CADTH

CADTH TECHNOLOGY REVIEW

Dual Antiplatelet Therapy Following Percutaneous Coronary Intervention: A Review of the Clinical Impact of Treatment Duration

Service Line:	CADTH Technology Review
Issue Number:	8
Publication Date:	August 2017
Report Length:	146 Pages

CADTH

Authors: George A. Wells, Jesse Elliott, Shannon Kelly, Derek So, Michel Boucher, Zemin Bai, Wenfei Liu, Becky Skidmore

Cite As: Dual antiplatelet therapy following percutaneous coronary intervention: a review of the clinical impact of treatment duration. Ottawa: CADTH; 2017 Aug. (CADTH technology review; no.8).

ISSN: 2369-7385 (online)

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.

Reviewers

Content Expert

Derek So, MD, FRCPC, FACC, MSc
Staff Cardiologist and Clinician Investigator
University of Ottawa Heart Institute
Associate Professor, Department of Medicine
University of Ottawa, Ottawa, ON, Canada.

Authorship

George A. Wells contributed to protocol development and interpretation of the data and revised the report for important intellectual content.

Jesse Elliott led the project protocol development; selected studies; extracted, tabulated, and analyzed data; wrote the clinical section of the report; and revised the report based on reviewers' comments.

Shannon Kelly contributed to protocol development and interpretation of the data and revised the report for important intellectual content.

Derek So participated in the conceptualization of clinical approaches, the development of the protocol, and the preparation and review of the draft reports and revised the report for important intellectual content.

Michel Boucher developed the review scope; contributed to the protocol development; assisted with the refinement of the literature search strategy; contributed to the report writing; and critically reviewed draft versions of the report.

Zemin Bai contributed to article selection, study quality assessment, and data extraction and revised the report for important intellectual content.

Wenfei Liu contributed to article selection and revised the report for important intellectual content.

Becky Skidmore contributed to protocol development, executed the literature search, and revised the report for important intellectual content.

All authors approved the final draft report.

Contributors

CADTH would like to acknowledge the following individuals for their contributions: Dr. Shu-ching Hsieh (MAGIC, Ottawa, ON) for her assistance during the screening and data extraction phases of the project, and Ms. Heather MacDonald, MSc, MLIS, (Health and Biosciences Librarian; Carleton University) for her review of the draft search strategy.

Conflicts of Interest

Dr. So has received unrestricted grants from Eli Lilly Canada and Spartan Biosciences for physician-initiated studies. He has also served as an advisory board member for AstraZeneca Canada. No conflicts were declared by any other author.

CADTH

Table of Contents

Abbreviations

ACS	acute coronary syndrome
BARC	Bleeding Academic Research Consortium
BMS	bare-metal stent
CABG	coronary artery bypass grafting
CI	confidence interval
DAPT	dual antiplatelet therapy
DES	drug-eluting stent
GUSTO	Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries
LBBB	left bundle branch block
MACCE	major adverse cardiac and cerebrovascular event
HR	hazard ratio
OR	odds ratio
PCI	percutaneous coronary intervention
RCT	randomized controlled trial
RR	risk ratio
STEMI	ST-elevation myocardial infarction
TIMI	thrombolysis in myocardial infarction

Executive Summary

Context and Policy Issues

Dual antiplatelet therapy (DAPT), the combination of a P2Y12 inhibitor with ASA, is routinely given following percutaneous coronary intervention (PCI) with stenting with the aim of preventing stent thrombosis and other major cardiovascular adverse events.

The optimal duration of DAPT to balance its benefits and harms following PCI is topical. Updated guidelines by the American College of Cardiology and the American Heart Association recommend DAPT for six months following PCI in patients with stable coronary artery disease and for 12 months in patients with acute coronary syndrome (ACS).

In some jurisdictions, reimbursement of P2Y12 inhibitors after stenting may be limited to 12 months, which may impact access to DAPT for some patients who may benefit from extended therapy. Given the current uncertainty about the benefits and harms of extended DAPT therapy beyond one year, further elucidation of the controlled clinical trial data through a comprehensive overview of the evidence is required to inform health care decision-makers, policy-makers, clinicians, and patients.

Objectives

The objective of this overview is to systematically review and summarize the evidence of the benefits and harms associated with extended DAPT following PCI with stenting.

The research questions for this project reflect the information needs of CADTH jurisdictional clients with regard to comparative efficacy and safety:

1. What are the benefits and harms of extended DAPT (> 12 months) with ASA plus a P2Y12 inhibitor (clopidogrel, prasugrel, ticagrelor) compared with DAPT of a shorter duration (6 to 12 months) following PCI with stenting?
2. Are there subgroups of patients for whom the optimal duration of DAPT with ASA plus a P2Y12 inhibitor (clopidogrel, prasugrel, ticagrelor) is different?
3. Does the optimal duration of DAPT with ASA plus a P2Y12 inhibitor (clopidogrel, prasugrel, ticagrelor) depend on the type of stent implanted (bare-metal stent [BMS] or drug-eluting stent [DES])?
4. Is there a rebound effect after withdrawal of P2Y12 inhibitor (clopidogrel, prasugrel, ticagrelor) therapy?

Methods

We performed a systematic overview (umbrella review) of previously published systematic reviews that included randomized controlled trials (RCTs) that aimed to investigate the benefits and harms associated with extending DAPT beyond 12 months. Systematic reviews were selected for inclusion in the umbrella review if they included RCTs involving adult patients who received DAPT after stenting for six to 12 months compared with more than 12 months. The primary outcomes of the review are all-cause, cardiovascular, and noncardiovascular death. Secondary outcomes are myocardial infarction, stroke, stent thrombosis, urgent target vessel revascularization, major adverse cardiovascular events, and bleeding (major, minor,

gastrointestinal). The quality of each included systematic review was evaluated using the AMSTAR (A Measurement Tool to Assess Systematic Reviews) checklist.

Summary of Findings

To address research questions 1 to 4, the systematic umbrella review identified 19 unique systematic reviews that met our inclusion criteria. Of these, 11 provided usable data to assess the benefits and harms associated with extending DAPT beyond 12 months following PCI with stenting. Evidence was available from the systematic reviews to address research question 1, comparing six months, six to 12 months, or 12 months to more than 12 months of DAPT. One review compared durations of extended DAPT using network meta-analysis. To address research questions 2 through 4, we extracted primary data from the RCTs included in the 11 systematic reviews.

Research Question 1

What are the benefits and harms of extended DAPT (> 12 months) with ASA plus a P2Y12 inhibitor (clopidogrel, prasugrel, ticagrelor) compared with DAPT of a shorter duration (6 to 12 months) following PCI with stenting?

Data from 11 systematic reviews were available to address this research question. Relative to shorter-duration DAPT (6 months or 12 months), extending DAPT beyond 12 months was associated with a reduced risk of myocardial infarction, stent thrombosis, and major adverse cardiac and cerebrovascular event (MACCE). Extending the duration of DAPT beyond 12 months may increase the risk of all-cause and noncardiovascular death and major bleeding in this population (Table A).

Table A: Summary of Findings: Outcomes

Outcome	> 12 mo vs. 6 mo	> 12 mo vs. 6 to 12 mo	> 12 mo vs. 12 mo	> 12 mo vs. > 12 mo
All-cause death	⚪	⚪	🔴	⚪
Cardiovascular death	⚪	⚪	⚪	○
Noncardiovascular death	⚪	○	🔴	○
Myocardial infarction	⚪	🟢	🟢	⚪
Stroke	⚪	○	⚪	○
Stent thrombosis	🟢[a]	🟢	🟢	⚪
Urgent revascularization	⚪	○	⚪	○
MACCE	○	🟢	🟢	○
Major bleeding[b]	🔴	○	⚪	○
Minor bleeding	○	○	○	○
Gastrointestinal bleeding	○	○	○	○

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; mo = months; TIMI = thrombolysis in myocardial infarction; vs. = versus.
Notes:
Green circle indicates that extended DAPT is better than shorter-duration DAPT.
Red circle indicates that extended DAPT is worse than shorter-duration DAPT.
Grey circle indicates no significant difference between extended and shorter-duration DAPT.
White circle indicates that no evidence was available to inform the comparison.
[a] Conflicting evidence: 3 systematic reviews reported no significant difference in risk between 6 months and > 12 months of DAPT, while one network meta-analysis reported a significant reduction in risk with 30 months compared with 6 months.
[b] Based on TIMI, BARC, or GUSTO bleeding criteria.

Research Question 2

Are there subgroups of patients for whom the optimal duration of DAPT with ASA plus a P2Y12 inhibitor (clopidogrel, prasugrel, ticagrelor) is different?

Few systematic reviews addressed this research question. Therefore, we obtained primary data from eligible RCTs that were included in the systematic reviews. From a core set of seven RCTs, four provided data addressing the duration of DAPT among a subgroup of patients. Of the a priori–specified subgroups of interest, data were available for patients with ACS, myocardial infarction, diabetes, or peripheral artery disease, for smokers, and for patients with complex or simple lesions. No subgroup data were available for other a priori–specified subgroups: patients with heart failure, unstable angina, vein graft intervention, or left main intervention.

Acute Coronary Syndrome

Compared with six months, extending DAPT beyond 12 months may increase the risk of major bleeding in patients with ACS. Patients without ACS are also at risk of major bleeding with extended DAPT but may experience a reduction in the risk of stent thrombosis (Table B).

Table B: Summary of Findings: Acute Coronary Syndrome

Outcome	ACS			No ACS		
	> 12 mo vs. 6 mo	> 12 mo vs. 6 to 12 mo	> 12 mo vs. 12 mo	> 12 mo vs. 6 mo	> 12 mo vs. 6 to 12 mo	> 12 mo vs. 12 mo
All-cause death	○	○	○	○	○	○
Cardiovascular death	○	○	●	○	○	●
Noncardiovascular death	○	○	○	○	○	○
Myocardial infarction	○	○	●	○	○	●
Stroke	○	○	○	○	○	○
Stent thrombosis	●	○	●	●	○	●
Urgent revascularization	○	○	○	○	○	○
MACCE	○	○	●	○	○	●
Major bleeding	● [a]	○	○	● [b]	○	○
Minor bleeding	○	○	○	○	○	○
Gastrointestinal bleeding	○	○	○	○	○	○

ACS = acute coronary syndrome; BARC = Bleeding Academic Research Consortium; DAPT = dual antiplatelet therapy; MACCE = major adverse cardiac and cerebrovascular events; mo = months.
Notes:
Green circle indicates that extended DAPT is better than shorter-duration DAPT.
Red circle indicates that extended DAPT is worse than shorter-duration DAPT.
Grey circle indicates no significant difference between extended and shorter-duration DAPT.
White circle indicates that no evidence was available to inform the comparison.
[a] Significant increase in BARC type 2 bleeding. No difference for type 3 or type 5 bleeding.
[b] Significant increase in BARC type 2 bleeding. No difference for type 3 bleeding.

Age

Two RCTs provided data for patients aged more than 75 years or less than 75 years, comparing extended DAPT with 12 months.

Compared with 12 months, extending DAPT beyond 12 months may reduce the risk of myocardial infarction, stent thrombosis, and MACCE among patients aged less than 75 years. Patients above age 75 years do not appear to receive similar benefit from extended DAPT (Table C).

Table C: Summary of Findings: Age

Outcome	< 75 years			> 75 years		
	> 12 mo vs. 6 mo	> 12 mo vs. 6 to 12 mo	> 12 mo vs. 12 mo	> 12 mo vs. 6 mo	> 12 mo vs. 6 to 12 mo	> 12 mo vs. 12 mo
All-cause death	○	○	○	○	○	○
Cardiovascular death	○	○	○	○	○	○
Noncardiovascular death	○	○	○	○	○	○
Myocardial infarction	○	●	○	○	○	●
Stroke	○	○	○	○	○	○
Stent thrombosis	○	●	○	○	○	●
Urgent revascularization	○	○	○	○	○	○
MACCE	○	●[a]	○	○	○	●
Major bleeding	○	○	○	○	○	○
Minor bleeding	○	○	○	○	○	○
Gastrointestinal bleeding	○	○	○	○	○	○

DAPT = dual antiplatelet therapy; MACCE = major adverse cardiac and cerebrovascular events; mo = months; RCT = randomized controlled trial.
Notes:
Green circle indicates that extended DAPT is better than shorter-duration DAPT.
Red circle indicates that extended DAPT is worse than shorter-duration DAPT.
Grey circle indicates no significant difference between extended and shorter-duration DAPT.
White circle indicates that no evidence was available to inform the comparison.
[a] Conflicting data reported: One RCT reported a non-significant difference between 12 months and 18 to 30 months, while one RCT reported a significantly lower risk of MACCE for 30 months compared with 12 months.

Myocardial Infarction

Among patients with a prior myocardial infarction, extending DAPT beyond 12 months may increase the risk of major bleeding, while reducing the risk of a subsequent myocardial infarction, stent thrombosis, or MACCE (Table D).

Among patients without myocardial infarction, extending DAPT beyond 12 months may increase the risk of major bleeding and death (all-cause and noncardiovascular), but reduce the risk of a subsequent myocardial infarction and stent thrombosis (Table D).

Table D: Summary of Findings: Myocardial Infarction

Outcome	Myocardial Infarction			No Myocardial Infarction		
	> 12 mo vs. 6 mo	> 12 mo vs. 6 to 12 mo	> 12 mo vs. 12 mo	> 12 mo vs. 6 mo	> 12 mo vs. 6 to 12 mo	> 12 mo vs. 12 mo
All-cause death	○	○	●	○	○	●
Cardiovascular death	○	○	●	○	○	●
Noncardiovascular death	○	○	●	○	○	●
Myocardial infarction	○	○	●	○	○	●
Stroke	○	○	○	○	○	○
Stent thrombosis	○	○	●	○	○	●
Urgent revascularization	○	○	○	○	○	○
MACCE	○	○	●	○	○	●
Major bleeding	○	○	●	○	○	●
Minor bleeding	○	○	○	○	○	○
Gastrointestinal bleeding	○	○	○	○	○	○

DAPT = dual antiplatelet therapy; MACCE = major adverse cardiac and cerebrovascular events; mo = months.
Notes:
Green circle indicates that extended DAPT is better than shorter-duration DAPT.
Red circle indicates that extended DAPT is worse than shorter-duration DAPT.
Grey circle indicates no significant difference between extended and shorter-duration DAPT.
White circle indicates that no evidence was available to inform the comparison.

Diabetes

Among patients with diabetes, extending DAPT beyond 12 months may increase the risk of major bleeding. There were no significant differences in the risk of any other outcome reported between extended and shorter-duration DAPT (Table E).

Among patients without diabetes, extending DAPT beyond 12 months may reduce the risk of myocardial infarction, stent thrombosis, and MACCE (Table E).

Table E: Summary of Findings: Diabetes

Outcome	Diabetes			No Diabetes		
	> 12 mo vs. 6 mo	> 12 mo vs. 6 to 12 mo	> 12 mo vs. 12 mo	> 12 mo vs. 6 mo	> 12 mo vs. 6 to 12 mo	> 12 mo vs. 12 mo
All-cause death	○	○	●	○	○	●
Cardiovascular death	○	○	●	○	○	○
Noncardiovascular death	○	○	●	○	○	○
Myocardial infarction	○	○	●	○	○	●
Stroke	○	○	●	○	○	○
Stent thrombosis	○	○	●	○	○	●
Urgent revascularization	○	○	○	○	○	○
MACCE	●	○	●	●	○	● [a]
Major bleeding	○	○	●	○	○	○
Minor bleeding	○	○	○	○	○	○
Gastrointestinal bleeding	○	○	○	○	○	○

DAPT = dual antiplatelet therapy; MACCE = major adverse cardiac and cerebrovascular events; mo = months; RCT = randomized controlled trial.
Notes:
Green circle indicates that extended DAPT is better than shorter-duration DAPT.
Red circle indicates that extended DAPT is worse than shorter-duration DAPT.
Grey circle indicates no significant difference between extended and shorter-duration DAPT.
White circle indicates that no evidence was available to inform the comparison.
[a] Conflicting data reported: One RCT reported a reduced risk of MACCE among patients randomized to 30 months DAPT compared with 12 months, while two RCTs reported no significant difference in risk between 6 to 12 months and 18 to 30 months DAPT.

Smoking

Among smokers, extending DAPT beyond 12 months may reduce the risk of myocardial infarction, stent thrombosis, and MACCE. No data were available to assess the risk of the other outcomes. The results were consistent among non-smokers (Table F).

Table F: Summary of Findings: Smoking

Outcome	Smoker			Non-Smoker		
	> 12 mo vs. 6 mo	> 12 mo vs. 6 to 12 mo	> 12 mo vs. 12 mo	> 12 mo vs. 6 mo	> 12 mo vs. 6 to 12 mo	> 12 mo vs. 12 mo
All-cause death	○	○	○	○	○	○
Cardiovascular death	○	○	○	○	○	○
Noncardiovascular death	○	○	○	○	○	○
Myocardial infarction	○	○	●	○	○	●
Stroke	○	○	○	○	○	○
Stent thrombosis	○	○	●	○	○	●
Urgent revascularization	○	○	○	○	○	○
MACCE	○	○	● [a]	○	○	● [a]
Major bleeding	○	○	○	○	○	○
Minor bleeding	○	○	○	○	○	○
Gastrointestinal bleeding	○	○	○	○	○	○

DAPT = dual antiplatelet therapy; MACCE = major adverse cardiac and cerebrovascular events; mo = months; PAD = peripheral artery disease.
Notes:
Green circle indicates that extended DAPT is better than shorter-duration DAPT.
Red circle indicates that extended DAPT is worse than shorter-duration DAPT.
Grey circle indicates no significant difference between extended and shorter-duration DAPT.
White circle indicates that no evidence was available to inform the comparison.
[a] Conflicting data reported: One RCT reported a reduced risk of MACCE with extended DAPT among both smokers and non-smokers; however one RCT reported no significant difference between durations.

Lesion Complexity

Among patients with either a complex (type B2 or C) or simple lesion, the risk of MACCE was not significantly different between extended and shorter-duration DAPT.

Peripheral Artery Disease

Among patients with peripheral artery disease, extending DAPT beyond 12 months reduced the risk of all-cause death, cardiovascular death, and MACCE. There were no significant differences in risk for myocardial infarction or stent thrombosis (Table G).

Among patients without peripheral artery disease, extending DAPT beyond 12 months had no significant effect on the risk of all-cause death, cardiovascular death, myocardial infarction, stent thrombosis, or MACCE (Table G).

Table G: Summary of Findings: Peripheral Artery Disease

Outcome	PAD			No PAD		
	> 12 mo vs. 6 mo	> 12 mo vs. 6 to 12 mo	> 12 mo vs. 12 mo	> 12 mo vs. 6 mo	> 12 mo vs. 6 to 12 mo	> 12 mo vs. 12 mo
All-cause death	●	○	○	●	○	○
Cardiovascular death	●	○	○	●	○	○
Noncardiovascular death	○	○	○	○	○	○
Myocardial infarction	●	○	○	●	○	○
Stroke	○	○	○	○	○	○
Stent thrombosis	●	○	○	●	○	○
Urgent revascularization	○	○	○	○	○	○
MACCE	●	○	○	●	○	○
Major bleeding	○	○	○	○	○	○
Minor bleeding	○	○	○	○	○	○
Gastrointestinal bleeding	○	○	○	○	○	○

DAPT = dual antiplatelet therapy; MACCE = major adverse cardiac and cerebrovascular events; mo = months; PAD = peripheral artery disease.
Notes:
Green circle indicates that extended DAPT is better than shorter-duration DAPT.
Red circle indicates that extended DAPT is worse than shorter-duration DAPT.
Grey circle indicates no significant difference between extended and shorter-duration DAPT.
White circle indicates that no evidence was available to inform the comparison.

Research Question 3

Does the optimal duration of DAPT with ASA plus a P2Y12 inhibitor (clopidogrel, prasugrel, ticagrelor) depend on the type of stent implanted (BMS or DES)?

Drug-Eluting Stent

Among patients with an implanted DES, extending DAPT beyond 12 months may reduce the risk of myocardial infarction, stent thrombosis, and MACCE. However, extending the duration of DAPT beyond 12 months may increase the risk of all-cause death, noncardiovascular death, and major bleeding. There was no significant difference in the risk of cardiovascular death, stroke, urgent revascularization, or major bleeding between 12 and more than 12 months of DAPT (Table H).

Table H: Summary of Findings: Drug-Eluting Stent

Outcome	> 12 mo vs. 6 mo	> 12 mo vs. 6 to 12 mo	> 12 mo vs. 12 mo	> 12 mo vs. 12 mo
All-cause death	●	●	●	●
Cardiovascular death	●	○	●	○
Noncardiovascular death	●	○	●	○
Myocardial infarction	●	●	●	●
Stroke	○	○	●	○
Stent thrombosis	●	●	●	●
Urgent revascularization	●	○	●	○
MACCE	○	●	●	○
Major bleeding	●	○	●	○
Minor bleeding	○	○	○	○
Gastrointestinal bleeding	○	○	○	○

DAPT = dual antiplatelet therapy; MACCE = major adverse cardiac and cerebrovascular events; mo = months.
Notes:
Green circle indicates that extended DAPT is better than shorter-duration DAPT.
Red circle indicates that extended DAPT is worse than shorter-duration DAPT.
Grey circle indicates no significant difference between extended and shorter-duration DAPT.
White circle indicates that no evidence was available to inform the comparison.

Bare-Metal Stent

No systematic reviews provided data to address this research question. Data were available from two RCTS (PRODIGY, DAPT) for patients with a DES.

Among patients with a BMS, DAPT for more than 12 months was associated with an increased risk of major bleeding. There were no significant differences between extended and shorter-duration DAPT for any other outcome (Table I).

Table I: Summary of Findings: Bare-Metal Stent

Outcome	> 12 mo vs. 6 mo	> 12 mo vs. 6 to 12 mo	> 12 mo vs. 12 mo	> 12 mo vs. 12 mo
All-cause death	●	●	●	○
Cardiovascular death	●	○	○	○
Noncardiovascular death	○	○	○	○
Myocardial infarction	●	●	●	○
Stroke	●	●	●	○
Stent thrombosis	●	○	●	○
Urgent revascularization	○	○	○	○
MACCE	●	●	●	○
Major bleeding	○	○	●	○
Minor bleeding	○	○	○	○
Gastrointestinal bleeding	○	○	○	○

DAPT = dual antiplatelet therapy; MACCE = major adverse cardiac and cerebrovascular events; mo = months.
Notes:
Green circle indicates that extended DAPT is better than shorter-duration DAPT.
Red circle indicates that extended DAPT is worse than shorter-duration DAPT.
Grey circle indicates no significant difference between extended and shorter-duration DAPT.
White circle indicates that no evidence was available to inform the comparison.

Research Question 4

Is there a rebound effect after withdrawal of P2Y12 inhibitor (clopidogrel, prasugrel, ticagrelor) therapy?

None of the included systematic reviews provided data to address this research question. One of the included RCTs provided data before and after discontinuation of DAPT for all-cause death, myocardial infarction, stroke, stent thrombosis, and MACCE.

Among patients who received 12 months of DAPT, there was no significant difference in the risk of all-cause death, myocardial infarction, stroke, stent thrombosis, or MACCE in the first three months after discontinuation of DAPT.

Among patients who received DAPT for 30 months, the risk of myocardial infarction and MACCE was higher in the first three months after discontinuation compared with the last three months before discontinuation. There was no significant difference in the risk of all-cause death, stent thrombosis, or stroke after discontinuation of DAPT.

Key Limitations

- Outcome definitions varied among the primary RCTs, especially for bleeding and MACCE. To increase homogeneity, we report separately data that were assessed with different bleeding classification scales, and we did not pool data that were not deemed to be clinically similar.
- Earlier RCTS primarily involved use of first-generation DESs, which may limit generalizability to current clinical practice.
- The timing of the randomization of patients varied between RCTs, with some patients being randomized within the first 30 days after stenting, while other trials randomized patients who completed 12 months of DAPT with no adverse events. This may have excluded some high-risk patients who may have obtained a larger benefit from extended DAPT.

Conclusions

Overall, long-term DAPT of greater than 12 months in patients after PCI was predominantly beneficial in reducing stent thrombosis, myocardial infarction, and MACCE; however, this benefit is contrasted by an increase in major bleeding. Of significant concern is the observed increase in noncardiovascular mortality. Subgroups, such as patients with prior myocardial infarction or aged less than 75 years, may derive the most benefit from long-term DAPT; accordingly, individualized risk assessments should be made to determine ideal duration of therapy.

Context and Policy Issues

Background and Rationale

Dual antiplatelet therapy (DAPT), the combination of a P2Y12 inhibitor with ASA, is routinely given following percutaneous coronary intervention (PCI) with stenting with the aim of preventing stent thrombosis and major adverse cardiovascular events. Extending DAPT beyond 12 months may reduce the risk of late stent thrombosis but may be associated with an increased risk of bleeding and death.[1] Guidelines by the Canadian Cardiovascular Society recommend the use of DAPT for 12 months after PCI,[2] while the European Society of Cardiology recommends DAPT for up to 12 months following PCI.[3] Furthermore, recent guidelines by the American College of Cardiology and American Heart Association[1] recommend that DAPT be given for at least six to 12 months in most clinical settings, and state that it may be reasonable to prolong DAPT beyond 12 months for some patients.

The optimal duration of DAPT to balance the risk and harms following PCI is unclear. In clinical practice, some patients receive DAPT beyond 12 months (extended DAPT). In some jurisdictions, reimbursement of P2Y12 inhibitors after stenting may be limited to 12 months, which may impact access to DAPT for some patients who may benefit from such therapy. Given the current uncertainty about the benefits and harms of extended DAPT therapy beyond one year, further elucidation of the controlled clinical trial data through a comprehensive overview of the evidence is required to inform health care decision-makers, policy-makers, clinicians, and patients.

In order to summarize the clinical benefits and harms associated with extending DAPT beyond 12 months, we performed a systematic overview (umbrella review) of previously published systematic reviews that have assessed the benefits and harms associated with extended DAPT. Of note, CADTH published a Health Technology Assessment report on the use of antiplatelet agents in patients undergoing PCI in June 2010 (www.cadth.ca/clopidogrel-versus-other-antiplatelet-agents-secondary-prevention-vascular-events-adults-undergoing). As such, this new report in part updates information from the 2010 report.

Objectives of the Report

The objective of this overview is to systematically review and summarize the evidence of the benefits and harms associated with extended DAPT following PCI with stenting.

Research Questions

The research questions for this project reflect the information needs of CADTH jurisdictional clients with regard to comparative efficacy and safety:

1. What are the benefits and harms of extended DAPT (> 12 months) with ASA plus a P2Y12 inhibitor (clopidogrel, prasugrel, ticagrelor) compared with DAPT of a shorter duration (6 to 12 months) following PCI with stenting?
2. Are there subgroups of patients for whom the optimal duration of DAPT with ASA plus a P2Y12 inhibitor (clopidogrel, prasugrel, ticagrelor) is different?

3. Does the optimal duration of DAPT with ASA plus a P2Y12 inhibitor (clopidogrel, prasugrel, ticagrelor) depend on the type of stent implanted (bare-metal stent [BMS] or drug-eluting stent [DES])?
4. Is there a rebound effect after withdrawal of P2Y12 inhibitor (clopidogrel, prasugrel, ticagrelor) therapy?

Because there is a possibility that extended DAPT is used in some patients, there is also interest in additional information related to the use of such therapy, in particular regarding the risk of drug interactions and dosing. More precisely, the requested additional information relates to the impact of using clopidogrel with a proton pump inhibitor as well as the impact of the ASA dosage prescribed in a DAPT regimen. As these questions require using a different literature search strategy than the search used for our four research questions, they were answered as supplemental rapid reviews through CADTH's Rapid Response service. A summary of each rapid review is available at the end of this report (see pages 144-146[4,5]).

Methods

Systematic Review

This review was designed using the methodology guidelines for umbrella reviews provided by the Joanna Briggs Institute.[6] As well, we followed the Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) guidelines.[7] This protocol is registered with PROSPERO (No. CRD42016047735).

Literature Search Strategy

An experienced medical information specialist developed and tested the strategy using an iterative process in consultation with the review team. Another senior information specialist peer reviewed the strategy before execution using the PRESS checklist.[8] The database searches were executed on August 12 and 13, 2016. Using the OVID platform, we searched Embase and Ovid MEDLINE, including Epub Ahead of Print and In-Process & Other Non-Indexed Citations. We also searched the Cochrane Library on Wiley. PubMed was searched for the most recent and not-yet-indexed citations only.

Strategies utilized a combination of controlled vocabulary (e.g., "Stents," "Percutaneous Coronary Intervention," "Purinergic P2Y Receptor Antagonists") and keywords (e.g., "DES," "PCI," "dual antiplatelet therapy"). Vocabulary and syntax were adjusted across databases. Results were limited to the publication years 2011 to the present. When possible, animal-only, opinion pieces, and conference abstracts were removed from the results.

We performed a grey literature search of major health technology assessment sources and clinical practice guidelines sources using CADTH's Grey Matters Light. Specific details regarding the strategies appear in Appendix 1.

Selection Criteria and Methods

The inclusion criteria for this umbrella review were set following the PICO (population, intervention, comparison, outcome) criteria (Table 1):

Table 1: PICO Criteria

Population	Adult patients who have undergone PCI with any type of stent and who are receiving DAPT.
Intervention	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.
Comparison	DAPT for 6 to 12 months.
Outcomes[a]	Primary outcome: death (cardiovascular, all-cause, noncardiovascular). Secondary outcomes: bleeding (as defined by TIMI or BARC classifications; gastrointestinal bleeding), urgent target vessel revascularization, major adverse cardiovascular events, myocardial infarction, stroke, and stent thrombosis.

ASA = acetylsalicylic acid; BARC = Bleeding Academic Research Consortium; DAPT = dual antiplatelet therapy; PCI = percutaneous coronary intervention; PICO = population, intervention, comparison, outcome; TIMI = thrombolysis in myocardial infarction.
[a] Studies will not be included or excluded on the basis of reported outcomes.

Study Designs

We included systematic evidence syntheses that included randomized controlled trials (RCTs) comparing different durations of DAPT following PCI. To be eligible for inclusion, studies had to have used a systematic process for literature searching and study selection. If both RCTs and non-randomized studies were included, the effect estimates from RCTs had to have been reported separately.

No language restrictions were used during the screening or study selection process.

