5 days post-PCI	Composite: death of any cause, MI, cerebrovascular accident	Italy	University of Ferrara; no external funding
Collet et al., 2014 (ARCTIC-Interruption; NCT00827411)[33]	Multi-centre, open-label, superiority RCT	≥ 18 yr who underwent DES implantation, who did not have an ischemic event of	SES, PES, ZES, EES	ASA (75 mg/d to 100 mg/d) alone or ASA (75 mg/d to 100 mg/d) + clopidogrel (75 mg/d to 150 mg/d) or prasugrel (10 mg/d)	12 mo post-PCI	Composite: death, MI, stent thrombosis, stroke, urgent revascularization	France	Allies in Cardiovascular Trials Initiatives and Organized Networks (ACTION)

RCT	Study Design	Population	Stent Types	Treatments	Timing of Randomization	Primary Outcome	Country	Funding Source
		the primary end point or any event of the primary safety end point during the first 12 months		DAPT: 12 mo vs. 18 mo to 30 mo Mean/median treatment duration not reported Median follow-up: 17 months (IQR 15 to 18)				Study Group, Fondation de France, Sanofi - Aventis, Cordis, Medtronic, Boston Scientific, Fondation SGAM
Lee et al., 2014 (DES-LATE; NCT01186146)[26]	Multi-centre, open-label RCT	≥ 18 yr who had undergone implantation with a DES 12 months before enrolment, had not had a major adverse cardiovascular event (myocardial infarction, stroke, or repeat revascularization) or major bleeding since implantation, and were receiving dual antiplatelet therapy at the time of enrolment	SES, PES, ZES, EES, and "other DES"	ASA (100 mg/d to 200 mg/d) alone or ASA (100 mg/d to 200 mg/d)+ clopidogrel (75 mg/d) DAPT: 12 mo vs. 24 mo Mean/median treatment duration not reported Median follow-up: 42 months (IQR 24.7 to 50.7)	12 mo to18 mo post-PCI	Composite: death resulting from cardiac causes, MI, or stroke	Korea	CardioVascular Research Foundation, Seoul, Korea; and the Health 21 R&D Project, Ministry of Health and Welfare, Korea
Gilard et al., 2015 (ITALIC; NCT01476020)[30]	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 mg/d to 325 mg/d + clopidogrel 75 mg/d, prasugrel 60 mg/d, or ticagrelor 90 mg twice daily DAPT: 6 mo vs. 24 mo Mean/median treatment duration or follow-up not reported	During PCI hospitalization; patients were withdrawn if an end point occurred during the first 6 mo of DAPT	Composite: death, MI, urgent target vessel revascularization, stroke, and major bleeding	Multi-national	Abbott Vascular

RCT	Study Design	Population	Stent Types	Treatments	Timing of Randomization	Primary Outcome	Country	Funding Source
Helft et al., 2016 (OPTIDUAL; NCT00822536)[29]	Multi-centre, open-label superiority RCT	≥ 18 yr with symptoms of stable angina, silent ischemia, or acute coronary syndrome (unstable angina, non-STEMI,, or STEMI), who had not experienced a major cardiovascular, cerebrovascular, or major bleeding event in the first 12 mo post-PCI	SES, PES, ZES, EES, BES	ASA (75 mg/d to 160 mg/d) alone or ASA (75 mg/d to 160 mg/d) + clopidogrel (75 mg/d) DAPT: 12 mo vs.18 mo to 48 mo Mean/median treatment duration not reported Median follow-up: 22 mo after randomization (median follow-up after stenting: 33.4 months)	12 +/– 3 mo post-PCI	Composite: death, MI, stroke, major bleeding	France	Assistance Publique– Hôpitaux de Paris (Département de la Recherche Clinique et du Développement), Programme Hospitalier de Recherche Publique-PHRC 2008, and unrestricted research grants from Fédération Française de Cardiologie, Cordis, Boston, Medtronic, Terumo, and Biotronik
Nakamura et al., 2017 (NIPPON; NCT01514227)[22]	Multi-centre, non-inferiority open-label RCT	21yr to 79 yr, with coronary artery disease, including acute MI	DES (Nobori[a])	ASA (81 mg/d to 162 mg/d) + clopidogrel (75 mg/d) or ticlopidine (200 mg/d)[b] DAPT: 6 vs. 18 months Mean/median treatment duration not reported Median follow-up: 435 days (14.5 mo) in the long-term DAPT group and 430 days (14.3 mo) in the short-term DAPT group	During hospitalization for PCI	Composite: all-cause mortality, MI, stroke, major bleeding	Japan	Associations for Establishment of Evidence in Interventions
Dadjou et al., 2016 (NCT02327741)[31]	Multi-centre, open-label[c] randomized	50 yr to70 yr, with stenosis more than 70% in any coronary vessel with reference	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)	At PCI	Composite: cardiovascular death, the incidence of stent reocclusion,	Iran	Baghiatollah University and the Education Development Center of Shiraz

RCT	Study Design	Population	Stent Types	Treatments	Timing of Randomization	Primary Outcome	Country	Funding Source
		diameter of more than 2.25 that was suitable for PCI		DAPT: < 1 yr vs. > 1 yr Mean/median treatment duration not reported Follow-up duration was at least 36 months		bleeding outcomes (not defined)		University of Medical Sciences

BES = biolimus-eluting stent; BMS = bare-metal stent; DAPT = dual antiplatelet therapy; d = day; DAPT = dual anti-platelet therapy; DES = drug-eluting stent; EES = everolimus-eluting stent; IQR = interquartile; IV = intravenous; 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.

[a] Biodegradable polymer-coated DES.
[b] Less than 3% of patients received ticlopidine.
[c] Open-label inferred from description of methods, not explicitly stated.