For the purpose of this review, evidence syntheses had to meet the following criteria to be considered systematic:

- Report using a comprehensive search strategy involving two or more electronic databases
- Provide an explicit statement describing the inclusion criteria applied to candidate RCTs
- Critically appraise the quality and risk of bias of the included RCTs and report the outcome of that appraisal.

Study Selection

The eligibility criteria were applied to each title and abstract identified in the literature search by two independent reviewers in a standardized manner. All records identified by at least one author as potentially relevant were obtained in full-text format, and the eligibility criteria were applied to the full-text records. A final consensus decision was made for inclusion, and conflicts were resolved by discussion. The reviewers were not blinded to study authors or centre of publication before study selection. Study screening and assessment of eligibility was facilitated and standardized through the use of the DistillerSR (Evidence Partners, 2017) online systematic review software.

Quality Assessment

Two independent reviewers applied the AMSTAR (A Measurement Tool to Assess Systematic Reviews)[9] checklist to each included study, and disagreements were resolved by consensus. Only reviews that met a minimum quality threshold were included in the summary of findings. “High quality” was not based on a numerical score on the AMSTAR checklist; rather, the following criteria had to be met:

- Use of a comprehensive search strategy involving two or more electronic databases, and use of an explicit statement describing the inclusion criteria applied to candidate RCTs
- Use of a formal critical appraisal or quality assessment process for all included studies and a report of the outcome of that process
- A report on findings on outcomes of interest using details on the study and patient characteristics of two or more studies
- Provision of the direction of the findings from any pooled analyses (narrative or meta-analysis) carried out, including direction of effect and any statistical significance.

Any included reviews that did not meet these minimum requirements remained included; however, no data were extracted.

Data Collection

All data were collected by use of piloted and standardized data abstraction forms in DistillerSR.

Extraction forms were developed following the Joanna Briggs Institute's recommended extraction items.[6] Data were extracted from each included systematic review by one reviewer and verified by a second reviewer. Any disagreements were resolved by consensus. The original, primary publication for each included review was used for data extraction, except where multiple publications for a unique review were found. Multiple publications for a unique review (e.g., supplemental online appendices, companion publications of specific outcomes or populations from the original study) were handled by extracting the most recently adjudicated data for each outcome specified a priori in this protocol.

The data extracted included specific details about the included RCTs (e.g., study population, the durations of DAPT investigated) and the review methods (e.g., number of databases searched, search date, and any date, location, or language restrictions on the search). Patient characteristics (e.g., age, sex, smoking status, diabetes, prior myocardial infarction, history of heart failure) were extracted from the included reviews, as reported by the review authors. We extracted the effect estimates for the outcomes of interest for the whole population and for any subgroups, as well as the method of synthesis (e.g., meta-analysis, network meta-analysis). The authors' overall conclusion or recommendations were extracted. Outcome data were extracted for the period while patients were on DAPT and after withdrawal of DAPT.

Outcomes

The primary outcome of this review is death (all-cause, cardiovascular death, noncardiovascular). Secondary outcomes are myocardial infarction, stroke, stent thrombosis, urgent target vessel revascularization, major adverse cardiovascular events, and bleeding (major or minor, as defined by TIMI [thrombolysis in myocardial infarction], BARC [Bleeding Academic Research Consortium], GUSTO [Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries], or REPLACE [Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events] classifications[10]; gastrointestinal). All outcomes were assessed based on the definitions applied in the systematic reviews, with the exception of bleeding and major adverse cardiovascular events

(depending on components of the composite). Data for bleeding outcomes are summarized by each classification system. The outcome definitions from each included RCT are available at the end of this report (see pages 139-143). Of note, studies were not included or excluded on the basis of reported outcomes.

Subgroups

Effect estimates were extracted separately for clinically important subgroups based on patient demographics (e.g., age, sex, smoking status, diabetes, prior myocardial infarction, history of heart failure), procedural parameters (e.g., vein graft intervention, stent type, lesion complexity, concurrent disease), and clinical presentation (e.g., acute coronary syndrome [ACS] versus no ACS; ST-elevation myocardial infarction [STEMI] versus non-STEMI).

The included systematic reviews did not report data for all subgroups of interest. Thus, to address research questions 2 to 4, we extracted data from the RCTs identified from the included systematic reviews where pooled data were not available from the systematic reviews. PubMed and ClinicalTrials.gov were searched to identify any companion publications to the RCTs.

Data Summary

The aim of this umbrella review is to present a summary of the existing research syntheses that have addressed the optimal duration of DAPT. The findings are summarized from the most recent high-quality systematic reviews using a narrative approach. In this report, review characteristics (year of publication, country of origin, number of included studies, setting or context, interventions, and AMSTAR assessment) are summarized in tabular format. Outcome data are summarized with respect to number of included studies, number of participants, effect estimates, and heterogeneity. The direction of odds ratios (ORs) was standardized for presentation in the tables; the original data as reported by the authors are included in the footnotes to each table.

Data for subgroups are presented separately.

Results

Selection of Primary Studies

The initial literature search returned 756 records (Appendix 2). An additional 61 citations were identified through grey literature searching. Of these, 119 records were considered potentially relevant. The full text of two records could not be located,[11,12] and 117 records were examined in full-text format. After full-text review, 98 records were excluded. In total, 21 records were included (representing 19 unique systematic reviews).[13-33] The full lists of included and excluded records are available in Appendix 3 and Appendix 4.

Of the 19 included reviews, 11 provided usable data to address research questions 1 to 4. No usable data were reported from eight reviews;[15,20,21,25-28,31] these reviews remained included, but no data were extracted.

Five systematic reviews[20,25-27,31] had a search date before publication of the DAPT trial.[34] Because this was the largest RCT to investigate the optimal duration of DAPT, we extracted data only from systematic reviews that (a) performed their literature search after publication of the DAPT trial and (b) included the DAPT trial. One additional review was performed after publication of the DAPT trial, but the DAPT trial was not included;[28] no data were included from this review.

Two additional systematic reviews[15,21] met the inclusion criteria but did not provide data for a time comparison of interest.

Thus, our evidence synthesis was based on data reported in 11 unique systematic reviews (Table 2).[13,14,16-19,22,23,29,30,33]

Table 2: Summary of Systematic Reviews Included in the Evidence Synthesis

Systematic Review	Country	Funding Source	Search Date	Intended Population[a]	Primary Outcome
Fei 2016[13]	China	Authors reported receiving no funding	January 28, 2016	Patients who underwent PCI with DES	MI, stent thrombosis, stroke
Palla 2015[14]	US	NR	February 15, 2015	Patients who underwent PCI with DES	Stent thrombosis, all-cause death, MI, cardiac death, stroke, major bleeding
D'Ascenzo 2016[16]	Italy	NR	April 2015	Patients who underwent PCI with second-generation DES	All-cause death
Tsoi 2015[17]	China	NR	November 18, 2014	Patients who underwent PCI with DES	NR
Verdoia 2016[18]	Italy	Pharma[b]	November 2014	Patients who underwent PCI with DES	All-cause death
Cassese 2015[19]	Germany	NR	January 10, 2015	Patients who underwent PCI with DES	Stent thrombosis, major bleeding, death
Palmerini 2015[22]	US	Authors reported receiving no	November 20, 2014	Patients who underwent PCI with DES	All-cause death

Table 2: Summary of Systematic Reviews Included in the Evidence Synthesis

Systematic Review	Country	Funding Source	Search Date	Intended Population[a]	Primary Outcome
		funding			
Navarese 2015[23]	Germany	Non-pharma	February 16, 2015	Patients who underwent PCI with DES	Cardiovascular mortality, MI, stent thrombosis, major bleeding, all-cause death
Xie 2016[29]	China	Non-pharma	December 31, 2014	Patients who underwent PCI with DES	NR
Zhang 2015[30]	China	Authors reported receiving no funding	November 18, 2014	Patients who underwent PCI with DES	All-cause death
Bittl 2016[33]	US	NR	NR	Patients who underwent PCI with "newer generation" DES	All-cause death, major hemorrhage, MI, stent thrombosis, MACCE

DES = drug-eluting stent; MACCE = major adverse cardiac and cerebrovascular events; MI = myocardial infarction; NR = not reported; PCI = percutaneous intervention.
[a] Although all systematic reviews intended to assess outcomes among participants with an implanted DES, most did not exclude participants with a bare-metal stent from their analysis.
[b] Two authors reported receiving "the following financial support for the research, authorship, and/or publication of this article: Prof. Montalescot reports receiving grant support from Abbott Laboratories, Accu-Metrics, AstraZeneca, Biotronik, Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly, Medicines Company, Medtronic, Menarini Group, Nanosphere Inc., Pfizer, Roche, Sanofi-Aventis, and Stentys. Prof. Collet reports receiving research grants from Bristol-Myers Squibb, Sanofi-Aventis, Eli Lilly, Medtronic, Boston Scientific, Cordis, Stago, Fondation de France, INSERM, Nanospheres, Fédération Française de Cardiologie, and Société Française de Cardiologie.

Study and Patient Characteristics

Most of the included systematic reviews aimed to look at the optimal duration of DAPT, thus including RCTs that compared any duration of DAPT. As such, most systematic reviews included RCTs that were beyond the scope of this review (e.g., three months versus 12 months DAPT). Data to address our research questions were taken from subgroup analyses of the systematic reviews or from RCTs that compared six to 12 months of DAPT with DAPT for more than 12 months (Table 3).

Table 3: Randomized Controlled Trials Included in the Systematic Reviews

Systematic Review	PRODIGY[38 a]	DES-LATE[36]	ARCTIC-Interruption[35]	ITALIC[37]	DAPT[34 a]	OPTIDUAL[39]	—
Author and Year	**Valgimigli 2012**	**Lee 2013**	**Collet 2014**	**Gilard 2014**	**Mauri 2014**	**Helft 2016**	**Hu 2012[40]**
Duration of DAPT, mo	**6 vs. 24**	**12 vs. 36**	**12 vs. 18 to 30**	**6 vs. 24**	**12 vs. 30**	**12 vs. 48**	**12 vs. 36**
Bittl 2016	X	X	X	X	X	X	—
D'Ascenzo 2016	X	X	—	X	X	—	—
Fei 2016	X	X	X	X	X	X	—
Verdoia 2016	X	X	X	X	X	—	X
Xie 2016	X	X	X	X	X	—	—
Cassese 2015	X	X	X	X	X	—	—

Table 3: Randomized Controlled Trials Included in the Systematic Reviews

Systematic Review	PRODIGY[38 a]	DES-LATE[36]	ARCTIC-Interruption[35]	ITALIC[37]	DAPT[34 a]	OPTIDUAL[39]	—
Author and Year	**Valgimigli 2012**	**Lee 2013**	**Collet 2014**	**Gilard 2014**	**Mauri 2014**	**Helft 2016**	**Hu 2012[40]**
Duration of DAPT, mo	**6 vs. 24**	**12 vs. 36**	**12 vs. 18 to 30**	**6 vs. 24**	**12 vs. 30**	**12 vs. 48**	**12 vs. 36**
Navarese 2015	X	X	X	X	X	—	—
Palla 2015	X	X	X	X	X	—	—
Palmerini 2015	X	X	X	X	X	—	—
Tsoi 2015	X	X	X	X	X	—	—
Zhang 2015	X	X	X	X	X	—	—

DAPT = dual antiplatelet therapy; mo = months; NA = not applicable; RCT = randomized controlled trial; X = indicates that an RCT was included in the review listed in the corresponding row heading.

[a] Included patients with implanted bare-metal stents and drug-eluting stents.

Of the RCTs included in the relevant systematic reviews, seven RCTs involved a time comparison of interest (6 to 12 months versus > 12 months).[34-40] The remaining RCTs involved comparison of short-term DAPT durations (e.g., three months or six months versus 12 months).[41-45] These comparisons were outside the scope of our review, and no data were extracted from these RCTs. Of note, this approach was motivated by the policy context for this review. Because some jurisdictional drug plans currently limit coverage of P2Y12 inhibitors to 12 months, only assessing the impact of treating for a longer period is relevant to inform policy work.

Two of the RCTs included in most of the systematic reviews included participants with an implanted BMS (PRODIGY,[38] DAPT trial[34]). Each of the included systematic reviews stated that they aimed to investigate the optimal duration of DAPT in patients with an implanted DES; however, most did not exclude the BMS patients from the PRODIGY trial in their analysis.[13,17-19,23,30] (About 25% of patients in the PRODIGY trial received a BMS.[38]) Of the included reviews, three[22,29,33] excluded PRODIGY[38] trial patients with a BMS in their analyses.

Although the DAPT trial[34] also randomized patients who had received a BMS, the primary publication of the trial data excluded the BMS patients. Therefore, only DAPT trial patients with a DES were included in most of the included systematic reviews.

Most of the included systematic reviews did not specify the generation of DES of interest, although one review included only RCTs that assessed duration of DAPT among patients who had received a second-generation stent,[16] and one stated that it focused on "newer generation stents" without defining "newer generation."[33]

Of the included reviews, four were based in China, with three from author groups based in the US (Table 2). The funding sources of the reviews were not well reported, with 45% (5/11) not reporting the source of funding. Of those that did report the funding source, three received no funding, two were funded by non-pharmaceutical sources, and one reported receiving "financial support for the research, authorship, and/or publication of the article" from multiple pharmaceutical companies (Table 2).

The included systematic reviews included a common set of five RCTs that met our inclusion criteria.[34-38] Two recent systematic reviews[13,33] also included an RCT published in 2016 (OPTIDUAL[39]), and one systematic review[18] included data from an RCT (Hu 2012[40]) published only in abstract form. The most recent search date was January 28, 2016.

The main inclusion and exclusion criteria for the RCTs that met our inclusion criteria are presented in Table 4.

Table 4: Major Inclusion and Exclusion Criteria of Included Randomized Controlled Trials

RCT	Major Inclusion Criteria[a]	Major Exclusion Criteria[a]
PRODIGY[38]	Stable angina or ACS including STEMI with at least 1 lesion in native coronary vessel ≥ 2.25 mm in diameter	STEMI, pre-procedural GPIIb/IIIa inhibitors, concomitant need of oral anticoagulant therapy, scheduled elective surgery within 12 months
DES-LATE[36]	All candidates for DAPT after DES implantation who were event free 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[35]	Planned DES implantation	STEMI, pre-procedural GPIIb/IIIa inhibitors, concomitant need of oral anticoagulant therapy, scheduled elective surgery within 12 months
ITALIC[37]	Candidates for DAPT after treatment with EES	STEMI, left main disease, prior DES implantation within 1 year, oral anticoagulation therapy or abciximab treatment during hospital stay, scheduled elective surgery within 12 months
DAPT[34]	All candidates for DAPT after treatment with FDA-approved DES and BMS who were event free 12 months after PCI	Use of stent with diameter 4.0 mm, scheduled elective surgery within 30 months, concomitant need of oral anticoagulant therapy, patient treated with both DES and BMS
OPTIDUAL[39]	Stable angina, silent ischemia, or ACSn with ≥ 1 lesion with stenosis > 50% located in a native vessel ≥ 2.25 mm in diameter and implanted with ≥ 1 DES	Requirement for oral anticoagulant, DES implantation in an unprotected left main coronary artery, malignancy or other coexisting conditions associated with life expectancy < 2 years
Hu 2012[40] [b]	Primary percutaneous left main coronary intervention	Patients who experienced an event during the first 12 months after stenting

ACS = acute coronary syndrome; BES = biolimus-eluting stents; BMS = bare-metal stent; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; EES = everolimus-eluting stent; PCI = percutaneous coronary intervention; PES = paclitaxel-eluting stent; SES = sirolius-eluting stent; STEMI = ST-elevation myocardial infarction; ZES = zotarolimus-eluting stent.

[a] Adapted from Palmerini 2015.[22]

[b] Published in abstract form only.

The characteristics of the patients in each RCT, including the types of stents implanted, are reported in Table 5.

Table 5: Characteristics of Patients Included in the Randomized Controlled Trials[a]

RCT	Treatment Duration (No. Randomized)	Type of Thienopyridine	Stent Type	Age (Years)	Male %	Diabetes %	Complex Lesions[b] %
PRODIGY	6 mo (983) 24 mo (987)	Clopidogrel	EES, PES, BMS	67.8	76.7	24.2	66.3
DES-LATE	12 mo (2,514) 24 mo (2,531)	Clopidogrel	SES, PES, ZES, EES and "other DES"	62.4	69.3	28.1	78.5
ARCTIC-Interruption	12 mo (641) 18 to 30 mo (645)	Clopidogrel, prasugrel	SES, PES, ZES, EES	64.0	80.5	33.5	NR
ITALIC	6 mo (926) 24 mo (924)	Clopidogrel, prasugrel, ticagrelor	ZES	61.6	80.0	38.0	NR
DAPT	12 mo (4,941) 30 mo (5,020)	Clopidogrel, prasugrel, ticagrelor	SES, ZES, PES, BMS[b]	61.7	74.6	30.6	43.3
OPTIDUAL	12 mo (697) 48 mo (701)	Clopidogrel	SES, PES, ZES, EES, BES	64.1	80.7	31.4	NR
Hu 2012[c]	12 mo (NR)[d] 36 mo (NR)	Clopidogrel	DES	NR	NR	NR	NR

BES = biolimus-eluting stent; BMS = bare-metal stent; DES = drug-eluting stent; EES = everolimus-eluting stent; mo = months; NR = not reported; PES = paclitaxel-eluting stent; SES = sirolius-eluting stent; ZES = zotarolimus-eluting stent.

[a] Adapted from Cassese et al.[19]

[b] Type B2 or C based on the American College of Cardiology and American Heart Association classification system.

[c] Published in abstract form only.

[d] 216 patients total.

The mean age of the included participants was more than 60 years in each RCT (Table 5). Most of the participants were male (69% to 81%), and about one-third of participants in each RCT had diabetes (24% to 38%). There was wide variation in the percentage of participants with ACS within the RCTs: Between 0.1% and 33.3% of participants had STEMI, between 7.1% and 22.9% of participants had non-STEMI, and between 9.1% and 38.6% of participants had unstable angina (Table 6). Two RCTs did not report the number of patients with ACS.[35,40] Three trials reported the percentage of participants with a complex lesion (class B2 or C; 43% to 79%).[34,36,38]

Table 6: Acute Coronary Syndrome Among Patients in the Randomized Controlled Trials

RCT	Treatment Duration (No. Randomized)	STEMI %	Non-STEMI %	Unstable Angina %
PRODIGY	6 mo (983) 24 mo (987)	33.3 32.5	22.5 22.9	18.5 18.5
DES-LATE	12 mo (2,514) 24 mo (2,531)	12.5 12.4	10.6 10.6	38.6 36.7
ARCTIC-Interruption	12 mo (641) 18-30 mo (645)	NR	NR	NR
ITALIC	6 mo (926) 24 mo (924)	0.1 0.3	7.3 7.1	15.7 16.4
DAPT	12 mo (4,941) 30 mo (5,020)	10.3 10.6	15.5 15.5	16.7 16.7
OPTIDUAL	12 mo (697) 48 mo (701)	11.9 10.7	17.0 14.2	9.1 9.5
Hu 2012	12 mo (NR)[a] 36 mo (NR)	NR	NR	NR

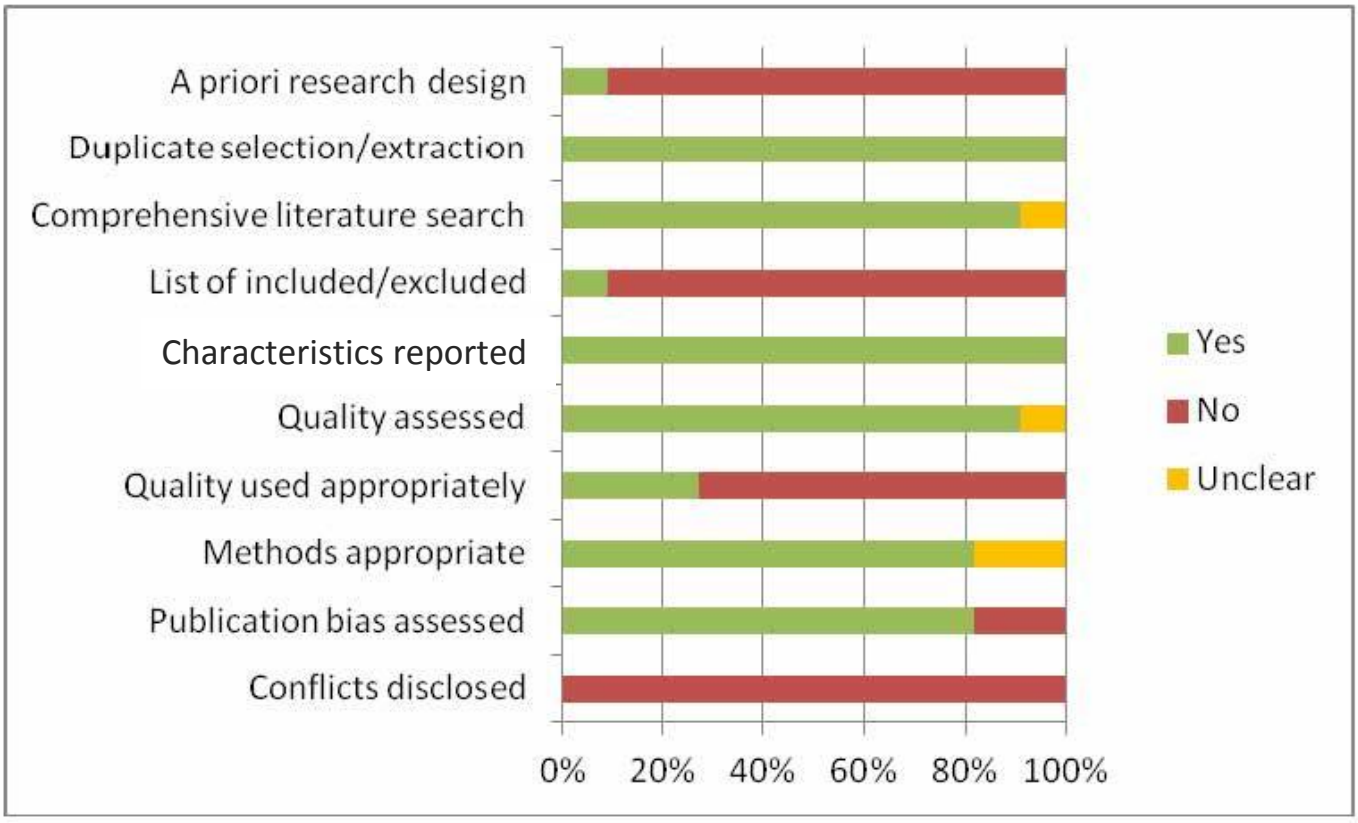
mo = months; NR = not reported; STEMI = ST-segment elevation myocardial infarction.
[a] 216 patients total.

Critical Appraisal of Included Studies

The AMSTAR checklist[9] was applied to the 11 included systematic reviews with usable data (Appendix 5).

Most of the included systematic reviews scored 6 or 7 points on the AMSTAR scale (out of 11 points), while one review scored 9 points,[16] and two scored 5 points.[18,33] Only one review[13] reported having an a priori research design, registered with the PROSPERO database. None of the included systematic reviews reported the sources of support for both the review and the included RCTs. All reviews reported using duplicate reviewers for selection or data extraction, and most performed a comprehensive literature search (Figure 1). We were unable to judge the quality of the literature search performed by one review[33] because insufficient details were reported; however, this review located the same RCTs as the reviews that used a comprehensive search strategy. Although all reviews addressed the quality of the included RCTs, few reviews commented on the quality of the RCTs in their publication or incorporated quality into their meta-analysis. However, the included RCTs were judged by most of the systematic reviews to be at low risk of bias, except for the category “blinding of participants and personnel,” because most of the included RCTs were open label. No data were excluded from our analysis on the basis of the AMSTAR assessment.

Figure 1: Proportion of Reviews That Fulfilled Each AMSTAR Criterion



We were unable to judge whether two reviews[22,30] used appropriate methods to pool data. Both reported that they pooled data using fixed-effects and random-effects models; however, neither study reported which model was used to create their published data. The remaining reviews reported the results of fixed-effects or random-effects meta-analysis. Heterogeneity was minor (0% to 40%) for most outcomes, and there was little difference between fixed-effects and random-effects estimates in the studies that reported both.[33]

Data Summary: Research Question 1

What are the benefits and harms of extended DAPT (> 12 months) with ASA plus a P2Y12 inhibitor (clopidogrel, prasugrel, ticagrelor) compared with DAPT of a shorter duration (6 to 12 months) following PCI with stenting?

In total, 11 systematic reviews addressed research question 1.[13,14,16-19,22,23,29,30,33]

Although each of the included systematic reviews reported that they aimed to evaluate all-cause death among patients with an implanted DES, two of the included RCTs also involved patients with BMS (DAPT,[34] PRODIGY[38]). Few systematic reviews excluded patients with BMS from their analysis. Therefore, the data used to address research question 1 are from a population of DES and BMS patients, unless otherwise noted.

All-Cause Death

In total, 11 systematic reviews assessed all-cause death with different durations of DAPT.[13,14,16-19,22,23,29,30,33] Comparisons included six months versus more than 12 months, six to 12 months versus more than 12 months, and 12 months versus more than 12 months. One publication included network meta-analyses that assessed all-cause death associated with different durations of extended DAPT (24 months, 30 months, and 36 months).[29]

Six Months Versus More Than 12 Months

Five systematic reviews assessed all-cause death reported in RCTs that compared six months of DAPT with extended DAPT (> 12 months).[13,16,17,22,29] Of these, four performed a meta-analysis, directly comparing six months with more than 12 months.[13,16,17,22] Each review included only one RCT for this time comparison (PRODIGY[38]), with a duration of six months compared with 24 months.

Each of reviews that compared six months with more than 12 months of DAPT reported no statistically significant difference in the odds or risk of all-cause death between durations (Table 7). One review[16] reported no significant difference in the odds of all-cause death among patients with a second-generation DES (OR 1.11; 95% confidence interval [CI], 0.35 to 3.57) (Table 7), with high heterogeneity (I^2 = 75%) between everolimus-eluting and zotarolimus-eluting stents.

Table 7: Summary of Evidence Available for All-Cause Death: 6 Months Versus > 12 Months

Systematic Review	Included RCTs	Stent Type	No. of Events/Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CI)	I^2
Fei 2016	PRODIGY	DES, BMS[a]	6 mo: 65/983 24 mo: 65/987	OR, RE	OR > 1 indicates higher odds in extended group	OR 1.00 (0.70 to 1.42)	NA
Tsoi 2015	PRODIGY	DES, BMS[a]	6 mo: 65/983 24 mo: 65/987	OR, RE	OR > 1 indicates higher odds in extended group	OR 1.00 (0.70 to 1.42)	NA
Palmerini 2015	PRODIGY	DES	6 mo:45/751 24 mo:49/750	HR[b]	HR > 1 indicates higher odds in extended group	HR 1.10 (0.73 to 1.64)[c]	NA
D'Ascenzo 2016	PRODIGY	Second-generation DES	6 mo: 24/492 24 mo: 29/496	OR, RE	OR > 1 indicates higher odds in extended group	OR 1.11 (0.35 to 3.57)[d]	75%[e]

BMS = bare-metal stent; CI = confidence interval; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; HR = hazard ratio; mo = months; NA = not applicable; OR = odds ratio; RCT = randomized controlled trial; RE = random effects.

[a] PRODIGY included about 25% BMS in each arm.

[b] Fixed effects or random effects not reported.

[c] Palmerini 2015 reported OR such that odds < 1 indicates lower odds in short DAPT group (HR 0.91; 95% CI, 0.61 to 1.37); the direction of comparison was reversed for inclusion in this table.

[d] D'Ascenzo 2016 reported OR such that OR < 1 indicates lower odds in short group (OR 0.90; 95% CI, 0.28 to 2.87); the direction of comparison was reversed for inclusion in this table.

[e] Heterogeneity between type of second-generation DES (everolimus-eluting stent versus zotarolimus-eluting stent).

One systematic review[29] compared all durations of DAPT via network meta-analysis involving patients who had undergone PCI with a DES. This analysis involved direct and indirect evidence from four RCTs having a total of 17,743 patients.[34-36,38] In their analysis, Xie et al.[29] found no significant difference in the odds of all-cause death between six months and 24, 30, or 36 months of DAPT (Table 8).

Table 8: Summary of Evidence Available for All-Cause Death: Network Meta-Analysis, 6 Months Versus > 12 Months

Systematic Review	Included RCTs	Stent Type	No. of Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CrI)
Xie 2016	• PRODIGY[a] • DES-LATE • ARCTIC-Interruption • DAPT	DES	17,743[b]	OR, RE	6 mo vs. 24 mo; OR < 1 indicates lower odds in extended group	OR 0.99 (0.45 to 2.63)[c]
					6 mo vs. 30 mo; OR > 1 indicates higher odds in extended group	OR 1.39 (0.56 to 4.55)[d]
					6 mo vs. 36 mo; OR < 1 indicates lower odds in short group	OR 0.67 (0.20 to 1.66)[e]

CI = confidence interval; CrI = credible interval; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; mo = months; OR = odds ratio; RCT = randomized controlled trial; RE = random effects; vs. = versus.

[a] Patients with a bare-metal stent were excluded from analysis.

[b] The full network including all DAPT durations included 17,743 patients. It is unclear how many patients contributed data to the 6 mo vs. 24 mo, 6 mo vs. 30 mo, and 6 mo vs. 36 mo comparisons.

[c] Data reversed for presentation: Original data reported such that OR > 1 indicates higher odds in short group (OR 1.01; 95% CI, 0.38 to 2.21).

[d] Data reversed for presentation: Original data reported such that OR < 1 indicates lower odds in short group (OR 0.72; 95% CI, 0.22 to 1.78).

[e] Data reversed for presentation: Original data reported such that OR < 1 indicates lower odds in short group (OR 0.67; 95% CI, 0.20 to 1.66).

Six to 12 Months Versus More Than 12 Months

Three systematic reviews[18,19,33] assessed all-cause death associated with six to 12 months of DAPT compared with extended DAPT (> 12 months). All three reviews included ARCTIC-Interruption, DAPT, DES-LATE, ITALIC, and PRODIGY. One review[18] also included an RCT reported only in abstract format,[40] and one review[33] included a recently published RCT (OPTIDUAL[39]).