Appendix 5: Baseline Participant Characteristics

Author, Year	DAPT Duration, Months (Number Randomized)	Age, Year, Mean (SD)	Number (%) of Participants					
			Male	Diabetes	Current Smoking	Former Smoking	Prior MI	History of Heart Failure
Nakamura et al., 2017 (NIPPON)[22a]	6 mo (1,886) 18 mo (1,887)	67.4 (9.6) 67.2 (9.9)	1,304 (78.8) 1,312 (79.4)	619 (37.4) 635 (38.4)	960 (58.0) 997 (60.3)	NR	201 (12.2) 195 (11.8)	NR
Dadjou et al., 2016[31b]	< 12 mo (502) > 12 mo (508)	60 (10[c])	647 (64.0)	283 (28.0)	341 (33.8)	NR	NR	NR
Helft et al., 2016 (OPTIDUAL)[29]	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 et al., 2015 (ITALIC)[30]	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 et al., 2014 (DAPT)[23]	12 mo (5,786) 30 mo (5,862)	61.2 (10.3) 61.4 (10.3)	4,318 (74.6) 4,405 (75.1)	1,654 (28.7) 1,737 (29.8)	1,560 (27.4) 1,582 (27.4)	NR	1,204 (21.1) 1,252 (21.7)	251 (4.4) 273 (4.7)
Lee et al., 2014 (DES-LATE)[26]	12 mo (2,415) 24 mo (2,531)	62.3 (10.1) 62.5 (10.0)	1,749 (69.6) 1,749 (69.1)	709 (28.2) 709 (28.0)	722 (28.7) 693 (27.4)	NR	92 (3.7) 103 (4.1)	NR
Collet et al.,2014 (ARCTIC-INT)[33]	12 mo (641) 18 mo to 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 et al., 2012 (PRODIGY)[24]	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

DAPT = dual anti-platelet therapy; MI = myocardial infarction; mo = months; NR = not reported; SD = standard deviation; yr = year.

[a] Characteristics data for patients who did not experience an event in the first six months of DAPT.

[b] Data reported for whole population, not by treatment arm.

[c] Assumed to be SD.

Appendix 6: Baseline Participant Characteristics (Continued)

Author, Year	DAPT Duration, Months (Number Randomized)	Number (%) of Participants[a]			
		Complex Lesions[c]	STEMI	NSTEMI	Unstable Angina
Nakamura et. al, 2017 (NIPPON)[22b]	6 mo (1,886) 18 mo (1,887)	NR	198 (12.0) 196 (11.9)	33 (2.0) 26 (1.6)	296 (17.9) 230 (20.0)
Dadjou et al., 2016[31]	< 12 mo (502) > 12 mo (508)	NR	NR	NR	NR
Helft et al., 2016 (OPTIDUAL)[29]	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 et al., 2015 (ITALIC)[30]	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 et al., 2014 (DAPT)[23]	12 mo (5,786) 30 mo (5,862)	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 et al., 2014 (DES-LATE)[26]	12 mo (2,415) 24 mo (2,531)	2,734 (78.2) 2,838 (78.8)	314 (12.5) 314 (12.4)	266 (10.6) 268 (10.6)	971 (38.6) 930 (36.7)
Collet et al., 2014 (ARCTIC-INT)[33]	12 mo (641) 18 to 30 mo (645)	NR	NR	NR	NR
Valgimigli et al., 2012 (PRODIGY)[24]	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)

DAPT = dual anti-platelet therapy; mo = months; NR = not reported; NSTEMI = non-ST-elevation myocardial infarction; STEMI = ST-elevation myocardial infarction.

[a] Unless otherwise stated.
[b] Characteristics data for patients who did not experience an event in the first six months of DAPT.
[c] Number (%) of lesions; type B2 or C based on the American College of Cardiology/American Heart Association classification system.

Appendix 7: Characteristics: Type of Implanted Drug-Eluting Stents Among Randomized Participants

Author, Year	Group	Number (%) of Participants			
		Everolimus	Paclitaxel	Zotarolimus	Sirolimus
Mauri 2014 et al., (DAPT)[23a]	12 mo 30 mo	2,358 (47.7) 2,345 (46.7)	1,316 (26.6) 1,350 (26.9)	622 (12.6) 642 (12.8)	541 (10.9) 577 (11.5)
Helft et al. 2016 (OPTIDUAL)[29]	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 et al., 2015 (ITALIC)[30]	6 mo 24 mo	912 (100) 910 (100)	NA	NA	NA
Lee et al., 2014 (DES-LATE)[26]	12 mo 24 mo	364 (10.4) 427 (11.9)	709 (20.3) 738 (20.5)	664 (19) 682 (18.9)	1,551 (44.3) 1,566 (43.5)
Collet et al., 2014 (ARCTIC-INT)[33b]	12 mo 18 to 30 mo	NR	NR	NR	NR
Valgimigli et al., 2012 (PRODIGY)[24a]	6 mo 24 mo	247 (25.1) 248 (25.1)	245 (24.9) 245 (24.8)	245 (24.9) 248 (25.1)	NR
Nakamura et al., 2017 (NIPPON)[22c]	6 mo 18 mo	NA	NA	NA	NA
Dadjou et al., 2016[31d]	< 12 mo > 12 mo	NR	NR	NR	NR

mo = months; NA = not applicable; NR = not reported.

[a] Participants with an implanted drug-eluting stent (DES).

[b] 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-month to 30-month group, 43% received a first-generation stent and 62% received a second-generation stent.

[c] All patients received Nobori DES.

[d] Included participants with a wide range of stent types (24 individual types); data for each stent type are available in Table 3 of Dadjou et al., 2016.[31]

Appendix 8: Inclusion and Exclusion Criteria for Included Studies

Table 43: Major Inclusion and Exclusion Criteria of Included Randomized Controlled Trials

RCT	Major Inclusion Criteria	Major Exclusion Criteria
PRODIGY[24]	Chronic, stable coronary artery disease or ACS including non-STEMI and STEMI with at least one lesion with a diameter stenosis of ≥ 50% and with a reference vessel diameter of ≥ 2.25 mm	Known allergy to ASA or clopidogrel, history of bleeding diathesis, active bleeding or previous stroke in the past six months, concomitant need of oral anticoagulant therapy, scheduled elective surgery within 24 months of PCI, major surgery within 15 days
DES-LATE[26]	All candidates for DAPT after DES implantation who had not had a major adverse cardiovascular event or major bleeding for 12 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[33]	Planned DES implantation	Primary PCI for STEMI, planned use of GPIIb/IIIa inhibitors, chronic anticoagulation treatment, or bleeding diathesis
ITALIC[30]	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, non-responders to ASA 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[23]	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 bleeding 12 months after PCI	Use of stent with diameter of < 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 of < 3 years
OPTIDUAL[29]	Symptoms of stable angina, silent ischemia, or ACS with ≥ 1 lesion, with stenosis of > 50% located in a native vessel ≥ 2.25 mm in diameter and implanted with ≥ 1 DES or BMS and treated with clopidogrel plus ASA 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 of < 2 years, other revascularization with a DES within 9 months or a BMS within 4 weeks prior to this study
NIPPON[22]	“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 of < 30%, life expectancy of < 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 re-stenosis of DES, or unprotected LMT lesion; history of intracranial bleeding or ischemic stroke within 6 months before enrolment; DES for another lesion within 6 months prior to index PCI

RCT	Major Inclusion Criteria	Major Exclusion Criteria
Dadjou et. al (2016)[31]	Patients with stenosis of more than 70% in any coronary vessel, with a reference diameter of more than 2.25 that was suitable for coronary stenting	Planned surgery within 6 months of PCI unless the DAPT could be continued throughout the perioperative period, history of bleeding diathesis, major surgery within 15 days, active bleeding, previous hemorrhagic stroke in the past 6 months that contraindicated the use of DAT, pregnancy, life expectancy of < 24 months

ACS = acute coronary syndrome; BMS = bare-metal stent; DAPT = dual anti-platelet therapy; DES = drug-eluting stent; GP = glycoprotein; LMT = left main trunk; MI = myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction.