All three systematic reviews reported no statistically significant difference in the odds of all-cause death between six to 12 months of DAPT and more than 12 months of DAPT (Table 9).[18,19,33]

Table 9: Summary of Evidence Available for All-Cause Death: 6 to 12 Months Versus > 12 Months

Systematic Review	Included RCTs	Stent Type	No. of Events/Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CI)	I^2
Verdoia 2016	• ARCTIC-Interruption • DAPT • DES-LATE • ITALIC • HU[a] • PRODIGY	DES, BMS	6 to 12 mo: 190/9,270 > 12 mo: 225/9,357	OR, FE	OR > 1 indicates higher odds in extended group	OR 1.18 (0.97 to 1.45)[b]	0%
Cassese 2015	• ARCTIC-Interruption • DAPT • DES-LATE • ITALIC • PRODIGY	DES, BMS	6 to 12 mo: 244/9978 > 12 mo: 281/10,079	OR, RE	OR > 1 indicates higher odds in extended group	OR 1.15 (0.96 to 1.37)	0%

Table 9: Summary of Evidence Available for All-Cause Death: 6 to 12 Months Versus > 12 Months

Systematic Review	Included RCTs	Stent Type	No. of Events/Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CI)	I^2
Bittl 2016	• ARCTIC-Interruption • DAPT • DES-LATE • PRODIGY[c] • ITALIC • OPTIDUAL	DES	6 to 12 mo: 192/10,432 > 12 mo: 223/10,541	OR, FE, and RE	OR > 1 indicates higher odds in extended group	OR, FE 1.16 (0.95 to 1.41) OR, RE 1.14 (0.92 to 1.42)	10.2%

BMS = bare-metal stent; CI = confidence interval; DES = drug-eluting stent; FE = fixed effects; mo = months; OR = odds ratio; RCT = randomized controlled trial; RE = random effects.

[a] Reported in abstract format only.[40]

[b] Data reversed for presentation: Original data reported such that OR < 1 indicates lower odds in the short group (OR 0.85; 95% CI, 0.69 to 1.03).

[c] Patients with BMS were excluded from analysis.

Twelve Months Versus More Than 12 Months

Seven systematic reviews compared all-cause death among patients receiving DAPT for 12 months with those receiving DAPT for more than 12 months.[13,14,16,17,22,23,30] Most of the reviews included three RCTS (DES-LATE,[36] ARCTIC-Interruption,[35] DAPT[34]). One review[13] also included a recently published RCT (OPTIDUAL[39]) that compared 12 months and 30 months of DAPT. One review[16] included only second-generation DESs from one RCT (DES-LATE[36]).

In total, six systematic reviews reported increased odds or risk of all-cause death among patients receiving DAPT for more than 12 months compared with those who received DAPT for 12 months (Table 10). Among patients with a second-generation DES, one review[16] reported no statistically significant difference in all-cause death between 12 months and more than 12 months of DAPT (Table 10).

Table 10: Summary of Evidence Available for All-Cause Death: 12 Months Versus > 12 Months

Systematic Review	Included RCTs	Stent Type	No. of Events/Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CI)	I^2
Fei 2016	• DES-LATE • DAPT[a] • ARCTIC-Interruption • OPTIDUAL	DES	12 mo: 122/8,769 > 12 mo: 176/8881	OR, RE	OR > 1 indicates higher odds in extended group	**OR 1.43 (1.14 to 1.81)**	65%
Palla 2015	• DES-LATE • ARCTIC-Interruption • DAPT[a]	DES	12 mo: 115/8,079 > 12 mo: 151/8,186	OR, FE	OR > 1 indicates higher odds in extended group	**OR 1.30 (1.02 to 1.66)**	0%
Tsoi 2015	• DES-LATE • ARCTIC-Interruption • DAPT[a]	DES	12 mo: 115/8,079 > 12 mo: 151/8,186	OR, RE	OR > 1 indicates higher odds in extended group	**OR 1.30 (1.02 to 1.66)**	0%

Table 10: Summary of Evidence Available for All-Cause Death: 12 Months Versus > 12 Months

Systematic Review	Included RCTs	Stent Type	No. of Events/Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CI)	I^2
Navarese 2015	• DES-LATE • ARCTIC-Interruption • DAPT[a]	DES	12 mo: 115/8,096 > 12 mo: 151/8,196	OR, FE	OR > 1 indicates higher odds in extended group	**OR 1.30 (1.02 to 1.66)**	0%
Zhang 2015	• DES-LATE • ARCTIC-Interruption • DAPT[a]	DES	12 mo: 115/8,079 > 12 mo: 151/8186	RR, FE or RE NR	OR > 1 indicates higher odds in extended group	**RR 1.30 (1.02 to 1.65)**	0%
Palmerini 2015	• DES-LATE • ARTIC-Interruption • DAPT[a]	DES	12 mo: NR/NR > 12 mo: NR/NR	HR[b]	HR > 1 indicates higher hazard in the extended group	**HR 1.32 (1.03 to 1.67)[c]**	0%
D'Ascenzo 2016	• DES-LATE	Second-generation DES	12 mo: 11/650 > 12 mo: 19/679	OR, RE	OR > 1 indicates higher odds in extended group	OR 1.67 (0.76 to 3.57)[d]	0%[e]

BMS = bare-metal stent; CI = confidence interval; DES = drug-eluting stent; FE = fixed effects; HR = hazard ratio; mo = months; NR = not reported; OR = odds ratio; RCT = randomized controlled trial; RE = random effects; RR = risk ratio.

[a] Patients with BMS were excluded from analysis.
[b] Fixed effects or random effects not reported.
[c] Data reversed for presentation: Original data reported such that HR < 1 indicated lower hazard in short group (HR 0.76; 95% CI, 0.60 to 0.97).
[d] Data reversed for presentation: Original data reported such that OR < 1 indicated lower odds in short group (OR 0.60; 95% CI, 0.28 to 1.29).
[e] Heterogeneity between second-generation stent types (everolimus-eluting stent versus zotarolimus-eluting stent).

One systematic review[29] compared all durations of DAPT via network meta-analysis. Xie et al.[29] reported no statistically significant difference in the odds of all-cause death between 12 months of DAPT and 24, 30, or 36 months of DAPT among patients with a DES (Table 11).

Table 11: Summary of Evidence Available for All-Cause Death: Network Meta-Analysis, 12 Months Versus > 12 Months

Systematic Review	Included RCTs	Stent Type	No. of Patients	Type of Analysis	Comparison; Direction of Estimate	Effect Estimate (95% CrI)
Xie 2016	• PRODIGY[a] • DES-LATE • ARCTIC-Interruption • DAPT[a]	DES	17,743[b]	OR, RE	12 mo vs. 24 mo; OR < 1 indicates lower odds in extended group	OR 0.78 (0.31 to 2.63)[c]
					12 mo vs. 30 mo; OR > 1 indicates higher odds in extended group	OR 1.20 (0.56 to 3.03)[d]
					12 mo vs. 36 mo; OR > 1 indicates higher odds in extended group	OR 1.30 (0.60 to 3.57)[e]

CI = confidence interval; CrI = credible interval; DAPT = dual antiplatelet therapy; mo = months; OR = odds ratio; RCT = randomized controlled trial; RE = random effects; vs. = versus.

[a] Patients with a bare-metal stent were excluded from analysis.

[b] The full network including all DAPT durations included 17,743 patients. It is unclear how many patients contributed data to the 6 month vs. 24 month, 6 month vs. 30 month, and 6 month vs. 36 month comparisons.

[c] Data reversed for presentation: Original data reported such that OR > 1 indicates higher odds in short group (OR 1.28; 95% CI, 38 to 3.21).

[d] Data reversed for presentation: Original data reported such that OR < 1 indicates lower odds in short group (OR 0.83; 95% CI, 0.33 to 1.77).

[e] Data reversed for presentation: Original data reported such that OR < 1 indicates lower odds in short group (OR 0.77; 95% CI, 0.28 to 1.67).

Longer Than 12 Months

One systematic review[29] compared all durations of DAPT via network meta-analysis. Xie et al.[29] reported no statistically significant difference in the odds of all-cause death between 24 months of DAPT and 30 or 36 months of DAPT or between 30 months of DAPT and 36 months (Table 12).

Table 12: Summary of Evidence Available for All-Cause Death: Network Meta-Analysis, > 12 Months Versus > 12 Months

Systematic Review	Included RCTs	Stent Type	No. of Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CrI)
Xie 2016	• PRODIGY • DES-LATE • ARCTIC-Interruption • DAPT[a]	DES	17,743[b]	OR, RE	24 mo vs. 30 mo; OR > 1 indicates higher odds in extended group	OR 1.14 (0.38 to 5.56)[c]
					24 mo vs. 36 mo; OR > 1 indicates higher odds in extended group	OR 1.23 (0.41 to 6.25)[d]
					30 mo vs. 36 mo; OR < 1 indicates lower odds in extended group	OR 0.91 (0.33 to 3.85)[e]

CI = confidence interval; CrI = credible interval; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; mo = months; OR = odds ratio; RCT = randomized controlled trial; RE = random effects; vs. = versus.

[a] Patients with a bare-metal stent were excluded from analysis.

[b] The full network including all DAPT durations included 17,743 patients. It is unclear how many patients contributed data to each comparison.

[c] Data reversed for presentation: Original data reported such that OR < 1 indicates lower odds in short group (OR 0.88; 95% CI, 0.18 to 2.66).

[d] Data reversed for presentation: Original data reported such that OR < 1 indicates lower odds in short group (OR 0.81; 95% CI, 0.16 to 2.46).

[e] Data reversed for presentation: Original data reported such that OR > 1 indicates higher odds in short group (OR 1.10; 95% CI, 0.26 to 3.02).

Cardiovascular Death

In total, nine systematic reviews assessed cardiovascular death with different durations of DAPT.[13,14,16-19,22,23,30] Comparisons included six months versus more than 12 months, six to 12 months versus more than 12 months, and 12 months versus more than 12 months.

The reviews did not individually define "cardiovascular death." Some review authors stated that they included cardiovascular death as defined in the included RCTs (Appendix 6).

Six Months Versus More Than 12 Months

Four systematic reviews compared cardiovascular death among patients who received six months of DAPT with those who received more than 12 months of DAPT.[13,16,17,22] Each review included only one RCT for this time comparison (PRODIGY[38]), with a duration of six months compared with 24 months.

Each review found no statistically significant difference in the odds or risk of cardiovascular death between six months and more than 12 months of DAPT (Table 13).

Table 13: Summary of Evidence Available for Cardiovascular Death: 6 Months Versus > 12 Months

Systematic Review	Included RCTs	Stent Type	No. of Events/Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CI)	I^2
Fei 2016	PRODIGY	DES, BMS	6 mo: 37/983 24 mo:36/987	OR, RE	OR < 1 indicates lower odds in the extended group	OR 0.97 (0.61 to 1.54)	NA
Tsoi 2015	PRODIGY	DES, BMS	6 mo: 37/983 24 mo: 36/987	OR, RE	OR < 1 indicates lower odds in the extended group	OR 0.97 (0.61 to 1.54)	NA
Palmerini 2015	PRODIGY	DES[a]	6 mo: 25/751 24 mo: 27/750	HR[b]	HR > 1 indicates higher hazard in extended group	HR 1.09 (0.63 to 1.89)[c]	NA
D'Ascenzo 2016	PRODIGY	Second-generation DES	6 mo: 13/247 24 mo: 8/248	OR, RE	OR < 1 indicates lower odds in the extended group	OR 0.60 (0.24 to 1.49)[d]	NA

BMS = bare-metal stent; CI = confidence interval; DES = drug-eluting stent; HR = hazard ratio; mo = months; OR = odds ratio; RCT = randomized controlled trial; RE = random effects.

[a] Patients with BMS were excluded from analysis.

[b] Fixed-effects or random-effects model not reported.

[c] Data reversed for presentation: Original data reported such that OR < 1 indicates lower odds in the short group (OR 1.67; 95% CI, 0.67 to 4.10).

[d] Data reversed for presentation: Original data reported such that HR < 1 indicates lower hazard in the shorter group (HR 0.92; 95% CI, 0.53 to 1.58)

Six to 12 Months Versus More Than 12 Months

Two systematic reviews assessed cardiovascular death among patients who received six to 12 months of DAPT compared with those who received more than 12 months of DAPT.[18,19] Four RCTs (DAPT,[34] DES-LATE,[36] ITALIC,[37] PRODIGY[38]) were included in both reviews. Verdoia et al. also included data from the RCT by Hu et al.,[40] which was reported in abstract form only.

Both reviews reported no statistically significant difference in the odds of cardiovascular death between six to 12 months of DAPT and more than 12 months of DAPT (Table 14).

Table 14: Summary of Evidence Available for Cardiovascular Death: 6 to 12 Months Versus > 12 Months

Systematic Review	Included RCTs	Stent Type	No. of Events/Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CI)	I^2
Verdoia 2016	• DAPT • DES-LATE • ITALIC • PRODIGY • HU[a]	DES, BMS	6 to 12 mo: 110/8,871 > 12 mo: 115/8,959	OR, FE	OR > 1 indicates higher odds in the extended group	OR 1.04 (0.79 to 1.35)	0%
Cassese 2015	• DAPT • DES-LATE • ITALIC • PRODIGY	DES, BMS	6 to 12 mo: 131/9,354 > 12 mo: 139/9,444	OR, RE	OR > 1 indicates higher odds in the extended group	OR 1.06 (0.83 to 1.34)	0%

BMS = bare-metal stent; CI = confidence interval; DES = drug-eluting stent; FE = fixed effects; mo = months; OR = odds ratio; RCT = randomized controlled trial; RE = random effects.
[a] Reported in abstract format only.[40]

Twelve Months Versus More Than 12 Months

Seven systematic reviews assessed cardiovascular death among patients who received 12 months of DAPT compared with those who received more than 12 months of DAPT.[13,14,16,17,22,23,30]

Five reviews included both the DAPT[34] and DES-LATE[36] trials, while one review also included OPTIDUAL.[39] One review[16] that aimed to assess the optimal DAPT duration among patients who received a second-generation DES included only data from the DES-LATE trial.[36]

Among patients with an implanted DES, each of the reviews reported that there was no statistically significant difference in cardiovascular death between 12 months and more than 12 months of DAPT (via OR, relative risk, or hazard ratio [HR]; Table 15). Among patients who received a second-generation DES, there was no significant difference in the odds of cardiovascular death between 12 months of DAPT and more than 12 months of DAPT (Table 15).

Table 15: Summary of Evidence Available for Cardiovascular Death: 12 Months Versus > 12 Months

Systematic Review	Included RCTs	Stent Type	No. of Events/Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CI)	I^2
Fei 2016	• OPTIDUAL • DAPT • DES-LATE	DES	12 mo: 80/8,145 > 12 mo: 83/8246	OR, RE	OR > 1 indicates higher odds in the extended group	OR 1.03 (0.75 to 1.40)	17%
Palla 2015	• DAPT • DES-LATE	DES	12 mo: 74/7,455 > 12 mo: 89/7,551	OR, FE	OR > 1 indicates higher odds in the extended group	OR 1.19 (0.87 to 1.62)	0%
Tsoi 2015	• DAPT • DES-LATE	DES	12 mo: 66/7,455 > 12 mo: 73/7,551	OR, RE	OR > 1 indicates higher odds in the extended group	OR 1.12 (0.73 to 1.71)	33%
Navarese	• DAPT	DES	12 mo: 71/7,455	OR, FE	OR > 1 indicates	OR 1.09	34%

Table 15: Summary of Evidence Available for Cardiovascular Death: 12 Months Versus > 12 Months

Systematic Review	Included RCTs	Stent Type	No. of Events/Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CI)	I^2
2015	• DES-LATE		> 12 mo: 78/7,551		higher odds in the extended group	(0.79 to 1.50)	
Palmerini 2015	• DAPT • DES-LATE	DES	12 mo: NR/NR > 12 mo: NR/NR	HR[a]	HR > 1 indicates higher hazard in the extended group	HR 1.10 (0.79 to 1.52)[b]	28%
Zhang 2015	• DAPT • DES-LATE	DES	12 mo: 66/7,455 > 12 mo: 73/7,551	RR[a]	RR > 1 indicates higher odds in the extended group	RR 1.09 (0.78 to 1.52)	32.6%
D'Ascenzo 2016	• DES-LATE	DES, second-generation	12 mo: 5/650 > 12 mo: 11/679	OR, RE	OR > 1 indicates higher odds in the extended group	OR 1.61 (0.28 to 9.09)[c]	32%[d]

CI = confidence interval; DES = drug-eluting stent; FE = fixed effects; HR = hazard ratio; mo = months; OR = odds ratio; RCT = randomized controlled trial; RE = random effects; RR = risk ratio.

[a] Fixed-effects or random-effects model not reported.

[b] Data reversed for presentation: Original data reported such that HR < 1 indicates lower hazard in the short group (HR 0.91; 95% CI, 0.66 to 1.26).

[c] Data reversed for presentation: Original data reported such that OR < 1 indicates lower odds in the short group (OR 0.62; 95% CI, 0.11 to 3.57).

[d] Heterogeneity between DES types.

Noncardiovascular Death

One systematic review[22] reported the risk of noncardiovascular death among patients randomized to short or extended DAPT (Table 16).

Among patients with an implanted DES, there was no significant difference in the risk of noncardiovascular death between those who received DAPT for six months and those who received DAPT for more than 12 months (Table 16). In contrast, there was a significant increase in the risk of noncardiovascular death among those who received DAPT for more than 12 months compared with those who received DAPT for 12 months (HR 1.89; 95% CI, 1.27 to 2.78) (Table 16).

Table 16: Summary of Evidence Available for Noncardiovascular Death

Systematic Review	Included RCTs	Stent Type	No. of Events/Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CI)	I^2
6 Months Versus > 1 Year							
Palmerini 2015	• PRODIGY	DES	6 mo: NR/NR > 12 mo: NR/NR	HR[a]	HR > 1 indicates increased risk in extended group	HR 1.11 (0.61 to 2.04)[b]	NA
1 Year Versus > 1 Year							
Palmerini 2015	• DAPT • DES-LATE	DES	12 mo: NR/NR > 12 mo: NR/NR	HR[a]	HR > 1 indicates increased risk in extended group	**HR 1.89 (1.27 to 2.78)[c]**	0%

CI = confidence interval; DES = drug-eluting stent; FE = fixed effects; HR = hazard ratio; mo = months; NA = not applicable; NR = not reported; RCT = randomized controlled trial; RE = random effects.

[a] Fixed-effects or random-effects model not reported.

[b] Data reversed for presentation: Original data reported such that HR < 1 indicates lower odds in the short group (HR 0.90; 95% CI, 0.49 to 1.65).

[c] Data reversed for presentation: Original data reported such that HR < 1 indicates lower hazard in the short group (HR 0.53; 95% CI, 0.36 to 0.79).

Myocardial Infarction

In total, 11 systematic reviews assessed the impact of DAPT duration on myocardial infarction.[13,14,16-19,22,23,29,30,33] Each of the reviews either did not report the definition of myocardial infarction or reported that they used the definitions of myocardial infarction used in the primary RCTs (Appendix 6).

Six Months Versus More Than 12 Months

Three systematic reviews[13,16,17] reported the odds of myocardial infarction for six months of DAPT compared with extended DAPT. Each review included data from one trial for this comparison (PRODIGY[38]), including patients with a DES or BMS.

Among patients with a DES or BMS, two reviews reported no statistically significant difference in the odds of myocardial infarction between participants randomized to six months or more than 24 months (Table 17).[13,17] Among patients with a second-generation DES, one review[16] reported no significant difference in the odds of myocardial infarction between six months of DAPT and more than 12 months of DAPT (Table 17).

Table 17: Summary of Evidence Available for Myocardial Infarction: 6 Months Versus > 12 Months

Systematic Review	Included RCTs	Stent Type	No. of Events/Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CI)	I^2
Fei 2016	• PRODIGY	DES, BMS	6 mo: 41/983 24 mo: 39/987	OR, RE	OR < 1 indicates lower odds with extended treatment	OR 0.95 (0.60 to 1.48)	NA
Tsoi 2015	• PRODIGY	DES, BMS	6 mo: 41/983 24 mo: 39/987	OR, RE	OR < 1 indicates lower odds with extended treatment	OR 0.95 (0.60 to 1.48)	NA
D'Ascenzo 2016	• PRODIGY	Second-generation DES	6 mo: 12/492 24 mo: 16/496	OR, RE	OR > 1 indicates higher odds with extended treatment	OR 1.23 (0.21 to 7.69)[a]	78%[b]

BMS = bare-metal stent; CI = confidence interval; DES = drug-eluting stent; mo = months; NA = not applicable; OR = odds ratio; RCT = randomized controlled trial; RE = random effects.

[a] Data reversed for presentation: Original data reported such that OR < 1 indicates lower odds with short treatment (OR 0.81; 95% CI, 0.13 to 4.87).

[b] Heterogeneity between type of second-generation stent (everolimus-eluting stent versus zotarolimus-eluting stent).

One systematic review[29] compared all durations of DAPT via network meta-analysis among patients with a DES. In their analysis, Xie et al.[29] found no significant difference in the odds of myocardial infarction between six months of DAPT and 24, 30, or 36 months (Table 18).

Table 18: Summary of Evidence Available for Myocardial Infarction: Network Meta-Analysis, 6 Months Versus > 12 Months

Systematic Review	Included RCTs	Stent Type	No. of Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CrI)
Xie 2016	• PRODIGY[a] • DES-LATE • ARCTIC-Interruption • DAPT	DES	17,743[b]	OR, RE	6 mo vs. 36 mo; OR < 1 indicates lower odds in extended group	OR 0.46 (0.17 to 1.75)[c]
					6 mo vs. 24 mo; OR < 1 indicates lower odds in extended group	OR 0.84 (0.35 to 2.5)[d]
					6 mo vs. 30 mo; OR < 1 indicates lower odds in extended group	OR 2.97 (0.91 to 7.48)[e]

CI = confidence interval; CrI = credible interval; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; mo = months; OR = odds ratio; RCT = randomized controlled trial; RE = random effects; vs. = versus.

[a] Patients with a bare-metal stent were excluded from analysis.

[b] The full network including all DAPT durations included 17,743 patients. It is unclear how many patients contributed data to each comparison.

[c] Data reversed for presentation: Original data reported such that OR > 1 indicates higher odds in short group (OR 2.17; 95% CI, 0.57 to 6.02).

[d] Data reversed for presentation: Original data reported such that OR > 1 indicates higher odds in short group (OR 1.19; 95% CI, 0.40 to 2.83).

[e] Data reversed for presentation: Original data reported such that OR > 1 indicates higher odds in short group (OR 2.97; 95% CI, 0.91 to 7.48).

Six to 12 Months Versus More Than 12 Months

Three systematic reviews assessed myocardial infarction among patients who received DAPT for six to 12 months compared with more than 12 months.[18,19,33] Each review included the same five RCTs (DAPT, DES-LATE, ITALIC, PRODIGY, ARCTIC-Interruption), while one review[18] also included an RCT reported only in abstract form (Hu et al.[40]) (Table 19). Each of the included reviews reported that the odds of myocardial infarction were significantly lower among patients who received DAPT for at least 12 months compared with patients who received DAPT for six to 12 months (Table 19). Of note, two of these reviews included a mixed population of patients with a BMS or DES,[18,19] while one included only patients with a DES.[33]

Table 19: Summary of Evidence Available for Myocardial Infarction: 6 to 12 Months Versus > 12 Months

Systematic Review	Included RCTs	Stent Type	No. of Events/Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CI)	I^2
Verdoia 2016	• DAPT • DES-LATE • HU[a] • ITALIC • PRODIGY • ARCTIC-Interruption	DES, BMS	6 to 12 mo: 281/9,270 > 12 mo: 171/9,357	OR, FE	OR < 1 indicates lower odds in extended group	**OR 0.60 (0.50 to 0.73)[b]**	41%
Cassese 2015	• DAPT • DES-LATE • ITALIC • PRODIGY • ARCTIC-Interruption	DES, BMS	6 to 12 mo: 324/9978 > 12 mo: 224/10,079	OR, RE	OR < 1 indicates lower odds in extended group	**OR 0.68 (0.57 to 0.80)**	0%

Table 19: Summary of Evidence Available for Myocardial Infarction: 6 to 12 Months Versus > 12 Months

Systematic Review	Included RCTs	Stent Type	No. of Events/Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CI)	I^2
Bittl 2016	• DAPT • DES-LATE • ITALIC • PRODIGY • ARCTIC-Interruption	DES	6 to 12 mo: 266/10,432 > 12 mo: 156/10,541	OR, FE and RE	OR < 1 indicates lower odds in extended group	**OR 0.57 (0.47 to 0.70) (FE)** **OR 0.67 (0.47 to 0.65) (RE)**	42.8%

BMS = bare-metal stent; CI = confidence interval; DES = drug-eluting stent; FE = fixed effects; mo = months; OR = odds ratio; RE = random effects.
[a] Reported in abstract format only.[40]
[b] Data reversed for presentation: Original data reported such that OR > 1 indicates higher odds in short group (OR 1.66; 95% CI, 1.37 to 2.00).

Twelve Months Versus More Than 12 Months

Eight systematic reviews[13,14,16,17,22,23,29,30] assessed myocardial infarction among patients who received DAPT for 12 months compared with more than 12 months. Of these, two compared different durations of DAPT via meta-analysis,[22,29] while the others compared 12 months with more than 12 months via meta-analysis.

Among patients with a DES, five reviews reported that the odds of myocardial infarction were significantly lower among patients who received DAPT for more than 12 months compared with 12 months (Table 20). In one review, there was no difference in the odds of myocardial infarction among patients with a second-generation DES (Table 20).

Table 20: Summary of evidence available for myocardial infarction: 12 v. > 12 months

Systematic review	Included RCTs	Stent type	No. of events /patients	Type of analysis	Direction of estimate	Effect estimate (95% CI)	I^2
Fei 2016	• DES-LATE • OPTIDUAL • DAPT • ARCTIC-Interruption	DES	12 mo: 250/8769 > 12 mo: 138/8881	Odds ratio, RE	OR < 1 indicates lower odds in extended group	**OR: 0.54 (0.43, 0.66)**	13%
Palla 2015	• DES-LATE • ARCTIC Interruption- • DAPT •	DES	12 mo: 251/8079 > 12 mo: 167/8186	Odds ratio, FE	OR < 1 indicates lower odds in extended group	**OR: 0.65 (0.53, 0.79)**	10%
Tsoi 2015	• DES-LATE • ARCTIC Interruption • DAPT	DES	12 mo: 234/8079 > 12 mo: 127/8186	Odds ratio, RE	OR < 1 indicates lower odds in extended group	**OR: 0.58 (0.40, 0.84)**	35%
Navarese 2015	• DES-LATE • ARCTIC-Interruption • DAPT	DES	12 mo: 234/8096 > 12 mo: 127/8196	Odds ratio, FE	OR < 1 indicates lower odds in extended group	**OR: 0.53 (0.42, 0.66)**	37%

Table 20: Summary of evidence available for myocardial infarction: 12 v. > 12 months

Systematic review	Included RCTs	Stent type	No. of events /patients	Type of analysis	Direction of estimate	Effect estimate (95% CI)	I^2
Zhang 2015	• DES-LATE • ARCTIC-Interruption • DAPT	DES	12 mo: 234/8079 > 12 mo: 127/8186	Risk ratio†	RR > 1 indicates lower odds in extended group	**RR: 0.53 (0.43, 0.66)**	32.5%
D'Ascenzo 2016	• DAPT • DES-LATE	Second-generation DES	12 mo: 97/3630 > 12 mo: 61/3666	Odds ratio, RE	OR < 1 indicates lower odds in extended group	**OR: 0.62 (0.45, 0.86)***	0%

Note: CI = confidence interval, DES = drug-eluting stent, FE = fixed effects, mo = month, OR = odds ratio, RE = random effects, RR = risk ratio.
*Data reversed for presentation: original data reported such that OR < 1 indicates that odds of myocardial infarction is lower with short treatment (OR 1.61, 95% CI 1.16, 2.22).
† Fixed or random effects model not reported.

Two of the included reviews[22,29] used network meta-analyses to assess the optimal duration of DAPT among patients with a DES.

Compared with DAPT for 12 months, Palmerini et al.[22] reported that the odds of a myocardial infarction were significantly lower among patients who received DAPT for more than 12 months (HR 0.59; 95% CI, 0.48 to 0.71) (Table 21). Among patients who received DAPT for more than 12 months, Xie et al.[29] found no significant differences in the odds of myocardial infarction between 24 months and 30 or 36 months or between 30 months and 36 months (Table 21).

Table 21: Summary of Evidence Available for Myocardial Infarction: Network Meta-Analysis

Systematic Review	Included RCTs	No. of Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CrI)
Xie 2016	• PRODIGY[a] • DES-LATE • ARCTIC-Interruption • DAPT	17,743[b]	OR, RE	24 mo vs. 30 mo; OR < 1 indicates lower odds in extended group	OR 0.31 (0.09 to 1.69)[c]
				24 mo vs. 36 mo; OR < 1 indicates lower odds in extended group	OR 0.42 (0.12 to 2.63)[d]
				30 mo vs. 36 mo OR > 1 indicates higher odds in extended group	OR 1.14 (0.37 to 5.26)[e]
Palmerini 2015	NR	NR	HR, RE or FE NR	12 mo vs. > 12 mo; HR < 1 indicates lower risk in extended group	**HR 0.59 (0.48 to 0.71)[f]**

CI = confidence interval; CrI = credible interval; DAPT = dual antiplatelet therapy; FE = fixed effects; HR = hazard ratio; mo = months; NR = not reported; OR = odds ratio; RCT = randomized controlled trial; RE = random effects; vs. = versus.
[a] Patients with a bare-metal stent were excluded from analysis.
[b] The full network including all DAPT durations included 17,743 patients. It is unclear how many patients contributed data to each comparison.
[c] Data reversed for presentation: Original data reported such that OR > 1 indicates higher odds in short group (OR 3.26; 95% CI, 0.59 to 10.55).
[d] Data reversed for presentation: Original data reported such that OR > 1 indicates higher odds in short group (OR 2.37; 95% CI, 0.38 to 8.22).
[e] Data reversed for presentation: Original data reported such that OR < 1 indicates lower odds in short group (OR 0.88; 95% CI, 0.19 to 2.67).
[f] Data reversed for presentation: Original data reported such that HR > 1 indicates higher risk in short group (HR 1.70; 95% CI, 1.40 to 2.10).

Stroke

Four systematic reviews assessed the impact of DAPT duration on stroke.[13,14,17,30] Data were available comparing either six months or 12 months of DAPT with DAPT extended for more than 12 months.

None of the included reviews reported the definition of stroke used. The definitions of stroke used in the primary RCTs are reported in Appendix 6.

Six Months Versus More Than 12 Months

Two systematic reviews[13,17] assessed stroke among patients who received DAPT for six months compared with more than 12 months. Both reviews involved only data from the PRODIGY[38] trial. Among patients with a DES or BMS, both reviews reported no significant difference in the odds of stroke between six months and more than 12 months of DAPT (Table 22).

Table 22: Summary of Evidence Available for Stroke: 6 Months Versus > 12 Months

Systematic Review	Included RCTs	Stent Type	No. of Events/Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CI)	I^2
Fei 2016	PRODIGY	DES, BMS	6 mo: 14/983 24 mo: 21/987	OR, RE	OR < 1 indicates higher odds in extended group	OR 1.50 (0.76 to 2.98)	NA
Tsoi 2015	PRODIGY	DES, BMS	6 mo: 14/983 24 mo: 21/987	OR, RE	OR < 1 indicates higher odds in extended group	OR 1.50 (0.76 to 2.98)	NA

BMS = bare-metal stent; CI = confidence interval; DES = drug-eluting stent; mo = months; OR = odds ratio; RCT = randomized controlled trial; RE = random effects.

Six to 12 Months Versus More Than 12 Months

None of the included systematic reviews assessed stroke among patients with a DES or BMS who received DAPT for six to 12 months compared with more than 12 months following stenting.

Twelve Months Versus More Than 12 Months

Four systematic reviews[13,14,17,30] assessed stroke among patients with a DES who received DAPT for 12 months compared with more than 12 months. Each of the reviews included the same three RCTs (DAPT,[34] DES-LATE,[36] ARCTIC-Interruption[35]), with the most recently published review including one additional RCT (OPTIDUAL[39]). Among patients with a DES, each review reported no statistically significant difference in the odds or risk of stroke between patients who received DAPT for more than 12 months compared with those who received DAPT for 12 months (Table 23).

Table 23: Summary of Evidence Available for Stroke: 12 Months Versus > 12 Months

Systematic Review	Included RCTs	Stent Type	No. of Events/Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CI)	I^2
Fei 2016	• DAPT • DES-LATE • ARCTIC-Interruption • OPTIDUAL	DES	12 mo: 75/8,769 > 12 mo: 71/8,881	OR, RE	OR < 1 indicates lower odds with extended treatment	OR 0.93 (0.67 to 1.29)	0%

Table 23: Summary of Evidence Available for Stroke: 12 Months Versus > 12 Months

Systematic Review	Included RCTs	Stent Type	No. of Events/Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CI)	I^2
Palla 2015	• DAPT • DES-LATE • ARCTIC-Interruption	DES	12 mo: 75/8,079 > 12 mo: 73/8,186	OR, FE	OR < 1 indicates lower odds with extended treatment	OR 0.96 (0.69 to 1.33)	0%
Tsoi 2015	• DAPT • DES-LATE • ARCTIC-Interruption	DES	12 mo: 68/8,079 > 12 mo: 64/8,186	OR, RE	OR < 1 indicates lower odds with extended treatment	OR 0.93 (0.66 to 1.31)	0%
Zhang 2015	• DAPT • DES-LATE • ARCTIC-Interruption	DES	12 mo: 68/8,079 > 12 mo: 64/8,186	RR[a]	RR < 1 indicates lower risk with extended treatment	RR 0.93 (0.66 to 1.31)	0%

CI = confidence interval; DES = drug-eluting stent; FE = fixed effects; mo = months; OR = odds ratio; RCT = randomized controlled trial; RE = random effects; RR = risk ratio.
[a] Fixed-effects or random-effects model not reported.

Stent Thrombosis

In total, 11 systematic reviews assessed stent thrombosis with different durations of DAPT.[13,14,16-19,22,23,29,30,33] Comparisons included six months versus more than 12 months, six to 12 months versus more than 12 months, and 12 months versus more than 12 months. All of the included trials used the Academic Research Consortium criteria for defining stent thrombosis.[46]

Six Months Versus More Than 12 Months

Three systematic reviews assessed stent thrombosis among patients who received DAPT for six months compared with more than 12 months. Each review combined definite and probable stent thrombosis for this outcome, and each included data from the PRODIGY trial.[38]

Among patients with a DES or BMS, two reviews[13,17] found no significant difference in the odds of probable or definite stent thrombosis between patients who received six months of DAPT or more than 12 months of DAPT (Table 24). Among patients who received a second-generation DES, one review[16] reported no statistically significant difference between groups; however, the estimate was associated with a wide confidence interval (OR 2.50; 95% CI, 0.33 to 20.00) (Table 24).

Table 24: Summary of Evidence Available for Stent Thrombosis: 6 Months Versus > 12 Months

Systematic Review	Included RCTs	Stent Type	No. of Events/Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CI)	I^2
Fei 2016	• PRODIGY	DES, BMS	6 mo: 15/983 24 mo: 13/987	OR, RE	OR < 1 indicates lower odds in the extended group	OR 0.86 (0.41 to 1.82)	NA
Tsoi 2015	• PRODIGY	DES, BMS	6 mo: 15/983 24 mo: 13/987	OR, RE	OR < 1 indicates lower odds in the extended group	OR 0.86 (0.41 to 1.82)	NA
D'Ascenzo 2016	• PRODIGY	DES, second-generation	6 mo: 1/492 24 mo: 4/496	OR, RE	OR > 1 indicates higher odds in the extended group	OR 2.50 (0.33 to 20.00)[a]	0%[b]

BMS = bare-metal stent; CI = confidence interval; DES = drug-eluting stent; mo = months; NA = not applicable; OR = odds ratio; RCT = randomized controlled trial; RE = random effects.

[a] Data reversed for presentation: Original data reported such that OR < 1 indicates lower odds in the short group (OR 0.40; 95% CI, 0.05 to 3.07).
[b] Heterogeneity between types of second-generation stent (everolimus-eluting stent versus zotarolimus-eluting stent).

One review[29] compared six months of DAPT with 24, 30, or 36 months of DAPT via network meta-analysis. Where six months of DAPT was compared with 24 or 36 months, Xie et al.[29] reported no statistically significant difference in the odds of stent thrombosis (Table 25). However, the authors reported that 30 months of DAPT was associated with statistically lower odds of stent thrombosis compared with six months of DAPT (Table 25).

Table 25: Summary of Evidence Available for Stent Thrombosis: Network Meta-Analysis, 6 Months Versus > 12 Months

Systematic Review	Included RCTs	Stent Type	No. of Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CrI)
Xie 2016	• PRODIGY[a] • DES-LATE • ARCTIC-Interruption • DAPT	DES	17,743[b]	OR, RE	6 mo vs. 24 mo; OR < 1 indicates lower odds in extended group	OR 0.60 (0.19 to 3.33)[c]
					6 mo vs. 30 mo; OR < 1 indicates lower odds in extended group	**OR 0.09 (0.11 to 0.62)**[d]
					6 mo vs. 36 mo; OR < 1 indicates lower odds in extended group	OR 0.18 (0.04 to 1.56)[e]

CrI = credible interval; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; mo = months; OR = odds ratio; RCT = randomized controlled trial; RE = random effects; vs. = versus.

[a] Patients with a bare-metal stent were excluded from analysis.
[b] The full network including all DAPT durations included 17,743 patients. It is unclear how many patients contributed data to each comparison.

[c] Data reversed for presentation: Original data reported such that OR > 1 indicates higher odds in short group (OR 1.66; 95% CI, 0.30 to 5.36).
[d] Data reversed for presentation: Original data reported such that OR > 1 indicates higher odds in short group (OR 10.56; 95% CI, 1.62 to 9.17)
[e] Data reversed for presentation: Original data reported such that OR > 1 indicates higher odds in short group (OR 5.63; 95% CI, 0.64 to 23.2)

Six to 12 Months Versus More Than 12 Months

Three systematic reviews assessed stent thrombosis among patients who received DAPT for six to 12 months compared with more than 12 months.[18,19,33] It was not well defined within each review whether the outcome was definite, probable, or definite/probable stent thrombosis.

Each review included the same five RCTs (DAPT,[34] DES-LATE,[36] ITALIC,[37] PRODIGY,[38] ARCTIC-Interruption[35]), while one review[18] also included an RCT reported only in abstract form (Hu et al.[40]) (Table 26). Each reported that the odds of stent thrombosis were significantly lower among patients with a DES who received DAPT for at least 12 months compared with patients who received DAPT for six to 12 months (Table 26).

Table 26: Summary of Evidence Available for Stent Thrombosis: 6 to 12 Months Versus > 12 Months

Systematic Review	Included RCTs	Stent Type	No. of Events/Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CI)	I^2
Verdoia 2016	• DAPT • DES-LATE • ITALIC • PRODIGY • ARCTIC-Interruption • HU[a]	DES	6 to 12 mo: 97/9,270 > 12 mo: 39/9,357	OR, FE	OR < 1 indicates lower odds in the extended group	**OR 0.40 (0.28 to 0.58)[b]**	45%
Cassese 2015	• DAPT • DES-LATE • ITALIC • PRODIGY • ARCTIC-Interruption	DES	6 to 12 mo: 115/9,978 > 12 mo: 57/10,079	OR, RE	OR < 1 indicates lower odds in the extended group	**OR 0.50 (0.36 to 0.69)**	0%
Bittl 2016	• DAPT • DES-LATE • ITALIC • PRODIGY • ARCTIC-Interruption	DES	6 to 12 mo: 92/9,742 > 12 mo: 34/9,846	OR, FE and RE	OR < 1 indicates lower odds in the extended group	**OR 0.37 (0.25 to 0.55) (FE)** **OR 0.42 (0.24 to 0.74) (RE)**	28.9%

CI = confidence interval; DES = drug-eluting stent; FE = fixed effects; mo = months; OR = odds ratio; RCT = randomized controlled trial; RE = random effects.
[a] Reported in abstract format only.[40]
[b] Data reversed for presentation: Original data reported such that OR > 1 indicates higher odds in short group (OR 2.47; 95% CI, 1.72 to 3.55).

Twelve Months Versus More Than 12 Months

Six systematic reviews assessed stent thrombosis among patients who received DAPT for 12 months compared with more than 12 months.[13,14,16,17,23,30] Each review assessed definite/probable stent thrombosis; as well, Navarese et al.[23] assessed definite stent thrombosis and very late stent thrombosis (stent thrombosis occurring more than one year after PCI) (Table 27).

Table 27: Summary of Evidence Available for Stent Thrombosis: 12 Months Versus > 12 Months

Systematic Review	Included RCTs	Stent Type	No. of Events/Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CrI)	I^2
Definite or Probable Stent Thrombosis							
Fei 2016	• DES-LATE • DAPT • ARCTIC-Interruption • OPTIDUAL	DES	12 mo: 80/8,769 > 12 mo: 29/ 8,881	OR, RE	OR < 1 indicates lower odds in extended group	**OR 0.36 (0.24 to 0.55)**	49%
Palla 2015	• DES-LATE • ARCTIC-Interruption • DAPT	DES	12 mo: 83/8,079 > 12 mo: 38/8,186	OR, FE	OR < 1 indicates lower odds in extended group	**OR 0.45 (0.31 to 0.66)**	4%
Tsoi 2015	• DES-LATE • ARCTIC-Interruption • DAPT	DES	12 mo: 79/8,079 > 12 mo: 26/8,186	OR, RE	OR < 1 indicates lower odds in extended group	**OR 0.35 (0.20 to 0.62)**	18%
Navarese 2015	• DES-LATE • ARCTIC-Interruption • DAPT	DES	12 mo: 79/8,096 > 12 mo: 26/8,196	OR, FE	OR < 1 indicates lower odds in extended group	**OR 0.33 (0.21 to 0.51)**	18%
Zhang 2015	• DES-LATE • ARCTIC-Interruption • DAPT	DES	12 mo: 79/8,096 > 12 mo: 26/8,196	RR[a]	RR > 1 indicates lower risk in extended group	**RR 0.33 (0.21 to 0.51)**	17.2%
D'Ascenzo 2016	• DAPT • DES-LATE	Second-generation DES	12 mo: 29/3,630 > 12 mo: 16/3,666	OR, RE	OR < 1 indicates lower odds in extended group	OR 0.54 (0.87 to 1.02)[b]	0%
Definite Stent Thrombosis							
Navarese 2015	• DES-LATE • ARCTIC-Interruption • DAPT	DES	12 mo: 72/8,096 > 12 mo: 22/8,196	OR, FE	OR < 1 indicates lower odds in extended group	**OR 0.30 (0.19 to 0.49)**	32%
Very Late[c] Stent Thrombosis							
Navarese 2015	• DES-LATE • ARCTIC-Interruption • DAPT	DES	12 mo: 8,096 > 12 mo: 8,196	OR, FE	OR < 1 indicates lower odds in extended group	**OR 0.33 (0.21 to 0.51)**	18%

CI = confidence interval; CrI = credible interval; DES = drug-eluting stent; FE = fixed effects; mo = months; OR = odds ratio; RCT = randomized controlled trial; RE = random effects; RR = risk ratio.

[a] Fixed-effects or random-effects model not reported.

[b] Data reversed for presentation: Original data reported such that OR > 1 indicates higher odds in short group (OR 1.84; 95% CI, 0.98 to 3.46).

[c] Stent thrombosis occurring more than one year after percutaneous coronary intervention.

Among patients with a DES, five reviews[13,14,17,23,30] reported that the odds of probable or definite stent thrombosis were significantly lower among patients who received DAPT for at least 12 months compared with patients who received DAPT for 12 months (Table 27).

Similarly, one review[23] reported that the odds of definite stent thrombosis was significantly lower among patients who received more than 12 months of DAPT compared with those who received 12 months of DAPT (OR 0.30; 95% CI, 0.19 to 0.49) (Table 27). Navarese et al.[23] also reported significantly lower odds of very late stent thrombosis among patients who received more than 12 months of DAPT (OR 0.33; 95% CI, 0.21 to 0.51) (Table 27).

Among patients with a second-generation DES, one review[16] reported no statistically significant difference in probable or definite stent thrombosis between 12 months and more than 12 months of DAPT (OR 0.54; 95% CI, 0.87 to 1.02) (Table 27).

Via network meta-analysis, Palmerini et al.[22] found a significantly lower risk of probable or definite stent thrombosis among patients who received more than 12 months of DAPT compared with 12 months of DAPT (Table 28). The numbers of trials and participants that informed this comparison were not reported. One review[29] compared 12 months of DAPT with 24, 30, or 36 months of DAPT via network meta-analysis. Where 12 months of DAPT was compared with 24 or 36 months, Xie et al.[29] reported no significant difference in the odds of stent thrombosis. However, the authors reported that 30 months of DAPT was associated with a statistically lower odds of stent thrombosis compared with 12 months of DAPT (OR 0.25; 95% CI, 0.09 to 0.99) (Table 28).

Table 28: Summary of Evidence Available for Stent Thrombosis: Network Meta-Analysis, 12 Months Versus > 12 Months

Systematic Review	Included RCTs	Stent Type	No. of Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CrI)
Xie 2016	• PRODIGY[a] • DES-LATE • ARCTIC-Interruption • DAPT	DES	17,743[b]	OR, RE	12 mo vs. 24 mo; OR > 1 indicates higher odds in extended group	OR 1.16 (0.31 to 11.11)[c]
					12 mo vs. 30 mo; OR < 1 indicates lower odds in extended group	**OR 0.25 (0.09 to 0.99)**[d]
					12 mo vs. 36 mo; OR < 1 indicates lower odds in extended group	OR 0.46 (0.14 to 2.56)[e]
Palmerini 2015	Unclear	Unclear	NR	HR[f]	HR < 1 indicates lower risk in extended group	**HR 0.40 (0.25 to 0.59)**[g]

CrI = credible interval; DAPT = dual antiplatelet therapy; HR = hazard ratio; mo = months; NR = not reported; OR = odds ratio; RE = random effects.
[a] Patients with a bare-metal stent were excluded from analysis.
[b] The full network including all DAPT durations included 17,743 patients. It is unclear how many patients contributed data to the each comparison.
[c] Data reversed for presentation: Original data reported such that OR < 1 indicates lower odds in short group (OR 0.86; 95% CrI, 0.09 to 3.27).
[d] Data reversed for presentation: Original data reported such that OR > 1 indicates higher odds in short group (OR 4.05; 95% CrI, 1.01 to 11.46).
[e] Data reversed for presentation: Original data reported such that OR > 1 indicates higher odds in short group (OR 2.16; 95% CrI, 0.39 to 7.29).
[f] Fixed-effects or random-effects model not reported.
[g] Data reversed for presentation: Original data reported such that indicates increased risk of thrombosis in short group (HR 2.50; 95% CrI, 1.70 to 4.00).

Longer Than 12 Months

Xie et al.[29] compared the odds of stent thrombosis among treatment durations longer than 12 months via network meta-analysis. Among patients with a DES, the authors found no statistically significant difference in the odds of stent thrombosis between 24 months and 30 months, between 24 months and 36 months, or between 30 months and 36 months (Table 29).

Table 29: Summary of Evidence Available for Stent Thrombosis: Network Meta-Analysis, > 12 Months

Systematic Review	Included RCTs	Stent Type	No. of Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CrI)
Xie 2016	• PRODIGY[a] • DES-LATE • ARCTIC-Interruption • DAPT	DES	17,743[b]	OR, RE	24 mo vs. 30 mo; OR < 1 indicates lower odds in extended group	OR 0.09 (0.33 to 1.37)[c]
					24 mo vs. 36 mo; OR < 1 indicates lower odds in extended group	OR 0.17 (0.03 to 3.33)[d]
					30 mo vs. 36 mo; OR > 1 indicates higher odds in extended group	OR 1.28 (0.31 to14.29)[e]

CrI = credible interval; DAPT = dual antiplatelet therapy; mo = months; OR = odds ratio, RE = random effects; vs. = versus.
[a] Patients with a bare-metal stent were excluded from analysis.
[b] The full network including all DAPT durations included 17,743 patients. It is unclear how many patients contributed data to the each comparison.
[c] Data reversed for presentation: Original data reported such that OR > 1 indicates higher odds in short group (OR 11.18; 95% CI, 0.73 to 3.02).
[d] Data reversed for presentation: Original data reported such that OR > 1 indicates higher odds in short group (OR 5.92; 95% CI, 0.30 to 29.37).
[e] Data reversed for presentation: Original data reported such that OR < 1 indicates lower odds in short group (OR 0.78; 95% CI, 0.07 to 3.26).

Urgent Target Revascularization

None of the included systematic reviews assessed urgent revascularization. This outcome was reported in two of the included RCTs (ITALIC37, ARCTIC-Interruption35); findings are summarized in Table 30. There were no significant differences in risk between short and extended DAPT in either trial.

Table 30: Summary of Evidence Available for Urgent Target Revascularization

RCT	Stent Type	No. of Events/Patients	Direction of Estimate	Reported HR (95% CI)
ARCTIC-Interruption	DES	12 mo: 9/641 18 to 30 mo: 8/645	HR > 1 indicates higher risk in extended group	HR 1.17 (0.45 to 3.04)
ITALIC	DES	6 mo: 5/926 24 mo: 2/924	HR < 1 indicates lower risk in extended group	HR 0.4 (0.08 to 2.04)[a]

CI = confidence interval; DES = drug-eluting stent; HR = hazard ratio; mo = months.
[a] Data reversed for presentation: Original data reported such that HR > 1 indicates higher risk in short group (HR 2.50; 95% CI, 0.49 to 12.88).

Major Adverse Cardiovascular Events

Two systematic reviews assessed major adverse cardiovascular events associated with different durations of DAPT.[23,33] One review compared six to 12 months of DAPT with more than 12 months[33] and one compared 12 months of DAPT with more than 12 months of DAPT.[23]

The components of the MACCE (major adverse cardiac and cerebrovascular event) outcome differed in each included RCT (Table 31). As such, it is difficult to draw conclusions from meta-analyses of these data.

Table 31: Definitions of MACCE Used in Included Randomized Controlled Trials

RCT	Definition
DES-LATE	Cardiac death, myocardial infarction, or stroke
PRODIGY	Death, myocardial infarction, stroke, or transient ischemic attack
ARCTIC-Interruption	Any death, myocardial infarction, stent thrombosis, stroke or transient ischemic attack, urgent revascularization
ITALIC	Death, myocardial infarction, urgent revascularization, stroke, major bleeding
DAPT	Death, myocardial infarction, or stroke
OPTIDUAL	Death, myocardial infarction, stroke, major bleeding

MACCE = major adverse cardiac and cerebrovascular events; RCT = randomized controlled trial.

Despite differences in definitions, both Bittl et al.[33] and Navarese et al.[23] reported significantly lower odds of an event among patients with a DES who received more than 12 months of DAPT compared with a shorter duration (Table 32).

Table 32: Summary of Evidence Available for MACCE

Systematic Review	Included RCTs	Stent Type	No. of Events/Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CI)	I^2
6 to 12 Months Versus > 12 Months							
Bittl 2016	• DES-LATE • PRODIGY[a] • ARCTIC • ITALIC • DAPT[a] • OPTIDUAL	DES	6 to 12 mo: 534/10,664 > 12 mo: 450/10,778	OR, FE and RE	OR < 1 indicates lower odds in the extended group	**OR 0.82 (0.72 to 0.94) (FE)** **OR 0.85 (0.72 to 1.00) (RE)**	23%
12 Months Versus > 12 Months							
Navarese 2015	• DES-LATE • ARCTIC-Interruption • DAPT[a]	DES	12 mo: 369/8,096 > 12 mo: 296/8,196	OR, FE	OR < 1 indicates lower odds in the extended group	**OR 0.78 (0.67 to 0.92)**	47%

BMS = bare-metal stent; CI = confidence interval; DES = drug-eluting stent; FE = fixed effects; MACCE = major adverse cardiac and cerebrovascular events; mo = months; OR = odds ratio; RE = random effects.
[a] Patients with BMS were excluded from analysis.

Bleeding

Major Bleeding

In total, 11 systematic reviews assessed major bleeding associated with different durations of DAPT.[13,14,16-19,22,23,29,30,33]

Each of the underlying RCTs used a different classification system for bleeding (Table 33), and it is not appropriate to combine all bleeding data via meta-analysis.[10] As such, we report the data separately for BARC, TIMI, and GUSTO classification systems. None of the eligible RCTs assessed bleeding by use of the REPLACE system.

Table 33: Bleeding Criteria Used in Included Randomized Controlled Trials

RCT	Bleeding Criteria
ARCTIC-Interruption	TIMI criteria, STEEPLE criteria
DAPT	BARC criteria, GUSTO criteria
DES-LATE	TIMI criteria
ITALIC	TIMI criteria
PRODIGY	TIMI criteria, BARC criteria
OPTIDUAL	ISTH criteria

BARC = Bleeding Academic Research Consortium; GUSTO = Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries; ISTH = International Society on Thrombosis and Haemostasis; RCT = randomized controlled trial; STEEPLE = Safety and Efficacy of Enoxaparin in PCI Patients; TIMI = thrombolysis in myocardial infarction.

Three systematic reviews assessed bleeding by use of TIMI criteria,[13,17,23] and one used BARC criteria (type 3 and 5).[16] One additional review[30] stated that they assessed TIMI major bleeding; however, the bleeding event counts included from the DAPT trial were assessed by use of GUSTO criteria; these data are not included in our analysis.

Compared with six months of DAPT, two reviews reported increased odds of TIMI major bleeding with more than 12 months of DAPT (Table 34). Both reviews included only one trial (PRODIGY[38]), in which about 25% of patients had a BMS.

Among participants with a second-generation DES, D'Ascenzo et al.[16] reported that more than 12 months of DAPT was associated with increased odds of BARC type 3 or type 5 bleeding (Table 34).

One review reported that there was no statistically significant increase in the odds of TIMI major bleeding (OR 1.60; 95% CI, 0.97 to 2.64) among patients who received more than 12 months of DAPT compared with 12 months.

None of the included reviews assessed major bleeding by use of the GUSTO classification system.

Table 34: Summary of Evidence Available for Major Bleeding

Systematic Review	Included RCTs	Stent Type	No. of Events/Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CI)	I^2
6 Months Versus > 12 Months							
TIMI Major Bleeding							
Fei 2016	PRODIGY	DES, BMS	12 mo: 6/986 > 12 mo: 16/987	OR, RE	OR > 1 indicates higher odds in extended group	**OR 2.68 (1.05 to 6.89)**	NA
Tsoi 2015	PRODIGY	DES, BMS	12 mo: 6/986 > 12 mo: 16/987	OR, RE	OR > 1 indicates higher odds in extended group	**OR 2.68 (1.05 to 6.89)**	NA
BARC Type 3 or 5							
D'Ascenzo 2016	PRODIGY	DES, BMS	12 mo: 19/986 > 12 mo: 34/987	OR, RE	OR > 1 indicates higher odds in extended group	**OR 1.82 (1.02 to 3.23)**[a]	NA
12 Months Versus > 12 Months							
TIMI Major Bleeding							
Navarese 2015	• DES-LATE • ARCTIC-Interruption	DES	12 mo: 25/3,155 > 12 mo: 40/3,176	OR, RE	OR > 1 indicates higher odds in extended group	OR 1.60 (0.97 to 2.64)	42%

BARC = Bleeding Academic Research Consortium; BMS = bare-metal stent; CI = confidence interval; DES = drug-eluting stent; mo = months; NA = not applicable; OR = odds ratio; RCT = randomized controlled trial; RE = random effects; TIMI = thrombolysis in myocardial infarction.
[a] Data reversed for presentation: Original data reported such that OR < 1 indicates lower odds in short DAPT group (OR 0.55; 95% CI, 0.31 to 0.98).

Minor Bleeding

None of the included systematic reviews assessed minor bleeding.

Gastrointestinal Bleeding

None of the included systematic reviews or RCTs assessed gastrointestinal bleeding.

Data Summary: Research Question 2

Are there subgroups of patients for whom the optimal duration of DAPT with ASA plus a P2Y12 inhibitor (clopidogrel, prasugrel, ticagrelor) is different?

Limited data were available from the included systematic reviews to address this question: One review[23] assessed outcomes among patients with and without ACS and for patients in different age groups (< 62.5 years versus > 62.5 years). The outcomes assessed in this review were cardiovascular death, myocardial infarction, and stent thrombosis.

Among patients with ACS, Navarese et al.[23] reported no significant differences in the odds of cardiovascular death, myocardial infarction, or stent thrombosis between DAPT for 12 months and DAPT for longer than 12 months (Table 35). It was unclear which RCTs contributed data to the analysis and which stent types were included.

Among patients without ACS, the authors found no significant differences in cardiovascular death or myocardial infarction between DAPT for 12 months and DAPT for longer than 12 months. DAPT for longer than 12 months was associated with significantly lower odds of stent thrombosis compared with DAPT for 12 months among patients without ACS (Table 35).

Table 35: Summary of Evidence Available: Acute Coronary Syndrome[a]

Outcome;Subgroup	Included RCTs	Stent Type	No. of Events/Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CI)	I^2
Cardiovascular Death							
ACS	NR	Unclear	12 mo:19/2,514 > 12 mo: 28/2,531	OR, FE	OR > 1 indicates higher odds in the extended group	OR 1.47 (0.82 to 2.64)	NR
No ACS	NR	Unclear	12 mo: 52/4,941 > 12 mo: 50/5,020	OR, FE	OR > 1 indicates higher odds in the extended group	OR 0.95 (0.64 to 1.40)	NR
Myocardial Infarction							
ACS	NR	Unclear	12 mo: 27/2,514 > 12 mo:19/2,531	OR, FE	OR < 1 indicates lower odds in the extended group	OR 0.70 (0.39 to 1.26)	NR
No ACS	NR	Unclear	12 mo: 207/5,582 > 12 mo:108/5,665	OR, FE	OR < 1 indicates lower odds in the extended group	OR 0.60 (0.31 to 1.15)	NR
Stent Thrombosis							
ACS	NR	Unclear	12 mo: 11/2,514 > 12 mo: 7/2,531	OR, FE	OR < 1 indicates lower odds in the extended group	OR 0.63 (0.24 to 1.63)	NR
No ACS	NR	Unclear	12 mo: 68/5,582 > 12 mo: 19/5,665	OR, FE	OR < 1 indicates lower odds in the extended group	**OR 0.28 (0.17 to 0.46)**	NR

ACS = acute coronary syndrome; CI = confidence interval; FE = fixed effects; mo = months; NR = not reported; OR = odds ratio; RCT = randomized controlled trial.

[a] Data reported by Navarese et al. 2015.[23]

Among patients aged less than 62.5 years, Navarese et al.[23] reported no significant differences in the odds of cardiovascular death, but lower odds of myocardial infarction and stent thrombosis between DAPT for 12 months and DAPT for longer than 12 months (Table 36).

Table 36: Summary of Evidence Available: Age[a]

Outcome;Subgroup	Included RCTs	Stent Type	No. of Events/Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CI)	I^2
Cardiovascular Death							
< 62.5 y	NR	Unclear	12 mo: 52/4941 > 12 mo: 50/5020	OR, FE	OR > 1 indicates higher odds in the extended group	OR 1.47 (0.82 to 2.64)	NR
> 62.5 y	NR	Unclear	12 mo: 19/2514 > 12 mo: 28/2531	OR, FE	OR > 1 indicates higher odds in the extended group	OR 0.95 (0.64 to 1.40)	NR
Myocardial Infarction							
< 62.5 y	NR	Unclear	12 mo: 198/4941 > 12 mo: 99/5020	OR, FE	OR < 1 indicates lower odds in the extended group	**OR 0.48 (0.38 to 0.62)**	NR
> 62.5 y	NR	Unclear	12 mo: 36/3155 > 12 mo: 28/3176	OR, FE	OR < 1 indicates lower odds in the extended group	OR 0.77 (0.47 to 1.27)	NR
Stent Thrombosis							
< 62.5 y	NR	Unclear	12 mo: 65/4941	OR, FE	OR < 1 indicates	**OR 0.29 (0.17 to**	NR

Table 36: Summary of Evidence Available: Age[a]

Outcome;Subgroup	Included RCTs	Stent Type	No. of Events/Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CI)	I^2
			> 12 mo: 19/5020		lower odds in the extended group	**0.48)**	
> 62.5 y	NR	Unclear	12 mo: 14/3155 > 12 mo: 7/3176	OR, FE	OR < 1 indicates lower odds in the extended group	OR 0.51 (0.21 to 1.24)	NR

FE = fixed effects; mo = months; NR = not reported; OR = odds ratio; RCT = randomized controlled trial; y = years.
[a] Data reported by Navarese et al. 2015.[23]

Among patients aged more than 62.5 years, there were no significant differences in cardiovascular death, myocardial infarction, or stent thrombosis between DAPT for 12 months and DAPT for longer than 12 months (Table 36).