Appendix 9: Study-Level Risk of Bias Assessment

Author, Year (Trial Name)	Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcomes Data	Selective Outcomes Reporting	Other Sources of Bias
Collet et al., 2014 (ARCTIC-INT)[33]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Dadjou et al., 2016[31]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Gilard et al., 2015 (ITALIC)[30]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear
Helft et al., 2016 (OPTIDUAL)[29]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear
Lee et al., 2014 (DES-LATE)[26]	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk
Mauri et al., 2014 (DAPT)[23]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Nakamura et al., 2017 (NIPPON)[22]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear
Valgimigli et al., 2012 (PRODIGY)[24]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Appendix 10: Bleeding Classification System Definitions

BARC (Bleeding Academic Research Consortium)

Type 1: bleeding that is not actionable and does not cause the patient to seek an unscheduled performance of studies, hospitalization, or treatment by a health care professional; it may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a health care 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, type 4, or type 5 but does meet at least one of the following criteria: requiring nonsurgical, medical intervention by a health care professional; leading to hospitalization or increased level of care; or prompting evaluation.

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

Type 3b: overt bleeding plus a hemoglobin drop of 5 g/dL (provided the hemoglobin drop is related to bleed); cardiac tamponade; bleeding requiring surgical intervention for control (excluding dental, nasal, skin, and 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: coronary artery bypass grafting-related bleeding; perioperative intracranial bleeding within 48 hours; reoperation after closure of sternotomy for the purpose of controlling bleeding; transfusion of 5 U of whole blood or packed red blood cells within a 48-hour period; chest tube output 2 L within a 24-hour 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 Streptokinase and t-PA for Occluded Coronary Arteries)

Severe (or life-threatening): intracerebral hemorrhage, resulting in substantial hemodynamic compromise requiring treatment.

Moderate: requiring a blood transfusion but not resulting in a hemodynamic compromise.

ISTH (International Society on Thrombosis and Haemostasis)

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 hemoglobin levels of 1.24 mmol/L (20 g/L or greater) or more, or leading to a transfusion of 2 U or more of whole blood or red cells.

Minor: all reported bleedings not classified as major.

REPLACE-2 (Randomized Evaluation in Percutaneous Coronary Intervention Linking Angiomax to Reduced Clinical Events)

Major: intracranial, intraocular, or retroperitoneal; overt blood loss with a hemoglobin decrease of greater than 3 g/dL; any hemoglobin decrease of greater than 4 g/dL; transfusion of 2 U blood products or more.

Minor: overt bleeding not meeting criteria for major bleeding.

STEEPLE (Safety and Efficacy of Enoxaparin in Percutaneous Coronary Intervention 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 or more of packed red blood cells or whole blood; clinically overt bleeding, causing a decrease in hemoglobin of 3 g/dL or more (or, if the hemoglobin level is not available, a decrease in hematocrit of 10% or greater).

Minor: Gross hematuria not associated with trauma (e.g., from instrumentation); epistaxis that is prolonged, is repeated, or requires plugging or intervention; gastrointestinal hemorrhage; hemoptysis; subconjunctival hemorrhage; hematoma greater than 5 cm or leading to prolonged or new hospitalization; clinically overt bleeding, causing a decrease in hemoglobin of 2 g/dL to 3 g/dL; uncontrolled bleeding requiring protamine sulfate administration.

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

Major: any intracranial bleeding (excluding microhemorrhages of less than 10 mm evident only on gradient-echo magnetic resonance imaging); clinically overt signs of hemorrhage associated with a drop in hemoglobin of 5 g/dL or greater; fatal bleeding (bleeding that directly results in death within seven days).

Minor: clinically overt (including imaging), resulting in a hemoglobin drop of 3 g/dL to less than 5 g/dL.

Appendix 11: Definitions Used in Randomized Controlled Trials

Adapted from Spencer et al., 2015[86] and Wells et al., 2017[1]

PRODIGY[24]

Myocardial Infarction

The diagnosis of acute myocardial infarction (MI) was based on the universal definition of MI. 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 MI:

1. Detection of an increase or decrease in the levels of cardiac biomarkers (preferably troponin) with at least one 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 [LBBB]), 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 three times the 99th percentile have been designated as defining PCI-related MI. 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 five 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 MI.

5. Pathologic findings of acute MI.

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 non-cardiovascular cause could be established.

DES-LATE[26]

Myocardial Infarction

The diagnosis of acute MI was based on the universal definition of MI (provided in the previous section 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 non-cardiac cause could be established.

ARCTIC-Interruption[33]

Myocardial Infarction

Periprocedural MI 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 creatine kinase [CK] level in the absence of CK-muscle/brain [MB]) is decreasing, troponin (or CK-MB) measured six hours after PCI is greater than three times the 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 MI is defined when the troponin (or CK- MB) level measured six hours after PCI is greater than three times the upper limit of normal. Measurements of biomarkers are requested before and six hours after PCI and at discharge.

Stroke

Not described.

Death

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

DAPT[23]

Myocardial Infarction

Periprocedural MI: when the troponin or CK-MB level is greater than three times the upper range limit (URL) within 48 hours of the procedure.

Periprocedural CABG MI: when the troponin or CK-MB level greater than five times the URL within 72 hours of the procedure, or the baseline value is less than the URL and any of the following:

- new pathologic Q waves or LBBB
- new native or graft vessel occlusion
- imaging evidence of loss of viable myocardium.

Spontaneous MI: when the troponin or CK-MB level is greater than the URL, with a baseline value of less than the URL and any of the following:

- symptoms of ischemia
- electrocardiogram changes indicative of new ischemia (new ST-T changes or new LBBB)
- development of pathologic Q waves
- imaging evidence of a new loss of viable myocardium or a new regional wall-motion abnormality.