Because limited data were available from the included systematic reviews and the data available were not well reported (e.g., it was unclear which RCTs contributed data to the analysis and which stent types were included), we sought data from eligible RCTs to address this research question.

Subgroup data were available from four RCTs (DAPT,[34] ARCTIC-Interruption,[35] ITALIC,[37] PRODIGY[38]) to address the optimal duration of DAPT among one of the a priori–defined subgroups of interest. These data are summarized below.

Acute Coronary Syndrome

Subgroup data for ACS were available from the included RCTs for three outcomes: stent thrombosis, MACCE, and bleeding.

Stent Thrombosis

One trial (PRODIGY[38]) reported stent thrombosis among patients with ACS (Table 37). Valgimigli et al.[38] reported no significant difference in the risk of definite stent thrombosis or definite/probable stent thrombosis between patients with ACS randomized to six months or 24 months of DAPT. No data were reported for patients without ACS.

Table 37: Summary of Randomized Controlled Trials That Reported Stent Thrombosis in Patients With Acute Coronary Syndrome

RCT	Stent Type	Outcome Definition	No. of Events/Patients	Reported HR (95% CI)[a]
PRODIGY	DES, BMS	Definite stent thrombosis	6 mo: NR/733 24 mo: NR/732	HR 0.99 (0.35 to 2.84)
		Definite/probable stent thrombosis	6 mo: NR/733 24 mo: NR/732	HR 0.66 (0.29 to 1.48)

BMS = bare-metal stent; CI = confidence interval; DES = drug-eluting stent; HR = hazard ratio; mo = months; NR = not reported, RCT = randomized controlled trial.
[a] As reported in the RCT, unless otherwise stated.

Major Adverse Cardiac and Cerebrovascular Events

Three RCTs reported MACCE among patients with and without ACS (PRODIGY, ARCTIC-Interruption, DES-LATE).[35,36,38] Each used a different definition of MACCE (Table 31).

Despite differences in the outcome definition, each RCT found no significant difference in the risk of MACCE between six to 12 months of DAPT and more than 12 months of DAPT among patients either with or without ACS (Table 38).

Table 38: Summary of Evidence Available for MACCE Among Patients With or Without Acute Coronary Syndrome

Subgroup, RCT	Stent Type	No. of Events/Patients	Outcome Definition	Direction of Estimate	Reported HR (95% CI)[a]
ACS					
ARCTIC-Interruption	DES	12 mo: 8/167 18 to 30 mo: 6/156	All-cause death, MI, stroke or transient ischemic attack, urgent coronary revascularization, and stent thrombosis	RR < 1 indicates lower risk in extended group	RR 0.78 (0.27 to 2.27)[b]
PRODIGY	DES, BMS	6 mo: 86/733 24 mo: 81/732	Death of any cause, nonfatal MI, or cerebrovascular accident	HR < 1 indicates lower risk in extended group	HR 0.94 (0.69 to 1.27)
DES-LATE	DES	12 mo: 2.4%[a] 36 mo: 2.5%[a]	Death resulting from cardiac causes, MI, or stroke	HR > 1 indicates higher risk in extended group	HR 1.04 (0.65 to 1.67)[c]
No ACS					
ARCTIC-Interruption	DES	12 mo: 19/457 18 to 30 mo: 18/479	All-cause death, MI, stroke or transient ischemic attack, urgent coronary revascularization, and stent thrombosis	RR < 1 indicates lower risk in extended group	RR 0.88 (0.46 to 1.69)[d]
PRODIGY	DES, BMS	6 mo: 12/250 24 mo: 19/255	Death of any cause, nonfatal MI, or cerebrovascular accident	HR > 1 indicates higher risk in extended group	HR 1.59 (0.77 to 3.28)
DES-LATE	DES	12 mo: 2.5%[e] 36 mo: 2.8%[e]	Death resulting from cardiac causes, MI, or stroke	HR > 1 indicates higher risk in extended group	HR 1.09 (0.62 to 1.89)[f]

ACS = acute coronary syndrome; BMS = bare-metal stent; CI = confidence interval; DES = drug-eluting stent; HR = hazard ratio; MACCE = major adverse cardiac and cerebrovascular events; MI = myocardial infarction; mo = months; RCT = randomized controlled trial; RR = relative risk.

[a] As reported in the RCT, unless otherwise stated.

[b] Data reversed for presentation: Original data reported such that RR > 1 indicates higher risk in short group (RR 1.28; 95% CI, 0.44 to 3.68).

[c] Data reversed for presentation: Original data reported such that HR > 1 indicates lower risk in short group (HR 0.96; 95% CI, 0.60 to 1.54).

[d] Data reversed for presentation: Original data reported such that HR > 1 indicates higher risk in short group (RR 1.13; 95% CI, 0.59 to 2.15).

[e] Data reported as % of participants. Number of events and number of participants randomized to each duration not reported.

[f] Data reversed for presentation: Original data reported such that HR < 1 indicates lower risk in short group (HR 0.92; 95% CI, 0.53 to 1.61).

Bleeding

One trial (PRODIGY[38]) reported bleeding among patients with ACS or stable coronary artery disease. The PRODIGY trial used the BARC bleeding classification system (Table 39).

Table 39: Summary of Evidence Available for Bleeding Among Patients With or Without Acute Coronary Syndrome

Subgroup, RCT	Stent Type	Bleeding Type	No. of Events/Patients	Reported HR (95% CI)[a]
ACS				
PRODIGY	DES, BMS	BARC type 2	6 mo: 13/733 24 mo: 29/733	**2.24 (1.16 to 4.30)**
		BARC type 3	6 mo: 12/733 24 mo: 18/733	1.50 (0.72 to 3.12)
		BARC type 5	6 mo: 5/733 24 mo: 5/733	1.00 (0.29 to 3.45)
		BARC type 2, 3, 5	6 mo: 30/733 24 mo: 52/733	**1.75 (1.11 to 2.74)**
		BARC type 3, 5	6 mo: 17/733 24 mo: 23/733	1.35 (0.72 to 2.53)
Stable Coronary Artery Disease				
PRODIGY	DES, BMS	BARC type 2	6 mo: 2/250 24 mo: 10/255	**5.02 (1.10 to 22.89)**
		BARC type 3	6 mo: 2/250 24 mo: 7/255	3.51 (0.73 to 16.88)
		BARC type 5	6 mo: 0/250 24 mo: 4/255	NR
		BARC type 2, 3, 5	6 mo: 4/250 24 mo: 21/255	**5.37 (1.84 to 14.65)**
		BARC type 3, 5	6 mo: 2/250 24 mo: 11/255	**5.53 (1.23 to 24.94)**

ACS = acute coronary syndrome; BARC = Bleeding Academic Research Consortium; BMS = bare-metal stent; CI = confidence interval; DES = drug-eluting stent; HR = hazard ratio; MI = myocardial infarction; mo = months; NR = not reported; RCT = randomized controlled trial.
[a] HR > 1 indicates increased risk in the extended group.

Among patients with ACS, Valgimigli et al.[38] reported an increased risk of BARC type 2 bleeding among those randomized to 24 months of DAPT compared with six months. A significant increase was also seen for BARC type 2, 3, and 5 bleeding (Table 39). There were no differences in type 3 or type 5 bleeding (individually) or in type 3 and 5 bleeding (together).

Among patients with stable coronary artery disease, extended DAPT was associated with a significant increase in type 2 bleeding, type 2, 3, and 5 bleeding, and type 3 and 5 bleeding. There were no differences in type 3 bleeding (Table 39).

Four patients with stable coronary artery disease randomized to 24 months of DAPT experienced a fatal bleed (type 5) compared with zero patients randomized to six months of DAPT (Table 39).

Myocardial Infarction

One RCT[34] reported outcome data for patients with prior acute myocardial infarction with a BMS or DES.[47] Of patients with a prior myocardial infarction, 47% had STEMI and 53% had non-STEMI.

Among patients with prior myocardial infarction, outcome data were available for all-cause death, cardiovascular death, noncardiovascular death, MACCE, stent thrombosis, bleeding, and myocardial infarction.

Data were not reported separately for patients with STEMI or non-STEMI.

All-Cause Death

One RCT (DAPT[34]) reported all-cause death among patients with or without prior acute myocardial infarction. Among patients with prior acute myocardial infarction, there was no significant difference in the risk of all-cause death with DAPT for 12 months compared with 30 months (Table 40). Among patients with no prior myocardial infarction, there was a significantly higher risk of all-cause death among participants who received DAPT for 30 months compared with 12 months (Table 40).

Table 40: Summary of Evidence Available for All-Cause Death Among Patients With or Without Prior Myocardial Infarction

Subgroup, RCT	Stent Type	No. of Events/Patients	Direction of Estimate	Reported HR (95% CI)[a]
Prior Acute MI				
DAPT	DES, BMS	12 mo: 27/1,771 30 mo: 24/1,805	HR < 1 indicates lower hazard in extended group	0.87 (0.50 to 1.50)
No Prior MI				
DAPT	DES, BMS	12 mo:57/4,015 30 mo: 82/4,057	HR > 1 indicates higher hazard in extended group	**1.43 (1.02 to 2.00)**

BMS = bare-metal stent; CI = confidence interval; DES = drug-eluting stent; HR = hazard ratio; MI = myocardial infarction; mo = months; RCT = randomized controlled trial.
[a] As reported in the RCT, unless otherwise stated.

Cardiovascular Death

One RCT (DAPT[34]) reported cardiovascular death among patients with or without prior acute myocardial infarction.

Among patients with or without prior acute myocardial infarction, there was no significant difference in the risk of cardiovascular death with DAPT for 30 months compared with 12 months (Table 41).

Table 41: Summary of Evidence Available for Cardiovascular Death Among Patients With or Without Prior Myocardial Infarction

Subgroup, RCT	Stent Type	No. of Events/Patients	Direction of Estimate	Reported HR (95% CI)[a]
Prior Acute MI				
DAPT	DES, BMS	12 mo: 16/1,771 30 mo: 11/1,805	HR < 1 indicates lower hazard in extended group	0.67 (0.31 to 1.44)
No Prior MI				
DAPT	DES, BMS	12 mo: 36/4,015 30 mo: 38/4,057	HR > 1 indicates higher hazard in extended group	1.05 (0.66 to 1.65)

BMS = bare-metal stent; CI = confidence interval; DES = drug-eluting stent; HR = hazard ratio; MI = myocardial infarction; mo = months; RCT = randomized controlled trial.
[a] As reported in the RCT, unless otherwise stated.

Noncardiovascular Death

One RCT (DAPT[34]) reported noncardiovascular death among patients with or without prior acute myocardial infarction (Table 42).

Table 42: Summary of Evidence Available for Noncardiovascular Death Among Patients With or Without Prior Myocardial Infarction

Subgroup, RCT	Stent Type	No. of Events/Patients	Direction of Estimate	Reported HR (95% CI)[a]
Prior Acute MI				
DAPT	DES, BMS	12 mo: 9/1,771 30 mo: 11/1,805	HR < 1 indicates lower hazard in extended group	1.19 (0.49 to 2.87)
No Prior MI				
DAPT	DES, BMS	12 mo: 18/4,015 30 mo: 41/4,057	HR > 1 indicates higher hazard in extended group	**2.26 (1.30 to 3.94)**

BMS = bare-metal stent; CI = confidence interval; DES = drug-eluting stent; HR = hazard ratio; MI = myocardial infarction; mo = months; RCT = randomized controlled trial.
[a] As reported in the RCT, unless otherwise stated.

Among patients with prior myocardial infarction, there was no significant difference in the risk of noncardiovascular death with DAPT for 30 months compared with 12 months (Table 42). However, among patients with no prior myocardial infarction, patients who received DAPT for 30 months were at increased risk of noncardiovascular death compared with those who received DAPT for 12 months (HR 2.26; 95% CI, 1.30 to 3.94) (Table 42).

Myocardial Infarction

One RCT (DAPT[34]) reported myocardial infarction among patients with or without prior acute myocardial infarction. Among patients with or without prior acute myocardial infarction, the risk of myocardial infarction was significantly lower among patients who received DAPT for 30 months compared with 12 months (Table 43).

Table 43: Summary of Evidence Available for Myocardial Infarction Among Patients With or Without Prior Myocardial Infarction

Subgroup, RCT	Stent Type	No. of Events/Patients	Direction of Estimate	Reported HR (95% CI)[a]
Prior Acute MI				
DAPT	DES, BMS	12 mo: 88/1,771 30 mo: 39/1,805	HR < 1 indicates lower hazard in extended group	**0.42 (0.29 to 0.62)**
No Prior MI				
DAPT	DES, BMS	12 mo: 135/4,015 30 mo: 82/4,057	HR < 1 indicates lower hazard in extended group	**0.60 (0.45 to 0.79)**

BMS = bare-metal stent; CI = confidence interval; DES = drug-eluting stent; HR = hazard ratio; MI = myocardial infarction; mo = months; RCT = randomized controlled trial.
[a] As reported in the RCT, unless otherwise stated.

Stent Thrombosis

One RCT (DAPT[34]) reported stent thrombosis among patients with or without prior acute myocardial infarction. Among patients with or without prior acute myocardial infarction, the risk of stent thrombosis was significantly lower among patients who received DAPT for 30 months compared with 12 months (Table 44).

Table 44: Summary of Evidence Available for Stent Thrombosis[a] Among Patients With or Without Prior Myocardial Infarction

Subgroup, RCT	Stent Type	No. of Events/Patients	Direction of Estimate	Reported HR (95% CI)[b]
Prior Acute MI				
DAPT	DES, BMS	12 mo: 32/1,771 30 mo: 9/1,805	HR < 1 indicates lower hazard in extended group	**0.27 (0.13 to 0.57)**
No Prior MI				
DAPT	DES, BMS	12 mo: 42/4,015 30 mo: 14/4,057	HR < 1 indicates lower hazard in extended group	**0.33 (0.18 to 0.60)**

BMS = bare-metal stent; CI = confidence interval; DES = drug-eluting stent; HR = hazard ratio; MI = myocardial infarction; mo = months; RCT = randomized controlled trial.
[a] Definite or probable stent thrombosis.
[b] As reported in the RCT, unless otherwise stated.

Major Adverse Cardiac and Cerebrovascular Events

One RCT (DAPT[34]) reported MACCE among patients with or without prior acute myocardial infarction (Table 45).

Table 45: Summary of Evidence Available for MACCE Among Patients With or Without Prior Myocardial Infarction

Subgroup, RCT	Stent Type	No. of Events/Patients	Direction of Estimate	Reported HR (95% CI)[a]
Prior Acute MI				
DAPT	DES, BMS	12 mo: 117/1,771 30 mo: 69/1,805	HR < 1 indicates lower hazard in extended group	**0.56 (0.42 to 0.76)[b]**
No Prior MI				
DAPT	DES, BMS	12 mo: 206/4,015 30 mo: 175/4,057	HR < 1 indicates lower hazard in extended group	0.83 (0.68 to 1.02)[b]

BMS = bare-metal stent; CI = confidence interval; DES = drug-eluting stent; HR = hazard ratio; MACCE = major adverse cardiac and cerebrovascular events; MI = myocardial infarction; mo = months; RCT = randomized controlled trial.
[a] As reported in the RCT, unless otherwise stated.
[b] Components of MACCE in the DAPT trial: all-cause death, MI, or stroke.

Among patients with prior acute myocardial infarction, the risk of experiencing an adverse cardiac or cerebrovascular event was significantly lower among patients who received DAPT for 30 months compared with 12 months (HR 0.56; 95% CI, 0.42 to 0.76) (Table 45). Among patients with no prior myocardial infarction, there was no statistically significant difference in the HR between the two durations of DAPT (HR 0.83; 95% CI, 0.68 to 1.02) (Table 45).

Bleeding

One RCT (DAPT[34]) reported bleeding among patients with or without prior acute myocardial infarction (Table 46).

Table 46: Summary of Evidence Available for Bleeding[a] Among Patients With or Without Prior Myocardial Infarction

Subgroup, RCT	Stent Type	No. of Events/Patients	Direction of Estimate	Reported HR (95% CI)[b]
Prior Acute MI				
DAPT	DES, BMS	12 mo: 35/1,771 30 mo: 76/1,805	HR > 1 indicates higher hazard in extended group	**2.14 (1.43 to 3.19)**
No Prior MI				
DAPT	DES, BMS	12 mo: 116/4,015 30 mo: 223/4,057	HR > 1 indicates higher hazard in extended group	**1.93 (1.55 to 2.42)**

BARC = Bleeding Academic Research Consortium; BMS = bare-metal stent; CI = confidence interval; DES = drug-eluting stent; HR = hazard ratio, MI = myocardial infarction; mo = months; RCT = randomized controlled trial.
[a] BARC 2, 3, or 5; data not provided separately for each type.
[b] As reported in the RCT, unless otherwise stated.

Among patients with prior acute myocardial infarction, the risk of a BARC type 2, 3, or 5 bleeding event was significantly higher for those who received DAPT for 30 months compared with 12 months (HR 2.14; 95% CI, 1.43 to 3.19) (Table 46). Among patients with no prior acute myocardial infarction, the risk of a BARC type 2, 3, or 5 bleeding event was significantly higher for those who received DAPT for 30 months compared with 12 months (HR 1.93; 95% CI, 1.55 to 2.42) (Table 46).

Although the data were not provided separately by bleeding type, the authors noted that fatal bleeding (type 5) was rare and not significantly different between patients with or without prior myocardial infarction (0.17% versus 0.08%, *P* = 0.145).[47]

Diabetes

In total, four RCTs (DAPT,[34] ARCTIC-Interruption,[35] DES-LATE,[36] PRODIGY[38]) provided subgroup data for participants with or without diabetes.[34-36,38] One RCT (DAPT[34]) reported death (all-cause, cardiovascular, noncardiovascular), stroke, myocardial infarction, MACCE, stent thrombosis, and major bleeding among those with or without diabetes. The remaining RCTs reported only MACCE among participants with or without diabetes.[35,36,38]

All-Cause Death

All-cause death was assessed among participants with and without diabetes in one RCT.[34] Data were not provided separately for participants with DES or BMS. In both those with and those without diabetes, there was no significant difference in the risk of all-cause death between DAPT for 30 months compared with 12 months (Table 47).

Table 47: Summary of Evidence Available for All-Cause Death Among Participants With or Without Diabetes

Subgroup, RCT	Stent Type	No. of Patients With an Event/ No. Randomized	Direction of Estimate	Reported Effect Estimate (95% CI)[a]
Diabetes				
DAPT	DES, BMS	12 mo: 35/1,654 30 mo: 46/1,737	HR > 1 indicates increased hazard in extended group	HR 1.25 (0.80 to 1.94)
No Diabetes				
DAPT	DES, BMS	12 mo: 50/4,135 30 mo: 62/4,125	RR > 1 indicates increased hazard in extended group	RR 1.24 (0.86 to 1.80)[b]

BMS = bare-metal stent; CI = confidence interval; DES = drug-eluting stent; HR = hazard ratio; mo = months; RCT = randomized controlled trial.
[a] As reported in the RCT, unless otherwise stated.
[b] Calculated based on the number of reported events in each group. HR could not be calculated because observation time was unknown.

Cardiovascular Death

Cardiovascular death was assessed among participants with diabetes in one RCT.[34] No data were provided for participants without diabetes. Among those with diabetes and either a DES or BMS, there was no significant difference in the risk of cardiovascular death between DAPT for 30 months compared with 12 months (Table 48).

Table 48: Summary of Evidence Available for Cardiovascular Death Among Participants With Diabetes

Subgroup, RCT	Stent Type	No. of Patients With an Event/ No. Randomized	Direction of Estimate	Reported HR (95% CI)[a]
Diabetes				
DAPT	DES, BMS	12 mo: 23/1,654 30 mo: 27/1,737	HR > 1 indicates increased hazard in extended group	1.11 (0.64 to 1.94)

BMS = bare-metal stent; CI = confidence interval; DES = drug-eluting stent; HR = hazard ratio; mo = months; RCT = randomized controlled trial.
[a] As reported in the RCT, unless otherwise stated.

Noncardiovascular Death

One systematic review[22] reported the risk of noncardiovascular death among patients with diabetes randomized to short or extended DAPT (Table 49). Among patients with diabetes, there was no significant difference in the risk of noncardiovascular death between those who received DAPT for 12 months or 30 months (HR 1.71; 95% CI, 0.79 to 3.70).

Table 49: Summary of Evidence Available for Noncardiovascular Death Among Participants With Diabetes

Subgroup, RCT	Stent Type	No. of Patients With an Event/ No. Randomized	Direction of Estimate	Reported HR (95% CI)[a]
Diabetes				
DAPT	DES, BMS	12 mo: 10/1,654 30 mo: 18/1,737	HR > 1 indicates increased hazard in extended group	1.71 (0.79 to 3.70)

BMS = bare-metal stent; CI = confidence interval; DES = drug-eluting stent; HR = hazard ratio; mo = months; RCT = randomized controlled trial.
[a] As reported in the RCT, unless otherwise stated.

Myocardial Infarction

Myocardial infarction was assessed among participants with and without diabetes in one RCT.[34]

Among participants with diabetes, there was no significant difference in the risk of myocardial infarction between DAPT for 30 months compared with 12 months (HR 0.72; 95% CI, 0.51 to 1.01) (Table 50).

Among participants without diabetes, DAPT for longer than 12 months was associated with a significantly lower risk of myocardial infarction compared with DAPT for 12 months (HR 0.42; 95% CI, 0.31 to 0.57) (Table 50).

Table 50: Summary of Evidence Available for Myocardial Infarction Among Participants With or Without Diabetes

Subgroup, RCT	Stent Type	No. of Patients With an Event/ No. Randomized	Direction of Estimate	Reported HR (95% CI)[a]
Diabetes				
DAPT	DES, BMS	12 mo: 77/1,654 30 mo: 59/1,737	HR > 1 indicates increased hazard in extended group	0.72 (0.51 to 1.01)
No Diabetes				
DAPT	DES, BMS	12 mo: 149/4,132 30 mo: 66/4,125	HR < 1 indicates lower hazard in extended group	**0.42 (0.31 to 0.57)**

BMS = bare-metal stent; CI = confidence interval; DES = drug-eluting stent; HR = hazard ratio; mo = months; RCT = randomized controlled trial.
[a] As reported in the RCT, unless otherwise stated.

Stroke

Stroke was assessed among participants with diabetes in one RCT.[34] No data were provided for participants without diabetes. Among those with diabetes, there was no significant difference in the risk of stroke between DAPT for 30 months compared with DAPT for 12 months (HR 1.00; 95% CI, 0.52 to 1.95) (Table 51).

Table 51: Summary of Evidence Available for Stroke Among Participants With Diabetes

Subgroup, RCT	Stent Type	No. of Patients With an Event/ No. Randomized	Direction of Estimate	Reported HR (95% CI)[a]
Diabetes				
DAPT	DES, BMS	12 mo: 17/1,654 30 mo: 18/1,737	HR > 1 indicates increased hazard in extended group	1.00 (0.52 to 1.95)

BMS = bare-metal stent; CI = confidence interval; DES = drug-eluting stent; HR = hazard ratio; mo = months; RCT = randomized controlled trial.
[a] As reported in the RCT, unless otherwise stated.

Stent Thrombosis

Stent thrombosis was assessed among participants with and without diabetes in one RCT.[34] Data were available for definite, probable, and probable or definite stent thrombosis among participants with diabetes, while data were available only for probable or definite stent thrombosis among participants without diabetes (Table 52).

Table 52: Summary of Evidence Available for Stent Thrombosis in Patients With or Without Diabetes

Subgroup, RCT	Stent Type	Stent Thrombosis	No. of Events/Patients	Direction of Estimate	Reported HR (95% CI)[a]
Diabetes					
DAPT	DES, BMS	Probable or definite	6 mo: 18/1,654 24 mo: 9/1,737	HR < 1 indicates lower hazard in extended group	0.47 (0.21 to 1.05)
		Probable	6 mo: 4/1,654 24 mo: 3/1,737	HR < 1 indicates lower hazard in extended group	0.71 (0.16 to 3.17)
		Definite	6 mo: 14/1,654 24 mo: 6/1,737	HR < 1 indicates lower hazard in extended group	0.41 (0.16 to 1.05)
No Diabetes					
DAPT	DES, BMS	Probable or definite	6 mo: 58/4,132 24 mo: 17/4,125	HR < 1 indicates lower hazard in extended group	**0.25 (0.14 to 0.45)**

BMS = bare-metal stent; CI = confidence interval; DES = drug-eluting stent; HR = hazard ratio; mo = months; RCT = randomized controlled trial.
[a] As reported in the RCT, unless otherwise stated.

Among participants with diabetes, there was no statistically significant difference in the risk of probable or definite stent thrombosis (HR 0.47; 95% CI, 0.21 to 1.05), probable stent thrombosis (HR 0.71; 95% CI, 0.16 to 3.17), or definite stent thrombosis (HR 0.41; 95% CI, 0.16 to 1.05) between DAPT for 30 months compared with DAPT for 12 months (Table 52). Among participants without diabetes and either a DES or BMS, DAPT for longer than 12 months was associated with a significantly lower risk of probable or definite stent thrombosis compared with DAPT for 12 months (HR 0.25; 95% CI, 0.14 to 0.45) (Table 52). Data were not provided separately for probable or definite stent thrombosis.

Major Adverse Cardiac and Cerebrovascular Events

Four RCTs (DAPT,[34] ARCTIC-Interruption,[35] DES-LATE,[36] PRODIGY[38]) reported MACCE among participants with and without diabetes. Each trial used a different definition of MACCE (Table 31), making it inappropriate to combine the data via meta-analysis.

Two trials included only participants with a DES (ARCTIC-Interruption,[35] DES-LATE), while two included participants with either a DES or a BMS (DAPT,[34] PRODIGY[38]). The DAPT trial provided data separately for participants with DES[34] as well as collectively for participants with either DES or BMS.[48]

Diabetes

Three RCTs[34-36] reported no significant differences in the risk of MACCE between DAPT for six to 12 months compared with DAPT for more than 12 months among patients with diabetes with DES (Table 53).

Table 53: Summary of Evidence Available for MACCE in Patients With or Without Diabetes

Subgroup, RCT	Stent Type	Outcome Definition	No. of Patients With an Event/ No. Randomized	Direction of Estimate	Reported Effect Estimate (95% CI)[a]
Diabetes					
ARCTIC-Interruption	DES	All-cause death, MI, stroke or transient ischemic attack, urgent coronary revascularization, and stent	12 mo: 10/222 18 to 30 mo: 11/198	RR < 1 indicates lower risk in extended group	RR 0.80 (0.34 to 1.89)

Table 53: Summary of Evidence Available for MACCE in Patients With or Without Diabetes

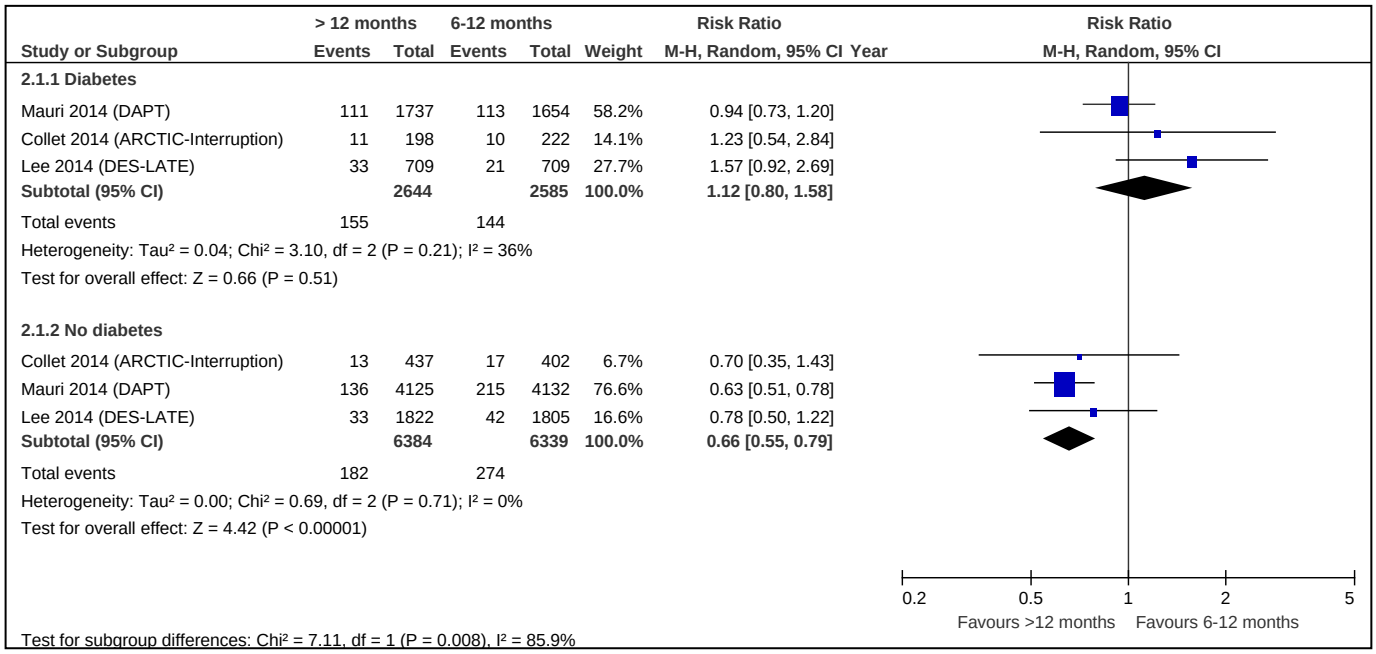
Subgroup, RCT	Stent Type	Outcome Definition	No. of Patients With an Event/ No. Randomized	Direction of Estimate	Reported Effect Estimate (95% CI)[a]
		thrombosis			
DAPT	DES	All-cause death, MI, stroke	12 mo: 100/NR 30 mo: 101/NR	HR < 1 indicates lower risk in extended group	HR 0.95 (0.72 to 1.25)
DES-LATE	DES	Death resulting from cardiac causes, MI, or stroke	12 mo: 21/709 36 mo: 33/709	HR > 1 indicates higher risk in extended group	HR 1.59 (0.89 to 2.86)[b]
DAPT	DES, BMS	All-cause death, MI, stroke	12 mo: 113/1,654 30 mo: 111/1,737	HR < 1 indicates lower risk in extended group	HR 0.92 (0.71 to 1.20)
PRODIGY	DES, BMS	All-cause of any cause, nonfatal MI, or cerebrovascular accident	6 mo: NR/233 24 mo: NR/244	HR > 1 indicates higher risk in extended group	HR 1.18 (0.72 to 1.89)[c]
No Diabetes					
ARCTIC-Interruption	DES	All-cause death, MI, stroke or transient ischemic attack, urgent coronary revascularization, and stent thrombosis	12 mo: 17/402 18 to 30 mo: 13/437	RR < 1 indicates lower risk in extended group	RR 0.68 (0.33 to 1.39)[d]
DAPT	DES	Death, MI, stroke	12 mo: 185/NR 30 mo: 110/NR	HR < 1 indicates lower risk in extended group	**HR 0.59 (0.46 to 0.74)**
DES-LATE	DES	Death resulting from cardiac causes, MI, or stroke	12 mo: 42/1,805 36 mo: 33/1,822	HR > 1 indicates lower risk in extended group	HR 0.8 (0.50 to 1.28)[e]
DAPT	DES, BMS	Death, MI, stroke	12 mo: 215/4,132 30 mo: 136/4,125	RR < 1 indicates lower risk in extended group	Calculated: **RR 0.63 (0.51 to 0.78)**[f]
PRODIGY	DES, BMS	All-cause of any cause, nonfatal MI, or cerebrovascular accident	6 mo: NR/750 24 mo: NR/743	HR > 1 indicates lower risk in extended group	HR 0.94 (0.67 to 1.32)[g]

CI = confidence interval; DES = drug-eluting stent; HR = hazard ratio; mo = months; NR = not reported; RCT = randomized controlled trial; RR = relative risk.
[a] As reported in the RCT, unless otherwise stated.
[b] Data reversed for presentation: Original data reported such that HR < 1 indicates lower risk in short group (HR 0.63; 95% CI, 0.35 to 1.12).
[c] Data reversed for presentation: Original data reported such that HR < 1 indicates lower risk in short group (HR 0.85; 95% CI, 0.53 to 1.38).
[d] Data reversed for presentation: Original data reported such RR > 1 indicates higher risk in short group (RR 1.48; 95% CI, 0.72 to 3.04).
[e] Data reversed for presentation: Original data reported such HR > 1 indicates lower risk in extended group (HR 1.25; 95% CI, 0.78 to 2.00).
[f] Calculated by use of reported event counts via random effects meta-analysis
[g] Data reversed for presentation: Original data reported such HR > 1 indicates lower risk in extended group (HR 1.06; 95% CI, 0.76 to 1.50).