Silent MI: when no biomarker data are available and there are 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:

- new ST elevation or LBBB
- documented thrombus by angiography or autopsy
- reinfarction, spontaneous, and periprocedural MI: stable or decreasing values on two samples obtained more than six hours apart and a 20% increase three to six hours after the second sample was obtained.

Stroke

A cerebrovascular accident was defined as the occurrence of cerebral infarction (ischemic stroke) or intracerebral hemorrhage and subarachnoid hemorrhage (hemorrhagic stroke). A stroke was defined as the 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:

- persists for more than 24 hours or results in death in less than 24 hours, or
- persists for less than 24 hours if pharmacologic therapy (a thrombolytic drug) or nonpharmacologic therapy (a neurointerventional procedure, such as intracranial angioplasty) is used, or
- persists for 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 non-cardiac cause could be established. Specifically, any unexpected death — even in persons with coexisting, potentially fatal non-cardiac disease (such as cancer or infection) — should be classified as cardiac.

ITALIC[30]

Myocardial Infarction

MI was classified as Q wave or non–Q wave MI. Q wave MI was defined by the recurrence of symptoms and/or the development of new pathologic Q waves in two or more contiguous leads, with elevated CK, CK-MB, or troponin levels. Non–Q wave MI was defined by a greater than two-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 non-cardiovascular death were provided.

OPTIDUAL[29]

MACCE

This uses a composite end point including all-cause mortality, MI, stroke, and major bleeding events.

Myocardial Infarction

MI was classified and adjudicated according to the Academic Research Consortium (ARC) definition.

NIPPON[22]

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):

- cardiac death — any death due to an immediate cardiac cause (e.g., MI, low-output failure, or fatal arrhythmia). Unwitnessed death and death from an unknown cause was classified as cardiac death. This included all procedure-related deaths, including those related to concomitant treatment.
- vascular death — death due to cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular cause.
- non-cardiovascular death.

Any death not covered by the abovementioned 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 two or more continuous electrocardiogram leads) or non–Q wave, and:

- periprocedural — a serum troponin or serum CK-MB level exceeding three times the upper limit of normal within 48 hours after PCI; a serum troponin or serum CK-MB level exceeding five 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; a serum CK-MB level exceeding the upper limit of normal should not be considered as a new MI but as an MI at registration
- spontaneous — when myocardial enzymes are at or above the upper limit of normal, it should be considered as an MI 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
- reinfarction — blood levels of biomarkers measured twice after the onset of MI are stable or decrease and the values at three to six hours after PCI show a greater than 20% increase compared with those obtained at index PCI.

Appendix 12: Use of Ticagrelor in the Pegasus-Timi 54 Trial

The PEGASUS-TIMI 54[34] randomized controlled trial involved participants in 31 countries with a prior myocardial infarction (MI) one to three years before enrolment (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 (older than 65 years, diabetes, a second prior MI, multivessel coronary artery disease, chronic renal dysfunction). In total, 83% of participants underwent stenting. About 17% of participants had more than one prior MI, and about 54% of these were ST-elevation MI.

At study enrolment, all participants were taking ASA 75 mg to 100 mg once daily. The use of P2Y12 inhibitors before enrolment 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 dual antiplatelet therapy before randomization was longer than the eligibility criteria (six months to 12 months), the PEGASUS-TIMI 54[34] randomized controlled trial was not eligible for inclusion in the current systematic review.

Participants in PEGASUS-TIMI 54[34] were randomized to ticagrelor 60 mg or 90 mg twice daily (b.i.d.) or placebo (n = 21,162) and were followed for a median of 33 months (interquartile range 28 month to 37 months). The primary efficacy outcome was a composite of cardiovascular death, MI, or stroke. The primary safety outcome was thrombolysis in MI (TIMI) major bleeding.

Among all participants (with or without percutaneous coronary intervention), both ticagrelor 60 mg and 90 mg b.i.d. reduced the primary outcome (cardiovascular death, MI, or stroke) relative to placebo (ticagrelor 60 mg versus placebo: hazard ratio [HR] 0.84, 95% CI, 0.74 to 0.95; ticagrelor 90 mg versus 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 three-year Kaplan-Meier analysis.[34]

For both doses, ticagrelor use was associated with a lower risk of MI compared with placebo (ticagrelor 60 mg versus placebo: HR 0.84, 95% CI, 0.72 to 0.98; ticagrelor 90 mg versus placebo: HR 0.81, 95% CI, 0.69 to 0.95), with no significant differences in all-cause death (ticagrelor 60 mg versus placebo: HR 0.89, 95% CI, 0.76 to 1.04; ticagrelor 90 mg versus placebo: HR 1.00, 95% CI, 0.86 to 1.16) or cardiovascular death (ticagrelor 60 mg versus placebo: HR 0.83, 95% CI, 0.68 to 1.01; ticagrelor 90 mg versus 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 versus placebo: HR 0.75, 95% CI, 0.57 to 0.98; ticagrelor 90 mg versus 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 versus placebo: HR 2.32, 95% CI, 1.68 to 3.21; ticagrelor 90 mg versus placebo HR 2.69, 95% CI, 1.96 to 3.70), as well as TIMI minor bleeding (ticagrelor 60 mg versus placebo: HR 3.31, 95% CI, 1.94 to 5.63; ticagrelor 90 mg versus placebo HR 4.15, 95% CI, 2.47 to 7.00).[34] Premature discontinuations of treatment were 32.0%, 28.7%, and 21.4% in ticagrelor 90 mg, 60 mg, 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, MI, or stroke) was significantly lower among those who had received ticagrelor (ticagrelor 60 mg versus placebo: HR 0.83, 95% CI, 0.72 to 0.96; ticagrelor 90 mg versus placebo HR 0.86, 95% CI, 0.74 to 0.98). The risk of TIMI major bleeding was, however, higher (ticagrelor 60 mg versus placebo: HR 2.42, 95% CI, 1.70 to 3.44; ticagrelor 90 mg versus placebo HR 2.76, 95% CI, 1.95 to 3.91).[34]

Appendix 13: Pharmacoeconomics

Table 44: 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[35]	2018	Canada	Patients undergoing PCI	DAPT 3 to 6 months versus DAPT 12 months versus DAPT 30 to 36 months	Markov patient-level simulation (lifetime horizon in 63-year-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[38]	2015	US	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 harms; sensitivity analysis on ACS (12 months and 18 months, only) and non-ACS patients	Markov states: • bleeding (major and minor) • death (CV and non-CV) • MI (non-fatal) • stent thrombosis • stroke (hemorrhagic)
Jiang M[42]	2017	US	ACS patients who had DAPT for 12 months after PCI (DES)	ASA 75mg to 162 mg + clopidogrel for 12 months versus further DAPT (ASA + clopidogrel) for 18 months post-PCI	Markov (lifetime in 60-year-old individuals)	Markov states: • bleeding (major) • death (CV) • MI (non-fatal) • stent thrombosis • stroke (non-fatal)
DAPT Versus ASA						
Beinart SC[36]	2005	US (using results from multinational CREDO trial)	Patients with coronary artery disease undergoing PCI	Clopidogrel 75 mg + ASA daily for 1 year versus Clopidrogrel 75 mg daily for 28 days + ASA daily for 1 year	Decision tree (lifetime horizon)	Using: • Health care resources and clinical events collected during the trial: major CV health care-related resources for death, bleeding, MI, stroke; revascularization procedures; in- and outpatient medications (all other ambulatory

First Author	Year Published	Country of Analysis	Patient Population	Interventions	Type of Model	Model Details
						care excluded) • Framingham Heart Study and Swedish database for long-term survival
Kolm P[44]	2007	Canada	ACS	Clopidogrel + ASA versus ASA + placebo for 1 year (CURE study) (PCI-CURE: subset who had a PCI)	Decision tree (1 year)	Health care resources from CURE trial Clinical events: bleeding, death, MI, stroke
Lindgren P[45]	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[46]	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 health care database Clinical events: bleeding, death, MI, stroke
Ringborg A[51]	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[53]	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)

First Author	Year Published	Country of Analysis	Patient Population	Interventions	Type of Model	Model Details
						• MI complication • PCI • stroke
P2Y12 Drugs in DAPT						

Davies A[37]	2013	Germany, Sweden, Netherlands, Turkey (using results of the 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:
						• 3-day acute phase
						• bleeds (major, minor)
						• death (CV)
						• MI (non-fatal)
						• stroke (non-fatal)
						
						Using theTRITON-TIMI trial;
						restricted to 1 primary event and 1 bleed event per patient;
						• risks are implemented in 2 stages:
						  ○ risk of composite end point from TRITON-TIMI trial
						  ○ risk of respective events
						
						Same process for bleeds
						
						No event beyond 12 months is modelled but lifetime related costs (e.g., ischemic events) are accounted for

Gasche D[39]	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 et al.[49])	Using:
						• health care resources and clinical events from the PLATO trial
						• Markov states (populated with external sources):
						  ○ death
						  ○ MI (non-fatal)
						  ○ MI (post-MI)
						  ○ stroke (non-fatal)
						  ○ stroke (post-stroke)

First Author	Year Published	Country of Analysis	Patient Population	Interventions	Type of Model	Model Details
Greenhalgh J[40]	2015	UK (NICE TA182)	ACS patients with PCI divided into 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: ○ death (other vascular) ○ death (non-vascular) ○ MI (fatal) ○ MI (non-fatal) ○ stroke (fatal hemorrhagic) ○ stroke (non-fatal hemorrhagic — not disabling) ○ stroke (non-fatal hemorrhagic — disabling) ○ stroke (ischemic)/TIA — fatal ○ stroke (ischemic)/TIA – non-fatal, not disabling ○ stroke (ischemic)/TIA — non-fatal, disabling
Kazi DS[43]	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) • feath (non-CV) • MI (non-fatal) • MI (post-MI) • revascularization (percutaneous or surgical) • stent thrombosis
Mahoney EM[47]	2010	US	PCI in ACS	Prasugrel + ASA versus clopidogrel + ASA for 6 to 15 months (TRITON-TIMI 38 trial)	Decision tree (15 months)	Health care resources from the TRITON-TIMI 38 trial (US, Australia, Canada, Germany, Italy, Spain, UK, France) Clinical events; bleeding, death, ischemia, MI, revascularization, stroke
Mauskopf JA[48]	2012	US	PCI in ACS	Prasugrel + ASA versus clopidogrel + ASA	Lifetime “disease-progression” model (separate rates for 1st	Model outcomes: • costs — medication, ER visits, in-patient stays • clinical — CV events (MI, stroke, angina,

First Author	Year Published	Country of Analysis	Patient Population	Interventions	Type of Model	Model Details
				for 15 months	month and months 2 to 15)	death), bleeding events; revascularization, rehospitalizations, LYG
Nikolic[49]	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[50]	2014	US	PCI in ACS	Prasugrel + ASA versus clopidogrel + ASA versus genotype-guided treatment	Decision tree (15 months)	Event subtree: • bleeding (major) • death • MI • revascularization • stroke Separate probabilities for month 1 and months 2 to15
Wein B[52]	2017	Denmark, Germany, Switzerland	ACS undergoing PCI	ASA 100 mg lifelong + clopidogrel 75 mg for 12 months versus ASA 100 mg lifelong + prasugrel 5 mg or 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 B[41]	2007	UK	Secondary prevention in patients at high risk of CV events or stroke,	Antiplatelets in secondary prevention; multiple comparisons: clopidogrel versus ASA; clopidrogrel 1	Markov (lifetime in a 60-year-old individual)	Health states: • death • MI (first) • MI (second)

First Author	Year Published	Country of Analysis	Patient Population	Interventions	Type of Model	Model Details
			or ACS	year versus clopidogrel 28 days; dipyridamole + ASA versus ASA; Dipyridamole + ASA versus clopidogrel; ASA versus placebo		• stroke (first) • stroke (second) • CV event (third) Transition probabilities depend on time since start of treatment (0 months to 6 months; 6 months to 12 months; after 12 months)

ACS = acute coronary syndrome; CABG = coronary artery bypass graft; CV = cardiovascular; DAPT = dual anti-platelet therapy; DES = drug eluting stent: DRG = diagnosis-related group; ER = emergency room; LYG = life-year gain; MACCE = major adverse cardiovascular and cerebrovascular event; MI = myocardial infarction; NL = Newfoundland and Labrador; NMA = network meta-analysis; NSTEMI = non–ST-elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST- elevation myocardial infarction; TIA = transient ischemic attack.