Two RCTs[34,38] reported no significant differences in the risk of MACCE between DAPT for six to 12 months compared with DAPT for more than 12 months among patients with diabetes and either a BMS or DES (Table 53).

When all available evidence was pooled via meta-analysis, there was no significant difference in the risk of MACCE among patients who received extended DAPT compared with six to 12 months of DAPT (risk ratio [RR] 1.12; 95% CI, 0.80 to 1.58) (Figure 2).

Figure 2: Relative Risk of MACCE Among Patients With or Without Diabetes



CI = confidence interval; MACCE = major adverse cardiac and cerebrovascular events.

No Diabetes

Three RCTs[34-36] reported there no significant differences in the risk of MACCE between DAPT for six to 12 months compared with DAPT for more than 12 months among patients without diabetes with a DES.

One RCT (PRODIGY[38]) reported no significant differences in the risk of MACCE between DAPT for six to 12 months compared with DAPT for more than 12 months among patients without diabetes with either a BMS or a DES.

When all available evidence was pooled via meta-analysis, there was an overall reduction in the risk of MACCE among patients who received extended DAPT compared with six to 12 months of DAPT (RR 0.66; 95% CI, 0.55 to 0.79) (Figure 2).

Major Bleeding

Major bleeding was assessed among participants with diabetes in one RCT.[34] The DAPT trial reported bleeding by use of the BARC system for patients with diabetes.

Among participants with diabetes, there was a statistically significant difference in the risk of type 2 and type 3 but not type 5 bleeding between DAPT for 30 months compared with 12 months (Table 54). When types 2, 3, and 5 bleeding were considered together, DAPT for 30 months was associated with an increased risk of bleeding compared with DAPT for 12 months (RR 1.60; 95% CI, 1.16 to 2.21) (Table 54). No data were provided for participants without diabetes.

Table 54: Summary of Evidence Available: Bleeding in Patients With Diabetes

Subgroup, RCT	Stent Type	Bleeding Type	No. of Events/ No. Randomized	Direction of Estimate	Risk Ratio (95% CI)[a,b]
Diabetes					
DAPT	DES, BMS	BARC type 2	12 mo: 33/1,654 30 mo: 58/1,737	RR > 1 indicates increased risk in extended group	**1.67 (1.10 to 2.55)**
		BARC type 3	12 mo: 24/1,654 30 mo: 44/1,737	RR > 1 indicates increased risk in extended group	**1.75 (1.07 to 2.86)**
		BARC type 5	12 mo: 2/1,654 30 mo: 1/1,737	RR < 1 indicates lower risk in extended group	0.48 (0.04 to 5.25)
		BARC type 2, 3, 5	12 mo: 57/1,654 30 mo: 96/1,737	RR > 1 indicates increased risk in extended group	**1.60 (1.16 to 2.21)**

BARC = Bleeding Academic Research Consortium; BMS = bare-metal stent; CI = confidence interval; DES = drug-eluting stent; mo = months; RCT = randomized controlled trial; RR = relative risk.

[a] Calculated based on reported no. of events.

[b] No. of participants included in the analysis: 12 mo: 1547; 30 mo: 1622.

Age

In total, four RCTs (DAPT,[34] ARCTIC-Interruption,[35] DES-LATE,[36] PRODIGY[38]) provided subgroup data for participants by age. One RCT (DAPT[34]) reported MACCE, myocardial infarction, and stent thrombosis, while the other RCTs reported only MACCE among participants by age group.[35,36,38]

Myocardial Infarction

Myocardial infarction was reported by age group in one trial (DAPT[34]). Although the DAPT trial included participants with either a DES or a BMS, data were reported by age only for those with a DES.

Among patients aged less than 75 years, DAPT for more than 12 months was associated with a significantly lower risk of myocardial infarction (HR 0.46; 95% CI, 0.36 to 0.60) (Table 55). Among patients aged greater than 75 years, the difference in risk of myocardial infarction between 12 months and 30 months of DAPT was not statistically significant (HR 0.76; 95% CI, 0.38 to 1.54) (Table 55).

Table 55: Summary of Evidence Available for Myocardial Infarction by Age Group

Subgroup, RCT	Stent Type	No. of Patients With an Event/No. Randomized (% of Patients)	Direction of Estimate	Reported HR (95% CI)
< 75 Years				
DAPT	DES	12 mo: 181/NR (4.2%) 30 mo: 85/NR (2.0%)	HR < 1 indicates lower hazard in extended group	**0.46 (0.36 to 0.60)**
> 75 Years				
DAPT	DES	12 mo: 17/NR (3.6%) 30 mo: 14/NR (2.7%)	HR < 1 indicates lower hazard in extended group	0.76 (0.38 to 1.54)

CI = confidence interval; DES = drug-eluting stent; HR = hazard ratio; mo = months; NR = not reported; RCT = randomized controlled trial.

Stent Thrombosis

Stent thrombosis was reported by age group in one trial (DAPT[34]). Although the DAPT trial included participants with either a DES or a BMS, data were reported by age only for those with a DES.

Among patients aged less than 75 years, DAPT for more than 12 months was associated with a significantly lower risk of probable or definite stent thrombosis (HR 0.29; 95% CI, 0.17 to 0.49) (Table 56). Among patients aged greater than 75 years, the difference in risk of probable or definite stent thrombosis between 12 months and 30 months of DAPT was not statistically significant (HR 0.23; 95% CI, 0.03 to 2.06) (Table 56).

Table 56: Summary of Evidence Available for Stent Thrombosis by Age Group

Subgroup, RCT	Stent Type	Stent Thrombosis	No. of Events/Patients (% of Patients)	Direction of Estimate	Reported HR (95% CI)[a]
< 75 Years					
DAPT	DES	Probable or definite	12 mo: 61/NR (1.4%) 30 mo: 18/NR (0.4%)	HR < 1 indicates lower hazard in extended group	**0.29 (0.17 to 0.49)**
> 75 Years					
DAPT	DES	Probable or definite	12 mo: 4/NR (0.8%) 30 mo: 1/NR (0.2%)	HR < 1 indicates lower hazard in extended group	0.23 (0.03 to 2.06)

CI = confidence interval; DES = drug-eluting stent; HR = hazard ratio; mo = months; NR = not reported; RCT = randomized controlled trial.
[a] As reported in the RCT.

Major Adverse Cardiac and Cerebrovascular Events

Four RCTs (DAPT,[34] ARCTIC-Interruption,[35] DES-LATE,[36] PRODIGY[38]) reported MACCE by age group. However, the data were grouped in different ways. For example, the DES-LATE and PRODIGY trials compared participants aged less than 65 years with those aged more than 65 years. However, the ARCTIC-Interruption and DAPT trials compared participants aged less than 75 years with those aged more than 75 years. In Table 57, data are presented for younger patients and older patients according to the classification used in the RCT.

Table 57: Summary of Evidence Available for MACCE by Age Group

Subgroup, RCT	Stent Type	Outcome Definition	No. of Patients With an Event (No. Randomized)	Direction of Estimate	Effect Estimate (95% CI)[a]
Younger Patients					
< 65 Years					
DES-LATE	DES	Death resulting from cardiac causes, MI, or stroke	12 mo: NR/NR (2.0%) 36 mo: NR/NR (1.7%)	HR < 1 indicates lower risk in extended group	HR 0.85 (0.48 to 1.49)[b]
PRODIGY	DES, BMS	All-cause of any cause, nonfatal MI, or cerebrovascular accident	6 mo: NR/NR (NR) 24 mo: NR/NR (NR)	HR > 1 indicates higher risk in extended group	HR 1.75 (0.86 to 3.57)[c]
< 75 Years					
ARCTIC-Interruption	DES	All-cause death, MI, stroke or transient ischemic attack, urgent coronary revascularization, and stent thrombosis	12 mo: NR/521 (3.5%) 18 to 30 mo: NR/518 (3.3%)	RR < 1 indicates lower risk in extended group	RR 0.93 (0.48 to 1.78)[d]

Table 57: Summary of Evidence Available for MACCE by Age Group

Subgroup, RCT	Stent Type	Outcome Definition	No. of Patients With an Event (No. Randomized)	Direction of Estimate	Effect Estimate (95% CI)[a]
DAPT	DES	All-cause death, MI, stroke	12 mo: 251/NR (5.8%) 30 mo: 176/NR (4.0%)	HR < 1 indicates lower risk in extended group	**HR 0.69 (0.57 to 0.83)**
Older Patients					
> 65 Years					
DES-LATE	DES	Death resulting from cardiac causes, MI, or stroke	12 mo: NR/NR (2.9%) 36 mo: NR/NR (3.7%)	HR > 1 indicates higher risk in extended group	HR 1.23 (0.77 to 1.96)[e]
PRODIGY	DES, BMS	All-cause of any cause, nonfatal MI, or cerebrovascular accident	6 mo: NR/NR (NR) 24 mo: NR/NR (NR)	HR < 1 indicates lower risk in extended group	HR 0.89 (0.66 to 1.21)[f]
> 75 Years					
ARCTIC-Interruption	DES	All-cause death, MI, stroke or transient ischemic attack, urgent coronary revascularization, and stent thrombosis	12 mo: NR/103 (8.7%) 18 to 30 mo: NR/117 (6.0%)	RR < 1 indicates lower risk in extended group	RR 0.67 (0.25 to 1.78)[g]
DAPT	DES	Death, MI, stroke	12 mo: 34/NR (7.1%) 30 mo: 35/NR (6.8%)	HR < 1 indicates lower risk in extended group	HR 0.95 (0.59 to 1.52)

CI = confidence interval; DES = drug-eluting stent; HR = hazard ratio; MACCE = major adverse cardiac and cerebrovascular events; MI = myocardial infarction; mo = months; NR = not reported; RCT = randomized controlled trial; RR = relative risk.

[a] As reported in the RCT.

[b] Data reversed for presentation: Original data reported such that HR > 1 indicates increased risk in short group (HR 1.18; 95% CI, 0.67 to 2.08).

[c] Data reversed for presentation: Original data reported such that HR < 1 indicates lower risk of major adverse cardiovascular events in short group (HR 0.57; 95% CI, 0.28 to 1.16).

[d] Data reversed for presentation: Original data reported such that RR > 1 indicates higher risk in short group (RR 1.08; 95% CI, 0.56 to 2.09).

[e] Data reversed for presentation: Original data reported such that HR < 1 indicates lower risk in short group (HR 0.81; 95% CI, 0.51 to 1.30).

[f] Data reversed for presentation: Original data reported such that HR > 1 indicates lower risk in extended group (HR 1.12; 95% CI, 0.82 to 1.51).

[g] Data reversed for presentation: Original data reported such that RR > 1 indicates higher risk in short group (RR 1.50; 95% CI, 0.56 to 4.02).

Although the DAPT trial included participants with either a DES or a BMS, data were reported by age only for those with a DES. Each of the included trials used a different definition of MACCE, making comparison of the findings difficult.

Among patients aged less than 75 years, three RCTs reported no statistically significant difference in the risk of MACCE. In contrast, one RCT[34] reported a significantly lower risk among participants who received DAPT for 30 months compared with 12 months (HR 0.69; 95% CI, 0.57 to 0.83) (Table 57).

Among patients aged greater than 65 years, each RCT reported a non-significant difference in risk of MACCE between extended DAPT and DAPT for 12 months or less (Table 57).

Smoking

Two RCTs reported outcomes among patients described as either current tobacco users or current smokers compared with non-tobacco users or non-smokers.[34,35] Both trials assessed MACCE among smokers and non-smokers, while one trial[34] assessed myocardial infarction and stent thrombosis.

In the DAPT trial,[34] the number of smokers and non-smokers assigned to continue DAPT (> 12 months) or to discontinue DAPT at 12 months was not reported. The total number of smokers in the trial was 2,432, while 7,529 patients reported no current tobacco use.

Myocardial Infarction

Myocardial infarction was assessed among smokers and non-smokers in the DAPT trial.[34] In both smokers and non-smokers, the risk of myocardial infarction was significantly lower among patients who received DAPT for 30 months compared with 12 months (Table 58).

Table 58: Summary of Evidence Available for Myocardial Infarction Among Smokers and Non-Smokers

Subgroup, RCT	Stent Type	% of Patients With an Event[a]	Direction of Estimate	HR (95% CI)[b]
Current Tobacco Use				
DAPT	DES, BMS	12 mo: 5.6% 30 mo: 2.1%	HR < 1 indicates lower hazard in extended group	**0.37 (0.24 to 0.59)**
No Current Tobacco Use				
DAPT	DES, BMS	12 mo: 3.7% 30 mo: 2.0%	HR < 1 indicates lower hazard in extended group	**0.54 (0.41 to 0.72)**

BMS = bare-metal stent; CI = confidence interval; DES = drug-eluting stent; HR = hazard ratio; mo = months; RCT = randomized controlled trial.
[a] Total number of patients in each group not reported.
[b] As reported in the RCT.

Stent Thrombosis

Stent thrombosis was assessed among smokers and non-smokers in the DAPT trial.[34] In both smokers and non-smokers, the risk of probable or definite stent thrombosis was significantly lower among patients who received DAPT for 30 months compared with 12 months (Table 59).

Table 59: Summary of Evidence Available for Stent Thrombosis[a] Among Smokers and Non-Smokers

Subgroup, RCT	Stent Type	% of Patients With an Event[b]	Direction of Estimate	HR (95% CI)[c]
Current Tobacco Use				
DAPT	DES, BMS	12 mo: 2.5% 30 mo: 0.5%	HR < 1 indicates lower hazard in extended group	**0.20 (0.08 to 0.49)**
No Current Tobacco Use				
DAPT	DES, BMS	12 mo: 1.0% 30 mo: 0.4%	HR < 1 indicates lower hazard in extended group	**0.35 (0.19 to 0.67)**

BMS = bare-metal stent; CI = confidence interval; DES = drug-eluting stent; HR = hazard ratio; mo = months; RCT = randomized controlled trial.
[a] Definite or probable.
[b] Total number of patients in each group not reported.
[c] As reported in the RCT.

Major Adverse Cardiac and Cerebrovascular Events

Two RTCs assessed MACCE among smokers and non-smokers.[34,35]

Among current tobacco users with a DES, Mauri et al. (DAPT[34]) reported a significant reduction in the risk of death, myocardial infarction, or stroke in patients who received DAPT for 18 to 30 months compared with 12 months (HR 0.66; 95% CI, 0.48 to 0.91) (Table 60). They reported a similar reduction in the risk of MACCE among non-smokers (HR 0.75; 95% CI, 0.61 to 0.93). Using a more inclusive definition of MACCE, Collet et al. (ARCTIC-Interruption[35]) found a non-significant difference in the odds of an event between

DAPT for 12 months and DAPT for 18 to 30 months among both smokers (RR 0.83; 95% CI, 0.25 to 2.70) and non-smokers (RR 0.86; 95% CI, 0.46 to 1.59) (Table 60).

Table 60: Summary of Evidence Available for MACCE Among Smokers and Non-Smokers

Subgroup, RCT	Stent Type	Outcome Definition	% of Patients With an Event (No. Randomized)	Direction of Estimate	Effect Estimate (95% CI)[a]
Current Tobacco Use					
ARCTIC-Interruption	DES	All-cause death, MI, stroke or transient ischemic attack, urgent coronary revascularization, and stent thrombosis	12 mo: 3.9% (152) 18 to 30 mo: 3.4% (147)	RR < 1 indicates lower risk in extended group	RR 0.83 (0.25 to 2.70)[b]
DAPT	DES	Death, MI, stroke	12 mo: 7.7% (NR) 30 mo: 5.2% (NR)	HR < 1 indicates lower risk in extended group	**HR 0.66 (0.48 to 0.91)**
No Current Tobacco Use					
ARCTIC-Interruption	DES	All-cause death, MI, stroke or transient ischemic attack, urgent coronary revascularization, and stent thrombosis	12 mo: 4.4% (472) 18 to 30 mo: 3.9% (488)	RR < 1 indicates lower risk in extended group	RR 0.86 (0.46 to 1.59)[c]
DAPT	DES	Death, MI, stroke	12 mo: 5.4% (NR) 30 mo: 4.1% (NR)	HR < 1 indicates lower risk in extended group	**HR 0.75 (0.61 to 0.93)**

CI = confidence interval; DES = drug-eluting stent; HR = hazard ratio; MACCE = major adverse cardiac and cerebrovascular events; MI = myocardial infarction; mo = months; RCT = randomized controlled trial; RR = relative risk.
[a] As reported in the RCT.
[b] Data reversed for presentation: Original data reported such that RR > 1 indicates higher risk in short group (RR 1.20; 95% CI, 0.37 to 3.94).
[c] Data reversed for presentation: Original data reported such that RR > 1 indicates higher risk in short group (RR 1.16; 95% CI, 0.63 to 2.16).

Lesion Complexity

One RCT reported subgroup data by lesion complexity (PRODIGY[38]). Data were provided for MACCE for patients with a simple or complex lesion and an implanted DES or BMS. Complex lesions were defined as those that met the criteria for a type B2 or C lesion according to the American College of Cardiology and American Heart Association's classification system.[49,50]

Among patients with a simple lesion, there was no significant difference in the risk of MACCE between participants who received extended DAPT compared with six months of DAPT (HR 1.28; 95% CI, 0.76 to 2.17) (Table 61). Similarly, among patients with a complex lesion, there was no significant different in the risk of MACCE between participants who received extended DAPT compared with six months of DAPT (HR 0.93; 95% CI, 0.67 to 1.30) (Table 61).

Table 61: Summary of Evidence Available for MACCE by Lesion Complexity[a]

Subgroup, RCT	Stent Type	Outcome Definition	No. of Patients With an Event/No. Randomized	Direction of Estimate	Reported Effect Estimate (95% CI)
Simple Lesion					
PRODIGY	DES, BMS	Death from any cause, MI, cerebrovascular accident	6 mo: NR/325 24 mo: NR/319	HR > 1 indicates higher risk in extended group	HR 1.28 (0.76 to 2.17)[b]
Complex Lesion					
PRODIGY	DES, BMS	Death from any cause, MI, cerebrovascular accident	6 mo: NR/664 24 mo: NR/662	HR < 1 indicates lower risk in extended group	HR 0.93 (0.67 to 1.30)[c]

BMS = bare-metal stent; CI = confidence interval; DES = drug-eluting stent; HR = hazard ratio; MACCE = major adverse cardiac and cerebrovascular events; MI = myocardial infarction; mo = months; NR = not reported; RCT = randomized controlled trial; RR = relative risk.

[a] Type B2 or C based on the American College of Cardiology and American Heart Association's classification system.

Type B: Moderately complex, tubular (length 10 to 20 mm), eccentric, moderate tortuosity of proximal segment, moderately angulated segment (> 45°, < 90°), irregular contour, moderate or heavy calcification, total occlusions < 3 months old, ostial in location, bifurcation lesions requiring double guidewires, and some thrombus present.

Type B2: One or more type B characteristics

Type C: Severely complex, diffuse (length > 2 cm), excessive tortuosity of proximal segment, extremely angulated segments > 90°, total occlusions > 3 months old and/or bridging collaterals, inability to protect major side branches, and degenerated vein grafts with friable lesions.

[b] Data reversed for presentation: Original data reported such that HR < 1 indicates lower risk in short group (HR 0.78; 95% CI, 0.46 to 1.32).

[c] Data reversed for presentation: Original data reported such that HR > 1 indicates lower risk in short group (HR 1.07; 95% CI, 0.77 to 1.49).

Other Concurrent Disease: Peripheral Artery Disease

One trial reported outcomes among patients with peripheral artery disease (PRODIGY[38]). Of the patients randomized in the PRODIGY trial, 12.5% had a history of peripheral artery disease.[51]

Outcome data were reported for all-cause death, cardiovascular death, myocardial infarction, stent thrombosis, and MACCE.

All-Cause Death

All-cause death was assessed among patients with or without peripheral artery disease in the PRODIGY trial.[34]

Among participants with peripheral artery disease, the risk of all-cause death was significantly lower among patients who received DAPT for 24 months compared with six months (HR 0.45; 95% CI, 0.23 to 0.88) (Table 62). Among participants without peripheral artery disease, there was no significant difference in the risk of all-cause death between DAPT for 24 months compared with six months (HR 1.39; 95% CI, 0.91 to 2.10) (Table 62).

Table 62: Summary of Evidence Available for All-Cause Death Among Patients With or Without Peripheral Artery Disease

Subgroup, RCT	Stent Type	No. of Patients With an Event/ No. Randomized	Direction of Estimate	Reported Effect Estimate (95% CI)
Peripheral Artery Disease				
PRODIGY	DES, BMS	6 mo: 27/128 24 mo: 12/118	HR < 1 indicates lower risk in extended group	**HR 0.45 (0.23 to 0.88)**
No Peripheral Artery Disease				
PRODIGY	DES, BMS	6 mo: 38/855 24 mo: 53/869	HR > 1 indicates higher risk in extended group	HR 1.39 (0.91 to 2.10)

BMS = bare-metal stent; CI = confidence interval; DES = drug-eluting stent; HR = hazard ratio; mo = months; RCT = randomized controlled trial; RR = relative risk.

Cardiovascular Death

Cardiovascular death was assessed among patients with or without peripheral artery disease in the PRODIGY trial.[34]

Among participants with peripheral artery disease, the risk of cardiovascular death was significantly lower among patients who received DAPT for 24 months compared with six months (HR 0.42; 95% CI, 0.17 to 1.00) (Table 63). Among participants without peripheral artery disease, there was no significant difference in the risk of all-cause death between DAPT for 24 months compared with six months (HR 1.44; 95% CI, 0.81 to 2.55) (Table 63).

Table 63: Summary of Evidence Available for Cardiovascular Death Among Patients With or Without Peripheral Artery Disease

Subgroup, RCT	Stent Type	No. of Patients With an Event/No. Randomized	Direction of Estimate	Reported Effect Estimate (95% CI)
Peripheral Artery Disease				
PRODIGY	DES, BMS	6 mo: 17/128 24 mo: 7/118	HR < 1 indicates lower risk in extended group	**HR 0.42 (0.17 to 1.00)**
No Peripheral Artery Disease				
PRODIGY	DES, BMS	6 mo: 20/855 24 mo: 29/869	HR > 1 indicates higher risk in extended group	HR 1.44 (0.81 to 2.55)

BMS = bare-metal stent; CI = confidence interval; DES = drug-eluting stent; HR = hazard ratio; mo = months; RCT = randomized controlled trial.

Myocardial Infarction

Myocardial infarction was assessed among patients with or without peripheral artery disease in the PRODIGY trial.[34]

Among participants with peripheral artery disease, there was no significant difference in the risk of myocardial infarction between patients who received DAPT for 24 months compared with six months (HR 0.68; 95% CI, 0.26 to 1.74) (Table 64). Among participants without peripheral artery disease, there was no significant difference in the risk of myocardial infarction between DAPT for 24 months compared with six months (HR 1.05; 95% CI, 0.64 to 1.73) (Table 64).

Table 64: Summary of Evidence Available for Myocardial Infarction Among Patients With or Without Peripheral Artery Disease

Subgroup, RCT	Stent Type	No. of Patients With an Event/No. Randomized	Direction of Estimate	Reported Effect Estimate (95% CI)
Peripheral Artery Disease				
PRODIGY	DES, BMS	6 mo: 11/128 24 mo: 7 /118	HR < 1 indicates lower risk in extended group	HR 0.68 (0.26 to 1.74)
No Peripheral Artery Disease				
PRODIGY	DES, BMS	6 mo: 30/855 24 mo: 32/869	HR > 1 indicates higher risk in extended group	HR 1.05 (0.64 to 1.73)

BMS = bare-metal stent; CI = confidence interval; DES = drug-eluting stent; HR = hazard ratio; mo = months; RCT = randomized controlled trial.

Stent Thrombosis

Stent thrombosis was assessed among patients with or without peripheral artery disease in the PRODIGY trial.[34]

Among participants either with or without peripheral artery disease, there was no significant difference in the risk of definite stent thrombosis between patients who received DAPT for 24 months compared with six months (Table 65).

Among participants with or without peripheral artery disease, there was no significant difference in the risk of definite or probable stent thrombosis between DAPT for 24 months compared with six months (Table 65).

Table 65: Summary of Evidence Available for Stent Thrombosis Among Patients With or Without Peripheral Artery Disease

Subgroup, RCT	Stent Type	No. of Patients With an Event/No. Randomized	Direction of Estimate	Reported Effect Estimate (95% CI)
Definite Stent Thrombosis				
Peripheral Artery Disease				
PRODIGY	DES, BMS	6 mo: 3/128 24 mo: 0/118	HR < 1 indicates lower risk in extended group	HR 0.15 (0.01 to 2.87)
No Peripheral Artery Disease				
PRODIGY	DES, BMS	6 mo: 4/855 24 mo: 8/869	HR > 1 indicates higher risk in extended group	HR 1.99 (0.60 to 6.61)
Definite or Probable Stent Thrombosis				
Peripheral Artery Disease				
PRODIGY	DES, BMS	6 mo: 7/128 24 mo: 0/118	HR < 1 indicates lower risk in extended group	HR 0.07 (0.00 to 1.21)
No Peripheral Artery Disease				
PRODIGY	DES, BMS	6 mo: 8/855 24 mo: 13/869	HR > 1 indicates higher risk in extended group	HR 1.62 (0.67 to 3.90)

BMS = bare-metal stent; CI = confidence interval; DES = drug-eluting stent; HR = hazard ratio; mo = months; RCT = randomized controlled trial.

Major Adverse Cardiac and Cerebrovascular Events

MACCE was assessed among patients with or without peripheral artery disease in the PRODIGY trial.[34]

Among participants with peripheral artery disease, there was a significantly lower risk of MACCE among patients who received DAPT for 24 months compared with six months (HR 0.54; 95% CI, 0.31 to 0.95) (Table 66). Among participants without peripheral artery disease, there was no significant difference in the risk of myocardial infarction between DAPT for 24 months compared with six months (HR 1.28; 95% CI, 0.92 to 1.77) (Table 66).

Table 66: Summary of Evidence Available for MACCE Among Patients With or Without Peripheral Artery Disease

Subgroup, RCT	Stent Type	Outcome Definition	No. of Patients With an Event/No. Randomized	Direction of Estimate	Reported Effect Estimate (95% CI)
Peripheral Artery Disease					
PRODIGY	DES, BMS	Death from any cause, MI, cerebrovascular accident	6 mo: 35/128 24 mo: 19/118	HR < 1 indicates lower risk in extended group	**HR 0.54 (0.31 to 0.95)**
No Peripheral Artery Disease					
PRODIGY	DES, BMS	Death from any cause, MI, cerebrovascular accident	6 mo: 63/855 24 mo: 81/869	HR > 1 indicates higher risk in extended group	HR 1.28 (0.92 to 1.77)

BMS = bare-metal stent; CI = confidence interval; DES = drug-eluting stent; HR = hazard ratio; MACCE = major adverse cardiac and cerebrovascular events; MI = myocardial infarction; mo = months; RCT = randomized controlled trials.

History of Heart Failure

None of the included studies reported data for subgroups of patients with a history of heart failure.

Unstable Angina

None of the included studies reported data for subgroups of patients with a history of unstable angina.

Vein Graft Intervention

None of the included studies reported data for subgroups of patients with a history of vein graft intervention.

Left Main Intervention

None of the included RCTs reported data separately for patients who had undergone left main intervention.

Two RCTs reported data for patients with either left main disease (DES-LATE[36]) or left main or proximal left anterior descending coronary artery disease (PRODIGY[38]). Of the patients with left main disease in the DES-LATE trial, 64% underwent left main intervention,[36] while 7% of patients with lumen narrowing of the left main or proximal left coronary artery underwent stenting of the left main artery in the PRODIGY trial.[38] Thus, no data were available to address the question of the optimal duration of DAPT among patients who had undergone left main intervention.

Data Summary: Research Question 3

Does the optimal duration of DAPT with ASA plus a P2Y12 inhibitor (clopidogrel, prasugrel, ticagrelor) depend on the type of stent implanted (BMS or DES)?

Each of the included systematic reviews involved RCTs that enrolled patients with a DES. Two RCTs also involved patients with a BMS (DAPT[34], PRODIGY[38])

To address this research question, data were extracted from systematic reviews that assessed outcomes only among participants with a DES. None of the included systematic

reviews reported outcomes among patients with a BMS. Thus, we sought out data from RCTs included in the systematic reviews to address this research question.