Table 45: Detailed Inputs Used to Estimate Transition Probabilities in the Extended Dual Antiplatelet Therapy Phase of the Model

Parameter	Study	Treatment	Monthly Rate	Alpha	Beta	Study Duration (Months)	Distribution
All-cause death	NIPPON[22]	6- to 12-month DAPT	0.000806	16	1,638	12	Beta
		Extended DAPT	0.000353	7	1,646		
	OPTIDUAL[29]	6- to 12-month DAPT	0.000956	24	673	36	
		Extended DAPT	0.000634	16	685		
	ITALIC[30]	6- to 12-month DAPT	0.000660	11	915	18	
		Extended DAPT	0.001203	20	904		
	PRODIGY[24]	6- to 12-month DAPT	0.002228	29	694	18	
		Extended DAPT	0.002452	32	693		
	ARCTIC[33]	6- to 12-month DAPT	0.000826	9	632	17	
		Extended DAPT	0.000638	7	638		
	DAPT[23]	6- to 12-month DAPT	0.000807	84	5,702	18	
		Extended DAPT	0.001005	106	5,756		
	DES-LATE[26]	6- to 12-month DAPT	0.000530	32	2,482	24	
		Extended DAPT	0.000757	46	2,485		
	Weighted average	6- to 12-month DAPT	0.000831				
		Extended DAPT	0.000930				
Bleeding	OPTIDUAL[29]	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	*0.000594*	*15*	*686*		
	ITALIC[30]	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[33]	6- to 12-month DAPT— major	0.000000	0	641	17	
		Extended DAPT—major	0.000000	0	643		
	DES-LATE[26] (Major)	6- to 12-month DAPT— all	0.000398	24	2,490	24	
		Extended DAPT— all	0.000560	34	2,497		
	Weighted average	6- to 12-month DAPT— all	0.000712				
		Extended DAPT— all	0.000826				
		6- to 12-month DAPT—	*0.000233*				

Parameter	Study	Treatment	Monthly Rate	Alpha	Beta	Study Duration (Months)	Distribution
		major					
		Extended DAPT— major	*0.000365*				
		6- to 12-month DAPT— minor	*0.000479*				
		Extended DAPT— minor	*0.000462*				
Non-fatal MI	NIPPON[22]	6- to 12-month DAPT	0.000202	4	1,650	12	Beta
		Extended DAPT	0.000050	1	1,652		
	OPTIDUAL[29]	6- to 12-month DAPT	0.000638	16	681	36	
		Extended DAPT	0.000436	11	690		
	ITALIC[30]	6- to 12-month DAPT	0.000720	12	914	18	
		Extended DAPT	0.000541	9	915		
	ARCTIC[33]	6- to 12-month DAPT	0.000826	9	632	17	
		Extended DAPT	0.000821	9	636		
	DAPT[23]	6- to 12-month DAPT	0.002141	223	5,563	18	
		Extended DAPT	0.001147	121	5,741		
	DES-LATE[26]	6- to 12-month DAPT	0.000447	27	2,487	24	
		Extended DAPT	0.000313	19	2,512		
	Weighted average	6- to 12-month DAPT	0.001268				
		Extended DAPT	0.000725				
Non-fatal stroke	NIPPON[22]	6- to 12-month DAPT	0.000353	7	1,647	12	Beta
		Extended DAPT	0.000302	6	1,647		
	OPTIDUAL[29]	6- to 12-month DAPT	0.000279	7	690	36	
		Extended DAPT	0.000198	5	696		
	ITALIC[30]	6- to 12-month DAPT	0.000360	6	920	18	
		Extended DAPT	0.000421	7	917		
	ARCTIC[33]	6- to 12-month DAPT	0.000367	4	637	17	
		Extended DAPT	0.000547	6	639		
	DAPT[23]	6- to 12-month DAPT	0.000461	48	5,738	18	
		Extended DAPT	0.000408	43	5,819		
	DES-LATE[26]	6- to 12-month DAPT	0.000348	21	2,493	24	
		Extended DAPT	0.000346	21	2,510		
	Weighted average	6- to 12-month DAPT	0.000400				
		Extended DAPT	0.000377				
Stent thrombosis	NIPPON[22]	6- to 12-month DAPT	0.000101	2	1,652	12	Beta
		Extended DAPT	0.000050	1	1,652		
	OPTIDUAL[29]	6- to 12-month DAPT	0.000040	1	696	36	
		Extended DAPT	0.000119	3	698		
	ITALIC[30]	6- to 12-month DAPT	0.000360	6	920	18	
		Extended DAPT	0.000180	3	921		
	ARCTIC[33]	6- to 12-month DAPT	0.000275	3	638	17	
		Extended DAPT	0.000000	0	645		
	DAPT[23]	6- to 12-month DAPT	0.000711	74	5,712	18	
		Extended DAPT	0.000218	23	5,829		
	Weighted average	6- to 12-month DAPT	0.000496				
		Extended DAPT	0.000165				

Parameter	Study	Treatment	Monthly Rate	Alpha	Beta	Study Duration (Months)	Distribution
Urgent revasc-ularization	ITALIC[30]	6- to 12-month DAPT	0.000540	9	917	18	Beta
		Extended DAPT	0.000481	8	916		
	ARCTIC[33]	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 46: 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	1,058	7,435			
	Year 2 (annual	0.018077	244	6,505			
	Years 3 and 4 (annual)	0.016336	441	6,308			
Stroke in MI patient	Overall (annual)	0.010947					Beta
	Year 1 (annual)	0.022136	188	8,305			
	Year 2 (annual	0.005482	74	6,675			
	Years 3 and 4 (annual)	0.005223	141	6,608			
Stroke in stroke patient	Overall	0.019660					Beta
	Year 1	0.030533	487	1,5463			
	Year 3	0.017513	838	1,5112			
	Year 5	0.010934	872	1,5078			
MI in stroke patient	Overall	0.007512					Beta
	Year 1	0.010408	166	15,784			
	Year 3	0.007315	350	15,600			
	Year 5	0.004815	384	15,566			
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; HR = hazard ratio; MI = myocardial infarction.

Table 47: List of ICD-10 Codes Used for Extracting Costs for Bleeding Events From the OCCI Database

Bleeding Site	ICD-10 Code	Description
Gastrointestinal	I850	Esophageal 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 48: Detailed Cost Inputs

Parameter	Value	SE	Alpha	Beta	95% CI LL	95% CI UL	Distribution
Medications							
ASA (monthly)	*$0.42*						Not varied
Clopidogrel	*$7.89*						
Prasugrel	*$57.48*						
Ticagrelor	*$92.82*						
Pharmacist dispensing fees	*$2.94*						
% Clopidogrel	*0.80*		*10,553*	*2,488*			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 centre	*$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	$567.08						Not varied

95% CI LL = lower limit of the 95% confidence interval; 95% CI UL = upper limit of the 95% confidence interval; MI = myocardial infarction; PCI = percutaneous coronary intervention; SE = standard error.

Table 49: Exploratory Subgroup Analysis Data Inputs — Prior Myocardial Infarction[a]

Parameter	Study	Treatment	Monthly Rate	Alpha	Beta	Study Duration (Months)	Distribution
All-cause death	ITALIC[30]	6- to 12-month DAPT	0.001543	4	140	18	Beta
		Extended DAPT	0.001610	4	134		
	DAPT[23]	6- to 12-month DAPT	0.001058	50	2,575	18	
		Extended DAPT	0.001105	54	2,661		
	Weighted average	6- to 12-month DAPT	0.001083				
		Extended DAPT	0.001129				
Bleeding	ITALIC[30]	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[23]	6- to 12-month DAPT— all	0.001164	55	2,570	18	
		6- to 12-month DAPT — major					
		6- to 12-month DAPT — minor					
		Extended DAPT all	0.002394	117	2,598		
		Extended DAPT — major					
		Extended DAPT — minor					
	Weighted average	6- to 12-month DAPT— all	0.001124				
		Extended DAPT — all	0.002278				
Non-fatal MI	ITALIC[30]	6- to 12-month DAPT	0.000772	2	142	18	Beta
		Extended DAPT	0.000403	1	137		
	DAPT[23]	6- to 12-month DAPT	0.002899	137	2,488	18	
		Extended DAPT	0.001391	68	2,647		
	Weighted average	6- to 12-month DAPT	0.002789				
		Extended DAPT	0.001344				
Non-fatal stroke	DAPT[23]	6- to 12-month DAPT	0.000508	24	2,601	18	Beta
		Extended DAPT	0.000389	19	2,696		
Stent thrombosis	DAPT[23]	6- to 12-month DAPT	0.000995	47	2,578	18	Beta
		Extended DAPT	0.000286	14	2,701		
Urgent revasc-ularization	ITALIC[30]	6- to 12-month DAPT	0.001157	3	141	18	Beta
		Extended DAPT	0.000403	1	138		

DAPT = dual antiplatelet therapy; MI = myocardial infarction.

[a] Cohort assumed to have same average age and gender distribution as full cohort.

Table 50: Exploratory Subgroup Analysis Data Inputs — No Prior Myocardial Infarction[a]

Parameter	Study	Treatment	Monthly Rate	Alpha	Beta	Study Duration (Months)	Distribution
All-cause death	DAPT[23]	6- to 12-month DAPT	0.000615	35	3,126	18	Beta
		Extended DAPT	0.001006	57	3,090		
Bleeding	DAPT[23]	6- to 12-month DAPT — all	0.001331	101	3,060	18	Beta
		Extended DAPT —all	0.002542	192	2,955		
Non-fatal MI	DAPT[23]	6- to 12-month DAPT	0.001670	95	3,066	18	Beta
		Extended DAPT	0.001059	60	3,087		
Non-fatal stroke	DAPT[23]	6- to 12-month DAPT	0.000492	28	3,133	18	Beta
		Extended DAPT	0.000441	25	3,122		
Stent thrombosis	DAPT[23]	6- to 12-month DAPT	0.000492	28	3,133	18	Beta
		Extended DAPT	0.000159	9	3,138		
Urgent revasc-ularization[b]		6- to 12-month DAPT	0.000657				Beta
		Extended DAPT	0.000396				

DAPT = dual antiplatelet therapy; MI = myocardial infarction.

[a] Cohort assumed to have same average age and gender distribution as full cohort.

[b] Assumed to be the same as the entire population (16% had a prior myocardial infarction).

Table 51: Exploratory Subgroup Analysis — Acute Coronary Syndrome Patients[a]

Parameter	Study	Treatment	Monthly rate	Alpha	Beta	Study duration (months)	Distribution
All-cause death	ITALIC[30]	6- to 12-month DAPT	0.000556	4	396	18	Beta
		Extended DAPT	0.001232	9	397		
	DAPT[23]	6- to 12-month DAPT	0.000878	28	1,743	18	
		Extended DAPT	0.000769	25	1,780		
	Weighted average	6- to 12-month DAPT	0.000819				
		Extended DAPT	0.000854				
Bleeding	ITALIC[30]	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[23]	6- to 12-month DAPT — all	0.000871	37		18	
		6- to 12-month DAPT — major					
		6- to 12-month DAPT — minor					
		Extended DAPT all	0.001801	78			

Parameter	Study	Treatment	Monthly rate	Alpha	Beta	Study duration (months)	Distribution
		Extended DAPT— major					
		Extended DAPT — minor					
	Weighted average	6- to 12-month DAPT — all	0.000761				
		Extended DAPT all	0.001570				
Non-fatal MI	ITALIC[30]	6- to 12-month DAPT	0.000972	7		18	Beta
		Extended DAPT	0.000821	6			
	DAPT[23]	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[23]	6- to 12-month	0.000376	12		18	Beta
		Extended DAPT	0.000400	13			
Stent thrombosis	DAPT[23]	6- to 12-month DAPT	0.001067	34		18	Beta
		Extended DAPT	0.000277	9			
Urgent revasc-ularization	ITALIC[30]	6- to 12-month DAPT	0.000833	6		18	Beta
		Extended DAPT	0.000000	0			

DAPT = dual antiplatelet therapy; MI = myocardial infarction.

[a] Cohort assumed to have the same average age and gender distribution as full cohort.

Table 52: Exploratory Subgroup Analysis — Diabetes Mellitus Patients[a]

Parameter	Study	Treatment	Monthly Rate	Alpha	Beta	Study Duration (Months)	Distribution
All-cause death	ITALIC[30]	6- to 12-month DAPT	0.001157	7		18	Beta
		Extended DAPT	0.001592	10			
	DAPT[23]	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[30]	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[23]	6- to 12-month DAPT — all	0.001982			18	
		6- to 12-month DAPT	0.001108	33			

Parameter	Study	Treatment	Monthly Rate	Alpha	Beta	Study Duration (Months)	Distribution
		— major					
		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[30]	6- to 12-month DAPT	0.000661	4		18	Beta
		Extended DAPT	0.000637	4			
	DAPT[23]	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[23]	6- to 12-month DAPT	0.000571	17		18	Beta
		Extended DAPT	0.000576	18			
Stent thrombosis	DAPT[23]	6- to 12-month DAPT	0.000605	18		18	Beta
		Extended DAPT	0.000288	9			
Urgent revascularization	ITALIC[30]	6- to 12-month DAPT	0.000496	3		18	Beta
		Extended DAPT	0.000796	3			

DAPT = dual antiplatelet therapy; MI = myocardial infarction.