Drug-Eluting Stents

All-Cause Death

Six Months Versus More Than 12 Months

Two systematic reviews assessed all-cause death among patients with a DES.[16,22]

Among patients with any type of DES, Palmerini et al.[22] reported no significant difference in the risk of all-cause death between six months and 24 months of DAPT (HR 1.10; 95% CI, 0.73 to 1.63) (Table 67). Among patients with a second-generation DES, D'Ascenzo et al.[16] reported no significant difference in the odds of all-cause death between six months and 24 months of DAPT (OR 1.11; 95% CI, 0.35 to 3.57) (Table 67).

Table 67: Summary of Evidence Available for All-Cause Death Among Patients With a Drug-Eluting Stent: 6 Months Versus > 12 Months

Systematic Review	Included RCTs	Stent Type	No. of Events/Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CI)	I^2
Palmerini 2015	PRODIGY	DES	6 mo:45/751 24 mo:49/750	HR	HR > 1 indicates higher hazard in extended group	HR 1.10 (0.73 to 1.64)[a]	NA
D'Ascenzo 2016	PRODIGY	Second-generation DES	6 mo: 24/492 24 mo: 29/496	OR, RE	OR > 1 indicates higher odds in extended group	OR 1.11 (0.35 to 3.57)[b]	75%[c]

CI = confidence interval; DES = drug-eluting stent; HR = hazard ratio; mo = months; NA = not applicable; OR = odds ratio; RCT = randomized controlled trial; RE = random effects.

[a] Palmerini 2015 reported HR such that HR < 1 indicates lower risk in the short group (HR 0.91; 95% CI, 0.61 to 1.37); the direction of comparison was reversed for inclusion in this table.

[b] D'Ascenzo 2016 reported OR such that OR < 1 indicates lower odds in short group (OR 0.90; 95% CI, 0.28 to 2.87); the direction of comparison was reversed for inclusion in this table.

[c] Heterogeneity between type of second-generation DES (everolimus-eluting stent versus zotarolimus-eluting stent).

One systematic review[29] compared all durations of DAPT via network meta-analysis involving patients who had undergone PCI with a DES. In their analysis, Xie et al.[29] found no significant difference in the odds of all-cause death between six months of DAPT and 24, 30, or 36 months of DAPT (Table 68).

Table 68: Summary of Evidence Available for All-Cause Death Among Patients With a Drug-Eluting Stent: Network Meta-Analysis, 6 Months Versus > 12 Months

Systematic Review	Included RCTs	Stent Type	No. of Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CrI)
Xie 2016	• PRODIGY[a] DES-LATE • ARCTIC-Interruption • DAPT	DES	17,743[b]	OR, RE	6 mo vs. 24 mo; OR < 1 indicates lower odds in extended group	OR 0.99 (0.45 to 2.63)[c]
					6 mo vs. 30 mo; OR > 1 indicates higher odds in extended group	OR 1.39 (0.56 to 4.55)[d]
					6 mo vs. 36 mo; OR < 1 indicates lower odds in short group	OR 0.67 (0.20 to 1.66)[e]

CrI = credible interval; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; HR = hazard ratio; mo = months; OR = odds ratio; RCT = randomized controlled trial; RE = random effects; vs. = versus.
[a] Patients with a bare-metal stent were excluded from analysis.
[b] The full network including all DAPT durations included 17,743 patients. It is unclear how many patients contributed data to each comparison.
[c] Data reversed for presentation: Original data reported such that OR > 1 indicates higher odds in short group (OR 1.01; 95% CrI, 0.38 to 2.21).
[d] Data reversed for presentation: Original data reported such that OR < 1 indicates lower odds in short group (OR 0.72; 95% CrI, 0.22 to 1.78).
[e] Data reversed for presentation: Original data reported such that OR < 1 indicates lower odds in short group (OR 0.67; 95% CrI, 0.20 to 1.66).

Six to 12 Months Versus More Than 12 Months

One review[33] assessed all-cause death among patients with a DES randomized to six to 12 months or more than 12 months of DAPT. Bittl et al.[33] reported no significant difference in the odds of all-cause death between those who received six to 12 months or more than 12 months of DAPT (OR 1.14; 95% CI, 0.92 to 1.42) (Table 69).

Table 69: Summary of Evidence Available for All-Cause Death Among Patients With a Drug-Eluting Stent: 6 to 12 Months Versus > 12 Months

Systematic Review	Included RCTs	Stent Type	No. of Events/Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CI)	I^2
Bittl 2016	• ARCTIC-Interruption • DAPT • DES-LATE • PRODIGY[a] • ITALIC • OPTIDUAL	DES	6 to 12 mo: 192/10,432 > 12 mo: 223/10,541	OR, FE and RE	OR > 1 indicates increased odds in extended group	OR 1.14 (0.92 to 1.42) (RE) OR 1.16 (0.95 to 1.41) (FE)	10.2%

CI = confidence interval; DES = drug-eluting stent; FE = fixed effects; mo = months; OR = odds ratio; RCT = randomized controlled trials; RE = random effects.
[a] Patients with BMS were excluded from analysis.

Twelve Months Versus More Than 12 Months

Six systematic reviews[13,14,16,17,22,23,30] assessed all-cause death among patients with any DES who received 12 months or more than 12 months of DAPT, while one review assessed death among those with a second-generation DES.[16]

Among patients who received any type of DES, six reviews reported an increased odds or risk of all-cause death among patients receiving DAPT for more than 12 months compared with those who received DAPT for 12 months (Table 70). Among patients with a second-

generation DES, one review[16] reported no statistically significant difference in all-cause death between 12 months and more than 12 months of DAPT (OR 1.67; 95% CI, 0.76 to 3.57) (Table 70).

Table 70: Summary of Evidence Available for All-Cause Death Among Patients With a Drug-Eluting Stent: 12 Months Versus > 12 Months, DES

Systematic Review	Included RCTs	Stent Type	No. of Events/Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CI)	I^2
Fei 2016	• DES-LATE • DAPT[a] • ARCTIC-Interruption • OPTIDUAL	DES	12 mo: 122/8,769 > 12 mo: 176/8,881	OR, RE	OR > 1 indicates higher odds in extended group	**OR 1.43 (1.14 to 1.81)**	65%
Palla 2015	• DES-LATE • ARCTIC-Interruption • DAPT[a]	DES	12 mo: 115/8,079 > 12 mo: 151/8,186	OR, FE	OR > 1 indicates higher odds in extended group	**OR 1.30 (1.02 to 1.66)**	0%
Tsoi 2015	• DES-LATE • ARCTIC-Interruption • DAPT[a]	DES	12 mo: 115/8,079 > 12 mo: 151/8,186	OR, RE	OR > 1 indicates higher odds in extended group	**OR 1.30 (1.02 to 1.66)**	0%
Navarese 2015	• DES-LATE • ARCTIC-Interruption • DAPT[a]	DES	12 mo: 115/8,096 > 12 mo: 151/8,196	OR, FE	OR > 1 indicates higher odds in extended group	**OR 1.30 (1.02 to 1.66)**	0%
Zhang 2015	• DES-LATE • ARCTIC-Interruption • DAPT[a]	DES	12 mo: 115/8,079 > 12 mo: 151/8,186	RR, FE or RE NR	OR > 1 indicates higher odds in extended group	**RR 1.30 (1.02 to 1.65)**	0%
Palmerini 2015	• DES-LATE • ARTIC-Interruption • DAPT[a]	DES	12 mo: NR/NR > 12 mo: NR/NR	HR[b]	HR > 1 indicates higher hazard in the extended group	**HR 1.32 (1.03 to 1.67)[c]**	0%
D'Ascenzo 2016	• DES-LATE	Second-generation DES	12 mo: 11/650 > 12 mo: 19/679	OR, RE	OR > 1 indicates higher odds in extended group	OR 1.67 (0.76 to 3.57)[d]	0%[e]

BMS = bare-metal stent; CI = confidence interval; DES = drug-eluting stent; FE = fixed effects; HR = hazard ratio; mo = months; NR = not reported; OR = odds ratio; RCT = randomized controlled trial; RE = random effects; RR = risk ratio.

[a] Patients with BMS were excluded from analysis.

[b] Fixed effects or random effects not reported. [c] Data reversed for presentation: Original data reported such that HR < 1 indicated lower hazard in short group (HR 0.76; 95% CI, 0.60 to 0.97).

[d] Data reversed for presentation: Original data reported such that OR < 1 indicated lower odds in short group (OR 0.60; 95% CI, 0.28 to 1.29).

[e] Heterogeneity between second-generation stent types (everolimus-eluting stent versus zotarolimus-eluting stent).

Among patients with any type of DES, Xie et al.[29] found no significant difference in the odds of all-cause death between 12 months and 24, 30, or 36 months of DAPT (Table 71).

Table 71: Summary of Evidence Available for All-Cause Death Among Patients With a Drug-Eluting Stent: Network Meta-Analysis, 12 Months Versus > 12 Months

Systematic Review	Included RCTs	Stent Type	No. of Patients	Type of Analysis	Comparison; Direction of Estimate	Effect Estimate (95% CrI)
Xie 2016	• PRODIGY[a] • DES-LATE • ARCTIC-Interruption • DAPT[a]	DES	17,743[b]	OR, RE	12 mo vs. 24 mo; OR < 1 indicates lower odds in extended group	OR 0.78 (0.31 to 2.63)[c]
					12 mo vs. 30 mo; OR > 1 indicates higher odds in extended group	OR 1.20 (0.56 to 3.03)[d]
					12 mo vs. 36 mo; OR > 1 indicates higher odds in extended group	OR 1.30 (0.60 to 3.57)[e]

CrI = credible interval; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; mo = months; OR = odds ratio; RCT = randomized controlled trial; RE = random effects; vs. = versus.

[a] Patients with a bare-metal stent were excluded from analysis.

[b] The full network including all DAPT durations included 17,743 patients. It is unclear how many patients contributed data to each comparison.

[c] Data reversed for presentation: Original data reported such that OR > 1 indicates higher odds in short group (OR 1.28; 95% CrI, 0.38 to 3.21).

[d] Data reversed for presentation: Original data reported such that OR < 1 indicates lower odds in short group (OR 0.83; 95% CrI, 0.33 to 1.77).

[e] Data reversed for presentation: Original data reported such that OR < 1 indicates lower odds in short group (OR 0.77; 95% CrI, 0.28 to 1.67).

> 12 Months Versus More Than 12 Months

Among patients with any type of DES, Xie et al.[29] reported no significant difference in the odds of all-cause death between 24 months and 30 or 36 months of DAPT or between 30 months and 36 months of DAPT (Table 72).

Table 72: Summary of Evidence Available for All-Cause Death Among Patients With a Drug-Eluting Stent: Network Meta-Analysis, > 12 Months

Systematic Review	Included RCTs	Stent Type	No. of Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CrI)
Xie 2016	• PRODIGY • DES-LATE • ARCTIC-Interruption • DAPT[a]	DES	17,743[b]	OR, RE	24 mo vs. 30 mo; OR > 1 indicates higher odds in extended group	OR 1.14 (0.38 to 5.56)[c]
					24 mo vs. 36 mo; OR > 1 indicates higher odds in extended group	OR 1.23 (0.41 to 6.25)[d]
					30 mo vs. 36 mo; OR < 1 indicates lower odds in extended group	OR 0.91 (0.33 to 3.85)[e]

CrI = credible interval; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; mo = months; OR = odds ratio; RCT = randomized controlled trial; RE = random effects; vs. = versus.

[a] Patients with a bare-metal stent were excluded from analysis.

[b] The full network including all DAPT durations included 17,743 patients. It is unclear how many patients contributed data to each comparison.

[c] Data reversed for presentation: Original data reported such that OR < 1 indicates lower odds in short group (OR 0.88; 95% CrI, 0.18 to 2.66).

[d] Data reversed for presentation: Original data reported such that OR < 1 indicates lower odds in short group (OR 0.81; 95% CrI, 0.16 to 2.46).

[e] Data reversed for presentation: Original data reported such that OR > 1 indicates higher odds in short group (OR 1.10; 95% CrI, 0.26 to 3.02).

Cardiovascular Death

Six Months Versus More Than 12 Months

In two systematic reviews, cardiovascular death among patients with a DES who received six months of DAPT was compared with patients receiving more than 12 months of

DAPT.[16,22] Both included only one RCT for this time comparison (PRODIGY[38]), with a duration of six months compared with 24 months. Although some patients in the PRODIGY trial had an implanted BMS, these patients were excluded from the analysis.

Among patients with any type of DES, Palmerini et al.[22] found no significant difference in the risk of cardiovascular death between six months and greater than 12 months of DAPT (HR 1.09; 95% CI, 0.63 to 1.89) (Table 73).

Among patients with a second-generation DES, D'Ascenzo et al.[16] found no significant difference in the odds of cardiovascular death between six months of DAPT and 24 months (OR 0.60; 95% CI, 0.24 to 1.49) (Table 73).

Table 73: Summary of Evidence Available: Cardiovascular Death Among Patients With a Drug-Eluting Stent: 6 Months Versus > 12 Months

Systematic Review	Included RCTs	Stent Type	No. of Events/Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CI)	I^2
Palmerini 2015	• PRODIGY	DES[a]	6 mo: 25/751 24 mo: 27/750	HR[b]	HR > 1 indicates higher hazard in extended group	HR 1.09 (0.63 to 1.89)[c]	NA
D'Ascenzo 2016	• PRODIGY	Second-generation DES	6 mo: 13/247 24 mo: 8/248	OR, RE	OR < 1 indicates lower odds in the extended group	OR 0.60 (0.24 to 1.49)[d]	NA

BMS = bare-metal stents; CI = confidence interval; DES = drug-eluting stent; HR = hazard ratio; mo = months; OR = odds ratio; RCT = randomized controlled trial; RE = random effects.

[a] Patients with BMS were excluded from analysis.

[b] Fixed-effects or random-effects model not reported.

[c] Data reversed for presentation: Original data reported such that HR < 1 indicates lower hazard in the shorter group (HR 0.92; 95% CI, 0.53 to 1.58).

[d] Data reversed for presentation: Original data reported such that OR < 1 indicates lower odds in the short group (OR 1.67; 95% CI, 0.67 to 4.10).

Twelve Versus More Than 12 Months

Seven systematic reviews assessed cardiovascular death among patients with a DES who received 12 months of DAPT compared with those who received more than 12 months of DAPT.[13,14,16,17,22,23,30]

Among patients with any type of DES, each review reported no significant difference in the odds or risk of cardiovascular death between 12 months and more than 12 months of DAPT (Table 74).

Among patients with a second-generation DES, D'Ascenzo et al.[16] reported no significant difference in the odds of cardiovascular death between 12 months and more than 12 months of DAPT (OR 1.61; 95% CI, 0.28 to 9.09) (Table 74).

Table 74: Summary of Evidence Available for Cardiovascular Death Among Patients With a Drug-Eluting Stent: 12 Months Versus > 12 Months

Systematic Review	Included RCTs	Stent Type	No. of Events/Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CI)	I^2
Fei 2016	• OPTIDUAL • DAPT • DES-LATE	DES	12 mo: 80/8,145 > 12 mo: 83/8,246	OR, RE	OR > 1 indicates higher odds in the extended group	OR 1.03 (0.75 to 1.40)	17%
Palla 2015	• DAPT • DES-LATE	DES	12 mo: 74/7,455 > 12 mo: 89/7,551	OR, FE	OR > 1 indicates higher odds in the extended group	OR 1.19 (0.87 to 1.62)	0%
Tsoi 2015	• DAPT • DES-LATE	DES	12 mo: 66/7,455 > 12 mo: 73/7,551	OR, RE	OR > 1 indicates higher odds in the extended group	OR 1.12 (0.73 to 1.71)	33%
Navarese 2015	• DAPT • DES-LATE	DES	12 mo: 71/7,455 > 12 mo: 78/7,551	OR, FE	OR > 1 indicates higher odds in the extended group	OR 1.09 (0.79 to 1.50)	34%
Palmerini 2015	• DAPT • DES-LATE	DES	12 mo: NR/NR > 12 mo: NR/NR	HR[a]	HR > 1 indicates higher hazard in the extended group	HR 1.10 (0.79 to 1.52)[b]	28%
Zhang 2015	• DAPT • DES-LATE	DES	12 mo: 66/7,455 > 12 mo: 73/7,551	RR[a]	RR > 1 indicates higher odds in the extended group	RR 1.09 (0.78 to 1.52)	32.6%
D'Ascenzo 2016	• DES-LATE	DES, second-generation	12 mo: 5/650 > 12 mo: 11/679	OR, RE	OR > 1 indicates higher odds in the extended group	OR 1.61 (0.28 to 9.09)[c]	32%[d]

CI = confidence interval; DES = drug-eluting stent; FE = fixed effects; HR = hazard ratio; mo = months; OR = odds ratio; RCT = randomized controlled trial; RE = random effects; RR = risk ratio.

[a] Fixed-effects or random-effects model not reported.

[b] Data reversed for presentation: Original data reported such that HR < 1 indicates lower hazard in the short group (HR 0.91; 95% CI, 0.66 to 1.26).

[c] Data reversed for presentation: Original data reported such that OR < 1 indicates lower odds in the short group (OR 0.62; 95% CI, 0.11 to 3.57).

[d] Heterogeneity between second-generation stent types (everolimus-eluting stent versus zotarolimus-eluting stent).

Noncardiovascular Death

One systematic review[22] reported the risk of noncardiovascular death among patients with a DES randomized to short DAPT or extended DAPT (Table 75).

Among patients with an implanted DES, there was no significant difference in the risk of noncardiovascular death between those who received DAPT for six months or more than 12 months (Table 75).

In contrast, there was a significant increase in the risk of noncardiovascular death among those who received DAPT for more than 12 months compared with those who received DAPT for 12 months (HR 1.89; 95% CI, 1.27 to 2.78) (Table 75).

Table 75: Summary of Evidence Available for Noncardiovascular Death Among Patients With a Drug-Eluting Stent

Systematic Review	Included RCTs	Stent Type	No. of Events/Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CI)	I^2
6 Months Versus > 1 Year							
Palmerini 2015	• PRODIGY	DES	6 mo: NR/NR > 12 mo: NR/NR	HR[a]	HR > 1 indicates increased risk in extended group	HR 1.11 (0.61 to 2.04)[b]	NA
1 Year Versus > 1 Year							
Palmerini 2015	• DAPT • DES-LATE	DES	12 mo: NR/NR > 12 mo: NR/NR	HR[a]	HR > 1 indicates increased risk in extended group	**HR 1.89 (1.27 to 2.78)[c]**	0%

CI = confidence interval; DES = drug-eluting stent; HR = hazard ratio; mo = months; NR = not reported; RCT = randomized controlled trial.
[a] Fixed-effects or random-effects model not reported.
[b] Data reversed for presentation: Original data reported such that HR < 1 indicates lower odds in the short group (HR 0.90; 95% CI, 0.49 to 1.65).
[c] Data reversed for presentation: Original data reported such that HR < 1 indicates lower hazard in the short group (HR 0.53; 95% CI, 0.36 to, 0.79).

Myocardial Infarction

Six Months Versus More Than 12 Months

Two systematic reviews[16,29] assessed the risk of myocardial infarction among patients with a DES.

Among patients with a second-generation DES, there was no significant difference in the odds of myocardial infarction between six months and 24 months of DAPT (OR 1.23; 95% CI, 0.21 to 7.69) (Table 76).

Table 76: Summary of Evidence Available for Myocardial Infarction Among Patients With a Drug-Eluting Stent: 6 Months Versus > 12 Months

Systematic Review	Included RCTs	Stent Type	No. of Events/Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CI)	I^2
D'Ascenzo 2016	• PRODIGY	Second-generation DES	6 mo: 12/492 24 mo: 16/496	OR, RE	OR > 1 indicates higher odds with extended treatment	OR 1.23 (0.21 to 7.69)[a]	78%[b]

CI = confidence interval; DES = drug-eluting stent; mo = months; OR = odds ratio; RCT = randomized controlled trial; RE = random effects.
[a] Data reversed for presentation: Original data reported such that OR < 1 indicates lower odds with short treatment (OR 0.81; 95% CI, 0.13 to 4.87).
[b] Heterogeneity between type of second-generation stent (everolimus-eluting stent versus zotarolimus-eluting stent).

Among patients with any generation of DES, Xie et al.[29] found no significant difference in the odds of myocardial infarction between six months of DAPT and 24, 30, or 36 months of DAPT (Table 77).

Table 77: Summary of Evidence Available for Myocardial Infarction Among Patients With a Drug-Eluting Stent: Network Meta-Analysis

Systematic Review	Included RCTs	Stent Type	No. of Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CrI)
Xie 2016	• PRODIGY[a] DES-LATE ARCTIC-Interruption • DAPT	DES	17,743[b]	OR, RE	6 mo vs. 36 mo; OR < 1 indicates lower odds in extended group	OR 0.46 (0.17 to 1.75)[c]
					6 mo vs. 24 mo; OR < 1 indicates lower odds in extended group	OR 0.84 (0.35 to 2.5)[d]
					6 mo vs. 30 mo; OR < 1 indicates lower odds in extended group	OR 2.97 (0.91 to 7.48)[e]

CrI = credible interval; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; mo = months; OR = odds ratio; RCT = randomized controlled trial; RE = random effects; vs. = versus.

[a] Patients with a bare-metal stent were excluded from analysis.

[b] The full network including all DAPT durations included 17,743 patients. It is unclear how many patients contributed data to each comparison.

[c] Data reversed for presentation: Original data reported such that OR > 1 indicates higher odds in short group (OR 2.17; 95% CrI, 0.57 to 6.02).

[d] Data reversed for presentation: Original data reported such that OR > 1 indicates higher odds in short group (OR 1.19; 95% CrI, 0.40 to 2.83).

[e] Data reversed for presentation: Original data reported such that OR > 1 indicates higher odds in short group (OR 2.97; 95% CrI, 0.91 to 7.48).

Six to 12 Months Versus More Than 12 Months

One systematic review assessed myocardial infarction among patients who received DAPT for six to 12 months compared with more than 12 months.

Bittl et al.[33] reported that the odds of myocardial infarction were significantly lower among patients with a DES who received DAPT for at least 12 months compared with patients who received DAPT for six to 12 months (OR 0.67; 95% CI, 0.47 to 0.65) (Table 78).

Table 78: Summary of Evidence Available for Myocardial Infarction Among Patients With a Drug-Eluting Stent: 6 to 12 Months Versus > 12 Months

Systematic Review	Included RCTs	Stent Type	No. of Events/Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CI)	I^2
Bittl 2016	• DES-LATE • PRODIGY[a] • ARCTIC-Interruption • ITALIC • DAPT[a]	DES	6 to 12 mo: 266/10,432 > 12 mo: 156/10,541	OR, FE and RE	OR < 1 indicates lower odds in extended group	**OR 0.67 (0.47 to 0.65) (RE)** **OR 0.57 (0.47 to 0.70) (FE)**	42.8%

BMS = bare-metal stent; CI = confidence interval; DES = drug-eluting stent; FE = fixed effects; mo = months; OR = odds ratio; RCT = randomized controlled trial; RE = random effects.

[a] Patients with BMS were excluded from this analysis.

Twelve Months Versus More Than 12 Months

Six systematic reviews[13,14,16,17,23,30] assessed myocardial infarction among patients with a DES who received DAPT for 12 months compared with more than 12 months. Five included patients with any type of DES,[13,14,17,23,30] while one included only participants with a second-generation DES.[16]

Among patients with any type of DES, all of the included reviews reported that the odds of myocardial infarction were significantly lower among patients who received DAPT for more than 12 months compared with patients who received DAPT for 12 months (Table 79). The findings were consistent among patients with a second-generation DES: The odds or risk of myocardial infarction were significantly lower among patients who received more than 12 months of DAPT compared with those who received 12 months of DAPT (OR 0.62; 95% CI, 0.45 to 0.86) (Table 79).

Table 79: Summary of Evidence Available for Myocardial Infarction Among Patients With a Drug-Eluting Stent: 12 Months Versus > 12 Months

Systematic Review	Included RCTs	Stent Type	No. of Events/Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CI)	I^2
Fei 2016	• DES-LATE • OPTIDUAL • DAPT • ARCTIC-Interruption	DES	12 mo: 250/8,769 > 12 mo: 138/8,881	OR, RE	OR < 1 indicates lower odds in extended group	**OR 0.54 (0.43 to 0.66)**	13%
Palla 2015	• DES-LATE • ARCTIC-Interruption • DAPT	DES	12 mo: 251/8,079 > 12 mo: 167/8,186	OR, FE	OR < 1 indicates lower odds in extended group	**OR 0.65 (0.53 to 0.79)**	10%
Tsoi 2015	• DES-LATE • ARCTIC-Interruption • DAPT	DES	12 mo: 234/8,079 > 12 mo: 127/8,186	OR, RE	OR < 1 indicates lower odds in extended group	**OR 0.58 (0.40 to 0.84)**	35%
Navarese 2015	• DES-LATE • ARCTIC-Interruption • DAPT	DES	12 mo: 234/8,096 > 12 mo: 127/8,196	OR, FE	OR < 1 indicates lower odds in extended group	**OR 0.53 (0.42 to 0.66)**	37%
Zhang 2015	• DES-LATE • ARCTIC-Interruption • DAPT	DES	12 mo: 234/8,079 > 12 mo: 127/8,186	RR[a]	RR < 1 indicates lower odds in extended group	**RR 0.53 (0.43 to 0.66)**	32.5%
D'Ascenzo 2016	• DAPT • DES-LATE	Second-generation DES	12 mo: 97/3,630 > 12 mo: 61/3,666	OR, RE	OR < 1 indicates lower odds in extended group	**OR 0.62 (0.45 to 0.86)**[b]	0%

CI = confidence interval; DES = drug-eluting stent; FE = fixed effects; MI = myocardial infarction; mo = months; OR = odds ratio; RCT = randomized controlled trial; RE = random effects; RR = risk ratio.

[a] Fixed-effects or random-effects model not reported.

[b] Data reversed for presentation: Original data reported such that OR < 1 indicates that odds of MI is lower with short treatment (OR 1.61, 95% CI, 1.16 to 2.22).

Via network meta-analysis, Xie et al.[29] found no significant differences in the odds of myocardial infarction between 24 months and 30 or 36 months or between 30 months and 36 months among patients with any type of DES (Table 80).

Table 80: Summary of Evidence Available for Myocardial Infarction Among Patients With a Drug-Eluting Stent: Network Meta-Analysis, > 12 Months

Systematic Review	Included RCTs	No. of Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CrI)
Xie 2016	• PRODIGY[a] • DES-LATE • ARCTIC-Interruption • DAPT[a]	17,743[b]	OR, RE	24 mo vs. 30 mo; OR < 1 indicates lower odds in extended group	OR 0.31 (0.09 to 1.69)[c]
				24 mo vs. 36 mo; OR < 1 indicates lower odds in extended group	OR 0.42 (0.12 to 2.63)[d]
				30 mo vs. 36 mo OR > 1 indicates higher odds in extended group	OR 1.14 (0.37 to 5.26)[e]

CrI = credible interval; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; mo = months; OR = odds ratio; RCT = randomized controlled trial; RE = random effects; vs. = versus.

[a] Patients with a bare-metal stent were excluded from analysis.

[b] The full network including all DAPT durations included 17,743 patients. It is unclear how many patients contributed data to each comparison.

[c] Data reversed for presentation: Original data reported such that OR > 1 indicates higher odds in short group (OR 3.26; 95% CrI, 0.59 to 10.55).

[d] Data reversed for presentation: Original data reported such that OR > 1 indicates higher odds in short group (OR 2.37; 95% CrI, 0.38 to 8.22).

[e] Data reversed for presentation: Original data reported such that OR < 1 indicates lower odds in short group (OR 0.88; 95% CrI, 0.19 to 2.67).

Stroke

Six Months Versus More Than 12 Months

None of the included systematic reviews assessed stroke among patients with a DES who received DAPT for six months compared with more than 12 months.

Six to 12 Months Versus More Than 12 Months

None of the included systematic reviews assessed stroke among patients with a DES who received DAPT for six to 12 months compared with more than 12 months.

Twelve Months Versus More Than 12 Months

Four systematic reviews[13,14,17,30] assessed stroke among patients with a DES who received DAPT for 12 months compared with more than 12 months.

Among patients with any type of DES, each review reported no statistically significant difference in the odds or risk of stroke between patients who received DAPT for 12 months and those who received DAPT for more than 12 months (Table 81).

Table 81: Summary of Evidence Available for Stroke Among Patients With a Drug-Eluting Stent: 12 Months Versus > 12 Months

Systematic Review	Included RCTs	Stent Type	No. of Events/Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CI)	I^2
Fei 2016	• DES-LATE • OPTIDUAL • DAPT • ARCTIC-Interruption	DES	12 mo: 75/8,769 > 12 mo: 71/8,881	OR, RE	OR < 1 indicates lower odds with extended treatment	OR 0.93 (0.67 to 1.29)	0%
Palla 2015	• DAPT • ARCTIC-	DES	12 mo: 75/8,079 > 12 mo: 73/8,186	OR, FE	OR < 1 indicates lower odds with	OR 0.96 (0.69 to 1.33)	0%

Table 81: Summary of Evidence Available for Stroke Among Patients With a Drug-Eluting Stent: 12 Months Versus > 12 Months

Systematic Review	Included RCTs	Stent Type	No. of Events/Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CI)	I^2
	Interruption • DES-LATE				extended treatment		
Tsoi 2015	• ARCTIC-Interruption • DAPT • DES-LATE	DES	12 mo: 68/8,079 > 12 mo: 64/8,186	OR, RE	OR < 1 indicates lower odds with extended treatment	OR 0.93 (0.66 to 1.31)	0%
Zhang 2015	• DAPT • DES-LATE • ARCTIC-Interruption	DES	12 mo: 68/8,079 > 12 mo: 64/8,186	RR[a]	RR < 1 indicates lower risk with extended treatment	RR 0.93 (0.66 to 1.31)	0%

CI = confidence interval; DES = drug-eluting stent; FE = fixed effects; mo = months; OR = odds ratio; RCT = randomized controlled trial; RE = random effects; RR = risk ratio.
[a] Fixed-effects or random-effects model not reported.

Stent Thrombosis

Six Months Versus More Than 12 Months

One systematic review[16] assessed stent thrombosis among patients with a DES who received DAPT for six months compared with more than 12 months. Definite and probable stent thrombosis events were combined in this analysis.