[a] Cohort assumed to have the same average age and gender distribution as the full cohort.

Table 53: Exploratory Subgroup Analysis — Patients Without Diabetes Mellitus[a]

Parameter	Study	Treatment	Monthly Rate	Alpha	Beta	Study Duration (Months)	Distribution
All-cause death	DAPT[23]	6- to 12-month DAPT	0.000622	50	4,082	18	Beta
		Long-DAPT	0.000835	62	4063		
Bleeding[b]	Weighted average	6- to 12-month DAPT — all	0.000712				Beta
		Extended DAPT —all	0.000803				
		6- to 12-month DAPT — major	0.000233				
		Extended DAPT — major	0.000341				
		6- to 12-month DAPT — minor	0.000479				
		Extended DAPT — minor	0.000462				
Non-fatal MI	DAPT[23]	6- to 12-month DAPT	0.002004	149	3,983	18	Beta
		Long-DAPT	0.000889	66	4,059		

Parameter	Study	Treatment	Monthly Rate	Alpha	Beta	Study Duration (Months)	Distribution
Non-fatal stroke[b]	Weighted average	6- to 12-month DAPT	0.000400				Beta
		Extended DAPT	0.000377				
Stent thrombosis	DAPT[23]	6- to 12-month DAPT	0.000780	58	4,074	18	Beta
		Long-DAPT	0.000229	17	4,108		
Urgent revascularization[b]	Weighted average	6- to 12-month DAPT	0.000657				Beta
		Extended DAPT	0.000396				

DAPT = dual antiplatelet therapy; MI = myocardial infarction.

[a] Cohort assumed to have the same average age and gender distribution as the full cohort.

[b] Assumed to be similar to the entire patient population (69% without diabetes).

Table 54: Exploratory Subgroup Analysis — Patients Greater Than 75 Years[a]

Parameter	Study	Treatment	Monthly Rate	Alpha	Beta	Study Duration (Months)	Distribution
All-cause death	ITALIC[30]	6- to 12-month DAPT	0.000896	2	122	18	Beta
		Extended DAPT	0.002839	7	130		
	PRODIGY[24]	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[30]	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[24]	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	0.001822				

Parameter	Study	Treatment	Monthly Rate	Alpha	Beta	Study Duration (Months)	Distribution
		Extended DAPT — all	0.006896				
Non-fatal MI	ITALIC[30]	6- to 12-month DAPT	0.000000	0	124	18	Beta
		Extended DAPT	0.001217	3	134		
	PRODIGY[24]	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[24]	6- to 12-month DAPT	0.000183	1	303	18	Beta
		Extended DAPT	0.001570	8	275		
Stent thrombosis	PRODIGY[24]	6- to 12-month DAPT	0.001096	6	298	18	Beta
		Extended DAPT	0.000785	4	279		
Urgent revascularization	ITALIC[30]	6- to 12-month DAPT	0.000448	1	123	18	Beta
		Extended DAPT	0.000406	1	136		

DAPT = dual antiplatelet therapy; MI = myocardial infarction.

[a] Age and gender distribution from PRODIGY study only: 80.4(standard deviation: 4.0)-years-old; 65.8% men.

Table 55: Exploratory Subgroup Analysis — Less Than 75-Years-Old[a]

Parameter	Study	Treatment	Monthly Rate	Alpha	Beta	Study Duration (Months)	Distribution
All-cause death	PRODIGY[24]	6- to 12-month DAPT	0.000818	10	669	18	Beta
		Extended DAPT	0.001342	17	687		
Bleeding	PRODIGY[24]	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[24]	6- to 12-month DAPT	0.000736	9	670	18	Beta
		Extended DAPT	0.000789	10	694		
Non-fatal stroke	PRODIGY[24]	6- to 12-month DAPT	0.000245	3	676	18	Beta
		Extended DAPT	0.000710	9	695		

Parameter	Study	Treatment	Monthly Rate	Alpha	Beta	Study Duration (Months)	Distribution
Stent thrombosis	PRODIGY[24]	6- to 12-month DAPT	0.000327	4	675	18	Beta
		Extended DAPT	0.000316	4	700		
Urgent revascularization[b]	Weighted average	6- to 12-month DAPT	0.000657				Beta
		Extended DAPT	0.000396				

DAPT = dual antiplatelet therapy; MI = myocardial infarction.

[a] Age and gender from the PRODIGY STUDY.

[b] Assumed to be similar to entire patient population.

Table 56: 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	0.003414		
	Major bleeding	6- to 12-month DAPT — major	0.000525		
	Minor bleeding	6- to 12-month DAPT — minor	0.002888		
	All bleeding	Extended DAPT —all	0.005703		
	Major bleeding	Extended DAPT — major	0.000877		
	Minor bleeding	Extended DAPT —minor	0.004825		
Initial DAPT 6 months (NIPPON,[22] ITALIC,[30]	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		

Analysis	Parameter	Group	Value	95% CI LL	95% CI UL
PRODIGY[24])	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		
		Extended DAPT	0.000097		
	Urgent revascularization	6- to 12-month DAPT	0.000540		
		Extended DAPT	0.000481		
Initial DAPT 12 months (DAPT, OPTIDUAL,[29] ARCTIC,[33] DES-LATE[26])	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[22])	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[a]	6- to 12-month DAPT	0.000657		
		Extended DAPT	0.000396		
DAPT duration 24 to 30 months (ITALIC,[30] PRODIGY,[24] ARCTIC,[33] DAPT[23])	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		
	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		

Analysis	Parameter	Group	Value	95% CI LL	95% CI UL
	Urgent revascularization	6- to 12-month DAPT	0.000657		
		Extended DAPT	0.000396		
DAPT duration 36 to 48 months (OPTIDUAL,[29] DES-LATE[26])	Overall death	6- to 12-month DAPT	0.000623		
		Extended DAPT	0.000731		
	Bleeding all	6- to 12-month DAPT	0.000984		
		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 [a]	6- to 12-month DAPT	0.000657		
		Extended DAPT	0.000396		

95% CI LL = lower limit of the 95% confidence interval; 95% CI UL = upper limit of the 95% confidence interval; DAPT = dual antiplatelet therapy; HR = hazard ratio.

[a] Assumed to be the same as the full analysis.