Among patients with a second-generation DES, D'Ascenzo et al.[16] reported no significant difference in the odds of stent thrombosis between six months of DAPT and more than 12 months of DAPT (OR 2.50; 95% CI, 0.33 to 20.00) (Table 82).

Table 82: Summary of Evidence Available for Stent Thrombosis Among Patients With a Drug-Eluting Stent: 6 Months Versus > 12 Months

Systematic Review	Included RCTs	Stent Type	No. of Events/Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CI)	I^2
D'Ascenzo 2016	• PRODIGY	DES, second-generation	6 mo: 1/492 24 mo: 4/496	OR, RE	OR > 1 indicates higher odds in the extended group	OR 2.50 (0.33 to 20.00)[a]	0%[b]

CI = confidence interval; DES = drug-eluting stent; mo = months; OR = odds ratio; RCT = randomized controlled trial; RE = random effects.
[a] Data reversed for presentation: Original data reported such that OR < 1 indicates lower odds in the short group (OR 0.40; 95% CI, 0.05 to 3.07).
[b] Heterogeneity between type of second-generation stent (everolimus-eluting stent versus zotarolimus-eluting stent).

Among patients with any type of DES, Xie et al.[29] reported no statistically significant difference in the odds of stent thrombosis between six months and 24 months or 30 months. However, the authors reported that 30 months of DAPT was associated with statistically lower odds of stent thrombosis compared with six months of DAPT in this population (OR 0.09; 95% CI, 0.11 to 0.62) (Table 83).

Table 83: Summary of Evidence Available for Stent Thrombosis Among Patients With a Drug-Eluting Stent: Network Meta-Analysis, 6 Months Versus > 12 Months

Systematic Review	Included RCTs	Stent Type	No. of Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CrI)
Xie 2016	• PRODIGY[a] • DES-LATE • ARCTIC-Interruption • DAPT[a]	DES	17,743[b]	OR, RE	6 mo vs. 24 mo; OR < 1 indicates lower odds in extended group	OR 0.60 (0.19 to 3.33)[c]
					6 mo vs. 30 mo; OR < 1 indicates lower odds in extended group	**OR 0.09** **(0.11 to 0.62)**[d]
					6 mo vs. 36 mo; OR < 1 indicates lower odds in extended group	OR 0.18 (0.04 to 1.56)[e]

CrI = credible interval; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; mo = months; OR = odds ratio; RCT = randomized controlled trial; RE = random effects; vs. = versus.

[a] Patients with a bare-metal stent were excluded from analysis.
[b] The full network including all DAPT durations included 17,743 patients. It is unclear how many patients contributed data to each comparison.
[c] Data reversed for presentation: Original data reported such that OR > 1 indicates higher odds in short group (OR 1.66; 95% CrI, 0.30 to 5.36).
[d] Data reversed for presentation: Original data reported such that OR > 1 indicates higher odds in short group (OR 10.56; 95% CrI 1.62, to 9.17).
[e] Data reversed for presentation: Original data reported such that OR > 1 indicates higher odds in short group (OR 5.63; 95% CrI, 0.64 to 23.2).

Six to 12 Months Versus More Than 12 Months

One systematic review[33] assessed stent thrombosis among patients who received DAPT for six to 12 months compared with more than 12 months.

Among patients with any type of DES, Bittl et al.[33] reported that the odds of stent thrombosis were significantly lower among patients who received DAPT for more than 12 months compared with patients who received DAPT for six to 12 months (OR 0.42; 95% CI, 0.24 to 0.74) (Table 84).

Table 84: Summary of Evidence Available for Stent Thrombosis Among Patients With a Drug-Eluting Stent: 6 to 12 Months Versus > 12 Months

Systematic Review	Included RCTs	Stent Type	No. of Events/Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CI)	I^2
Bittl 2016	• DES-LATE • PRODIGY[a] • ARCTIC • ITALIC • DAPT[a]	DES[b]	6 to 12 mo: 92/9,742 > 12 mo: 34/9,846	OR, FE and RE	OR < 1 indicates lower odds in the extended group	**OR 0.42** **(0.24 to 0.74)** **(RE)** **OR 0.37** **(0.25 to 0.55)** **(FE)**	28.9%

CI = confidence interval; DES = drug-eluting stent; FE = fixed effects; mo = months; OR = odds ratio; RE = random effects.
[a] Patients with a bare-metal stent were excluded from this analysis
[b] Data reversed for presentation: Original data reported such that OR > 1 indicates higher odds in short group (OR 2.47; 95% CI, 1.72 to 3.55).

Twelve Months Versus More Than 12 Months

Six systematic reviews assessed stent thrombosis among patients with a DES who received DAPT for 12 months compared with more than 12 months.[13,14,16,17,23,30] Each review assessed definite/probable stent thrombosis; as well, Navarese et al.[23] assessed definite

stent thrombosis and very late stent thrombosis (i.e., stent thrombosis occurring more than one year after PCI) (Table 85).

Table 85: Summary of Evidence Available for Stent Thrombosis Among Patients With a Drug-Eluting Stent: 12 Months Versus > 12 Months

Systematic Review	Included RCTs	Stent Type	No. of Events/Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CI)	I^2
Definite or Probable Stent Thrombosis							
Fei 2016	• DES-LATE • OPTIDUAL • DAPT • ARCTIC-Interruption	DES	12 mo: 80/8,769 > 12 mo: 29/ 8,881	OR, RE	OR < 1 indicates lower odds in extended group	**OR 0.36 (0.24 to 0.55)**	49%
Palla 2015	• DES-LATE • ARCTIC-Interruption • DAPT	DES	12 mo: 83/8,079 > 12 mo: 38/8,186	OR, FE	OR < 1 indicates lower odds in extended group	**OR 0.45 (0.31 to 0.66)**	4%
Tsoi 2015	• DES-LATE • ARCTIC-Interruption • DAPT	DES	12 mo: 79/8,079 > 12 mo: 26/8,186	OR, RE	OR < 1 indicates lower odds in extended group	**OR 0.35 (0.20 to 0.62)**	18%
Navarese 2015	• DES-LATE • ARCTIC-Interruption • DAPT	DES	12 mo: 79/8,096 > 12 mo: 26/8,196	OR, FE	OR < 1 indicates lower odds in extended group	**OR 0.33 (0.21 to 0.51)**	18%
Zhang 2015	• DES-LATE • ARCTIC-Interruption • DAPT	DES	12 mo: 79/8,096 > 12 mo: 26/8,196	RR[a]	RR < 1 indicates lower risk in extended group	**RR 0.33 (0.21 to 0.51)**	17.2%
D'Ascenzo 2016	• DAPT • DES-LATE	Second-generation DES	12 mo: 29/3,630 > 12 mo: 16/3,666	OR, RE	OR < 1 indicates lower odds in extended group	OR 0.54 (0.87 to 1.02)[b]	0%
Definite Stent Thrombosis							
Navarese 2015	• DES-LATE • ARCTIC-Interruption • DAPT	DES	12 mo:72/8,096 > 12 mo: 22/8,196	OR, FE	OR < 1 indicates lower odds in extended group	**OR 0.30 (0.19 to 0.49)**	32%
Very Late[c] Stent Thrombosis							
Navarese 2015	• DES-LATE • ARCTIC-Interruption • DAPT	DES	12 mo: 29/8,096 > 12 mo: 26/8,196	OR, FE	OR < 1 indicates lower odds in extended group	**OR 0.33 (0.21 to 0.51)**	18%

CI = confidence interval; DES = drug-eluting stent; FE = fixed effects; mo = months; OR = odds ratio; RCT = randomized controlled trial; RE = random effects; RR = risk ratio.

[a] Fixed-effects or random-effects model not reported.

[b] Data reversed for presentation: Original data reported such that OR > 1 indicates higher odds in short group (OR 1.84; 95% CI, 0.98 to 3.46).

[c] Stent thrombosis occurring more than one year after percutaneous coronary intervention.

Five reviews[13,14,17,23,30] that included any type of DES reported that the odds or risk of probable or definite stent thrombosis were significantly lower among patients who received

DAPT for more than 12 months compared with patients who received DAPT for 12 months (Table 85).

One review that included only second-generation DES (everolimus-eluting stent or zotarolimus-eluting stent) reported no statistically significant difference in probable or definite stent thrombosis between 12 months of DAPT and more than 12 months of DAPT (OR 0.54; 95% CI, 0.87 to 1.02) (Table 85).

One review[23] reported that more than 12 months of DAPT was associated with significantly lower odds of definite stent thrombosis compared with 12 months of DAPT in patients with any type of DES (OR 0.30; 95% CI, 0.19 to 0.49) (Table 85). Navarese et al.[23] also reported significantly lower odds of very late stent thrombosis among patients who received more than 12 months of DAPT in this population (OR 0.33; 95% CI, 0.21 to 0.51).

Among patients with a DES, Xie et al.[29] reported no statistically significant difference in the odds of stent thrombosis between 12 months and 24 or 36 months of DAPT (Table 86). The authors reported that 30 months of DAPT was associated with statistically lower odds of stent thrombosis compared with 12 months of DAPT in this population (OR 0.25; 95% CI, 0.09 to 0.99) (Table 86).

Table 86: Summary of Evidence Available for Stent Thrombosis Among Patients With a Drug-Eluting Stent: Network Meta-Analysis, 12 Months Versus > 12 Months

Systematic Review	Included RCTs	Stent Type	No. of Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CrI)
Xie 2016	• PRODIGY[a] • DES-LATE • ARCTIC-Interruption • DAPT	DES	17,743[b]	OR, RE	12 mo vs. 24 mo; OR > 1 indicates higher odds in extended group	OR 1.16 (0.31 to11.11)[c]
					12 mo vs. 30 mo; OR < 1 indicates lower odds in extended group	**OR 0.25 (0.09 to 0.99)**[d]
					12 mo vs. 36 mo; OR < 1 indicates lower odds in extended group	OR 0.46 (0.14 to 2.56)[e]

CrI = credible interval; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; mo = months; OR = odds ratio; RCT = randomized controlled trial; RE = random effects; vs. = versus.

[a] Patients with a bare-metal stent were excluded from analysis.

[b] The full network including all DAPT durations included 17,743 patients. It is unclear how many patients contributed data to the each comparison.

[c] Data reversed for presentation: Original data reported such that OR < 1 indicates lower odds in short group (OR 0.86; 95% CrI, 0.09 to 3.27).

[d] Data reversed for presentation: Original data reported such that OR > 1 indicates higher odds in short group (OR 4.05; 95% CrI, 1.01 to 11.46).

[e] Data reversed for presentation: Original data reported such that OR > 1 indicates higher odds in short group (OR 2.16; 95% CrI, 0.39 to 7.29).

Longer Than 12 Months

Among patients with any type of DES, Xie et al.[29] found no statistically significant difference in the odds of stent thrombosis between any durations longer than 12 months (Table 87).

Table 87: Summary of Evidence Available for Stent Thrombosis Among Patients With a Drug-Eluting Stent: Network Meta-Analysis, > 12 Months

Systematic Review	Included RCTs	Stent Type	No. of Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CrI)
Xie 2016	• PRODIGY[a] • DES-LATE • ARCTIC-Interruption • DAPT	DES	17,743[b]	OR, RE	24 mo vs. 30 mo; OR < 1 indicates lower odds in extended group	OR 0.09 (0.33 to 1.37)[c]
					24 mo vs. 36 mo; OR < 1 indicates lower odds in extended group	OR 0.17 (0.03 to 3.33)[d]
					30 mo vs. 36 mo; OR > 1 indicates higher odds in extended group	OR 1.28 (0.31 to14.29)[e]

CrI = credible interval; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; mo = months; OR = odds ratio; RCT = randomized controlled trial; RE = random effects; vs. = versus.

[a] Patients with a bare-metal stent were excluded from analysis.

[b] The full network including all DAPT durations included 17,743 patients. It is unclear how many patients contributed data to the each comparison.

[c] Data reversed for presentation: Original data reported such that OR > 1 indicates higher odds in short group (OR 11.18; 95% CrI, 0.73 to 3.02).

[d] Data reversed for presentation: Original data reported such that OR > 1 indicates higher odds in short group (OR 5.92; 95% CrI, 0.30 to 29.37).

[e] Data reversed for presentation: Original data reported such that OR < 1 indicates lower odds in short group (OR 0.78; 95% CrI, 0.07 to 3.26).

Urgent Target Revascularization

None of the included systematic reviews assessed urgent revascularization. This outcome was reported in two of the included RCTs (ITALIC,[37] ARCTIC-Interruption[35]); findings are summarized in Table 88. There were no significant differences in risk between short DAPT and extended DAPT in either trial.

Table 88: Summary of Evidence Available for Urgent Target Revascularization

RCT	Stent Type	No. of Events/Patients	Direction of Estimate	Reported HR (95% CI)
ARCTIC-Interruption	DES	12 mo: 9/641 18-30 mo: 8/645	HR > 1 indicates higher risk in extended group	HR 1.17 (0.45 to 3.04)
ITALIC	DES	6mo:5/926 24 mo:2/924	HR < 1 indicates lower risk in extended group	HR 0.4 (0.08 to 2.04)[a]

CI = confidence interval; DES = drug-eluting stent; HR = hazard ratio; mo = months; RCT = randomized controlled trial.

[a] Data reversed for presentation: Original data reported such that HR > 1 indicates higher risk in short group (HR 2.50; 95% CI, 0.49 to12.88).

Major Adverse Cardiovascular Events

Two systematic reviews assessed major adverse cardiovascular events associated with different durations of DAPT among patients with a DES.[23,33] One review each compared six to 12 months of DAPT with more than 12 months[33] of DAPT and 12 months of DAPT with more than 12 months of DAPT.[23] Bittl et al.[33] described this outcome as a comparison of the primary outcomes of each RCT (Table 89).

Despite differences in the outcome definition, both Bittl et al.[33] and Navarese et al.[23] reported significantly lower odds of an event among patients with a DES who received more than 12 months of DAPT (Table 89).

Table 89: Summary of Evidence Available for MACCE Among Patients With a Drug-Eluting Stent

Systematic Review	Included RCTs	Stent Type	No. of Events/Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CI)	I^2
6 to 12 Months Versus > 12 Months							
Bittl 2016	• DES-LATE • PRODIGY • ARCTIC • ITALIC • DAPT • OPTIDUAL	DES	6 to 12 mo: 534/10,664 > 12 mo: 450/10,778	OR, FE and RE	OR < 1 indicates lower odds in the extended group	**OR 0.82 (0.72 to 0.94) (FE)** **OR 0.85 (0.72 to 1.00) (RE)**	23%
12 Months Versus > 12 Months							
Navarese 2015	• DES-LATE • ARCTIC-Interruption • DAPT	DES	12 mo: 369/8,096 > 12 mo: 296/8,196	OR, FE	OR < 1 indicates lower odds in the extended group	**OR 0.78 (0.67 to 0.92)**	47%

CI = confidence interval; DES = drug-eluting stent; FE = fixed effects; MACCE = major adverse cardiac and cerebrovascular events; mo = months; OR = odds ratio; RCT = randomized controlled trial; RE = random effects.

Major Bleeding

Two systematic reviews assessed major bleeding among patients with a DES.[16,23]

Among patients with any type of DES, Navarese et al.[23] reported no statistically significant increase in the odds of TIMI major bleeding with extended DAPT (OR 1.60; 95% CI, 0.97 to 2.64) (Table 90). Among patients with a second-generation DES, D'Ascenzo et al.[16] found an increased odds of BARC type 3 or 5 bleeding associated with DAPT for 24 months compared with DAPT of six months (OR 1.82; 95% CI, 1.02 to 3.23) (Table 90).

Table 90: Summary of Evidence Available for Major Bleeding Among Patients With a Drug-Eluting Stent

Systematic Review	Included RCTs	Stent Type	No. of Events/Patients	Type of Analysis	Direction of Estimate	Effect Estimate (95% CI)	I^2
6 Months Versus > 12 Months							
BARC type 3 or 5							
D'Ascenzo 2016	• PRODIGY	Second-generation DES	6 mo: 19/986 24 mo: 34/987	OR, RE	OR > 1 indicates higher odds in extended group	**OR 1.82 (1.02 to 3.23)[a]**	NA
12 Months Versus > 12 Months							
TIMI major bleeding							
Navarese 2015	• DES-LATE • ARCTIC-Interruption	DES	12 mo: 25/3,155 > 12 mo: 40/3,176	OR, RE	OR > 1 indicates higher odds in extended group	OR 1.60 (0.97 to 2.64)	42%

BARC = Bleeding Academic Research Consortium; CI = confidence interval; DES = drug-eluting stent; mo = months; NA = not applicable; OR = odds ratio; RCT = randomized controlled trial; RE = random effects; TIMI = thrombolysis in myocardial infarction.

[a] Data reversed for presentation: Original data reported such that OR < 1 indicates lower odds in short DAPT group (OR 0.55; 95% CI, 0.31 to 0.98).

Minor Bleeding

None of the included systematic reviews assessed minor bleeding in patients with a drug-eluting stent.

Gastrointestinal Bleeding

None of the included systematic reviews assessed gastrointestinal bleeding among patients with a DES.

Bare-Metal Stents

None of the included systematic reviews reported outcomes among participants with a BMS. As such, data were extracted from the two RCTs that involved participants with a BMS as well as patients with a DES (DAPT,[34] PRODIGY[38]). Both RCTs supplied subgroup analyses for patients only with a BMS; however, not all outcomes were reported.

All-Cause Death

Two RCTs (DAPT,[34] PRODIGY[38]) reported all-cause death among participants with a BMS (Table 91).

Mauri et al.[34] reported that there was no significant difference in the risk of all-cause death between 12 months and 30 months of DAPT (HR 0.90; 95% CI, 0.35 to 2.33) (Table 91). The risk of all-cause death was also not significantly different between six months and 24 months of DAPT in the PRODIGY trial.[38]

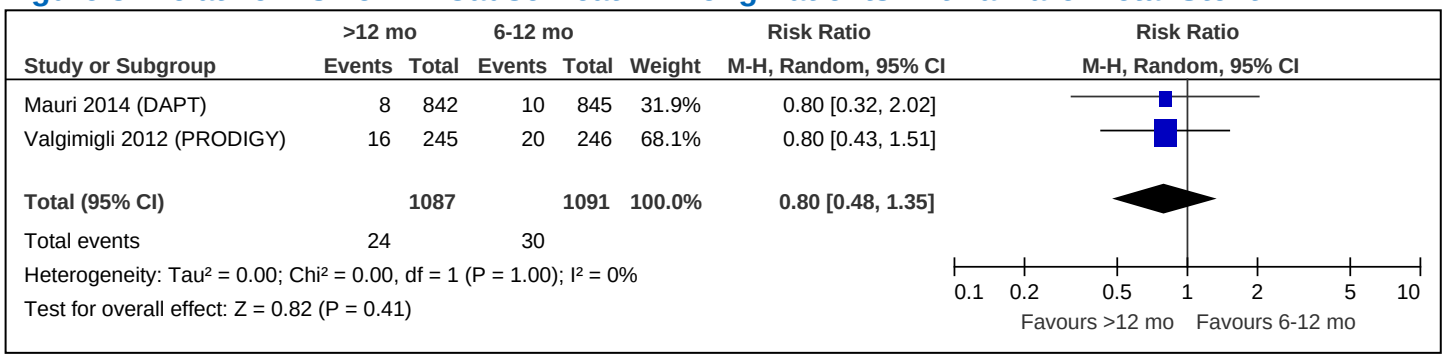
Table 91: Summary of Evidence Available: All-Cause Death Among Patients With a Bare-Metal Stent

RCT	Stent Type	No. of Events/ No. Randomized	Direction of Estimate	Reported Effect Estimate (95% CI)[a]
DAPT	BMS	12 mo: 10/845 30 mo: 8/842	HR < 1 indicates a lower risk in extended group	HR 0.90 (0.35 to 2.33)
PRODIGY	BMS	6 mo: 20/246 24 mo: 16/245	RR < 1 indicates a lower risk in extended group	Calculated RR 0.80 (0.43 to 1.51)[b]

BMS = bare-metal stent; CI = confidence interval; mo = months; OR = odds ratio; RCT = randomized controlled trial; RE = random effects; RR = risk ratio.
[a] Reported in the RCT, unless otherwise stated.
[b] Calculated via random-effects meta-analysis.

The pooled data from the DAPT[34] and PRODIGY[38] trials supports no significant difference in the risk of all-cause death between extended DAPT and six to 12 months of DAPT among patients with a BMS (RR 0.80; 95% CI, 0.48 to 1.35) (Figure 3).

Figure 3: Relative Risk of All-Cause Death Among Patients With a Bare-Metal Stent



CI = confidence interval; mo = months.

Cardiovascular Death

One RCT (PRODIGY[38]) reported cardiovascular death among participants with a BMS.

Calculated based on reported event counts, the risk of cardiovascular death was not significantly different between six months and 24 months of DAPT in the PRODIGY trial (Table 92).[38]

Table 92: Summary of Evidence Available: Cardiovascular Death Among Patients With a Bare-Metal Stent

RCT	Stent Type	No. of Events/ No. Randomized	Direction of Estimate	Calculated Effect Estimate (95% CI)
PRODIGY	BMS	6 mo: 12/246 24 mo: 9/245	RR < 1 indicates a lower risk in extended group	Calculated RR 0.75 (0.32 to 1.75)[a]

BMS = bare-metal stent; CI = confidence interval; mo = months; RCT = randomized controlled trial; RR = risk ratio.
[a] Calculated via random-effects meta-analysis.

Myocardial Infarction

Two RCTs (DAPT,[34] PRODIGY[38]) reported myocardial infarction among participants with a BMS.

Mauri et al.[34] reported no significant differences in the risk of myocardial infarction between 12 months and 30 months of DAPT (HR 0.91; 95% CI, 0.51 to 1.62) (Table 93). The risk of myocardial infarction was also not significantly different between six months of DAPT and 24 months of DAPT in the PRODIGY trial (RR 1.00; 95% CI, 0.50 to 2.01) (Table 93).[38]

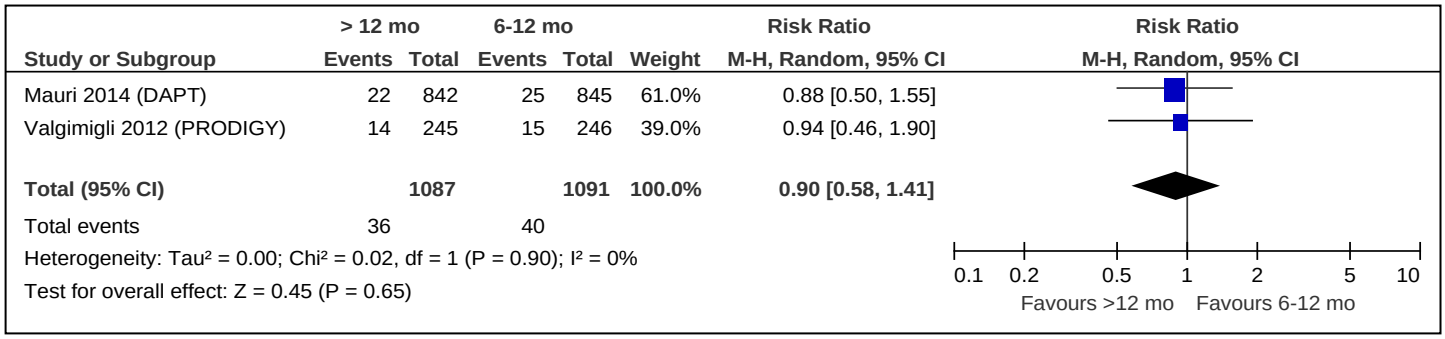
Table 93: Summary of Evidence Available for Myocardial Infarction Among Patients With a Bare-Metal Stent

RCT	Stent Type	No. of Events/ No. Randomized	Direction of Estimate	Reported Effect Estimate (95% CI)
DAPT	BMS	12 mo: 25/845 30 mo: 22/842	HR < 1 indicates a lower risk in extended group	HR 0.91 (0.51 to 1.62)
PRODIGY	BMS	6 mo: 15/246 24 mo: 14/245	RR < 1 indicates a lower risk in extended group	Calculated RR 1.00 (0.50 to 2.01)[a]

BMS = bare-metal stent; CI = confidence interval; HR = hazard ratio; mo = months; RR = risk ratio.
[a] Calculated via random-effects meta-analysis.

The pooled data from the DAPT[34] and PRODIGY[38] trials supports no significant difference in the risk of myocardial infarction between extended DAPT and six to 12 months of DAPT among patients with a BMS (RR 0.90; 95% CI, 0.58 to 1.41) (Figure 4).

Figure 4: Relative Risk of Myocardial Infarction Among Patients With a Bare-Metal Stent



CI = confidence interval; mo = months.

Stroke

Two RCTs (DAPT,[34] PRODIGY[38]) reported stroke among study participants with a BMS.

Mauri et al.[34] reported that there was no significant difference in the risk of stroke between 12 months and 30 months of DAPT (HR 1.22; 95% CI, 0.37 to 4.01) (Table 94). Calculated based on reported event counts, the risk of stroke was also not significantly different between six months and 24 months of DAPT in the PRODIGY trial (RR 1.41; 95% CI, 0.45 to 4.37) (Table 94).[38]

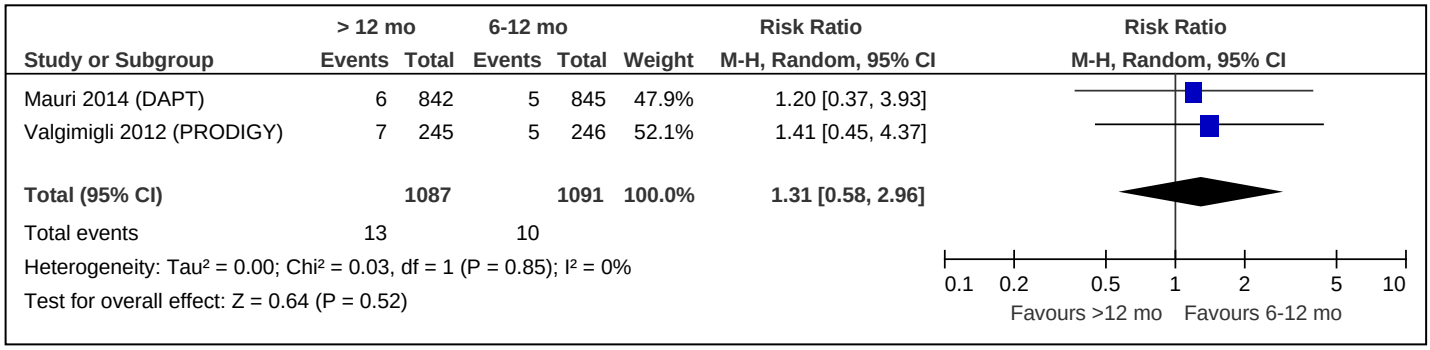
Table 94: Summary of Evidence Available for Stroke Among Patients With a Bare-Metal Stent

Systematic Review	Stent Type	No. of Events/ No. Randomized	Direction of Estimate	Reported Effect Estimate (95% CI)
DAPT	BMS	12 mo: 5/845 30 mo: 6/842	HR > 1 indicates a higher risk in the extended group	HR 1.22 (0.37 to 4.01)
PRODIGY	BMS	6 mo: 5/246 24 mo: 7/245	RR > 1 indicates a higher risk in extended group	Calculated RR 1.41 (0.45 to 4.37)[a]

BMS = bare-metal stent; CI = confidence interval; HR = hazard ratio; mo = months; RR = risk ratio.
[a] Calculated via random-effects meta-analysis.

The pooled data from the DAPT[34] and PRODIGY[38] trials supports no significant difference in the risk of stroke between extended DAPT and six to 12 months of DAPT among patients with a BMS (RR 1.31; 95% CI, 0.58 to 2.96) (Figure 5).

Figure 5: Relative Risk of Stroke Among Patients With a Bare-Metal Stent



CI = confidence interval; mo = months.

Stent Thrombosis

Two RCTs (DAPT,[34] PRODIGY[38]) reported stent thrombosis among participants with a BMS.

Mauri et al.[34] reported that there was no significant difference in the risk of stent thrombosis between 12 months and 30 months of DAPT (HR 0.49; 95% CI 0.15 to 1.64) (Table 95). The timing of stent thrombosis (late or very late) was not reported. The risk of definite or probable late stent thrombosis was not significantly different between six months and 24 months of DAPT in the PRODIGY trial (RR 1.00; 95% CI, 0.29 to 3.42) (Table 95).[38] Similarly, the risk of definite late stent thrombosis was not significantly different between six months of DAPT and 24 months of DAPT in the PRODIGY trial (RR 3.01; 95% CI, 0.32 to 28.76).[38]

Table 95: Summary of Evidence Available for Stent Thrombosis Among Patients With a Bare-Metal Stent

RCT	Stent Type	No. of Events/ No. Randomized	Direction of Estimate	Reported Effect Estimate (95% CI)
Definite or Probable				
PRODIGY (Late ST)	BMS	6 mo: 5/246 24 mo: 5/245	RR > 1 indicates a higher risk in extended group	Calculated RR 1.00 (0.29 to 3.42)[a]
PRODIGY (Very late ST)	BMS	6 mo: 0/246 24 mo: 0/245	NA	NA
DAPT[b]	BMS	12 mo: 9/845 30 mo: 4/842	HR < 1 indicates lower risk in extended group	HR 0.49 (0.15 to 1.64)
Definite				
PRODIGY (Late ST)	BMS	6 mo: 1/246 24 mo: 3/245	RR > 1 indicates a higher risk in extended group	Calculated RR 3.01 (0.32 to 28.76)[a]
PRODIGY (Very late ST)	BMS	6 mo: 0/246 24 mo: 0/245	NA	NA
DAPT[b]	BMS	12 mo: 9/845 30 mo: 4/842	HR < 1 indicates lower risk in extended group	HR 0.49 (0.15 to 1.64)

BMS = bare-metal stent; CI = confidence interval; HR = hazard ratio; mo = months; NA = not applicable; OR = odds ratio; RCT = randomized controlled trial; RR = risk ratio.

[a] Calculated via random-effects meta-analysis.

[b] Timing of stent thrombosis not reported.

Major Adverse Cardiac and Cerebrovascular Events

Two RCTs (DAPT,[34] PRODIGY[38]) reported MACCE among participants with a BMS.

Despite differences in the definition of MACCE in each trial, both the DAPT[34] and PRODIGY[38] trials reported non-significant differences in the risk of MACCE between DAPT for six to 12 months and DAPT for more than 12 months (Table 96).

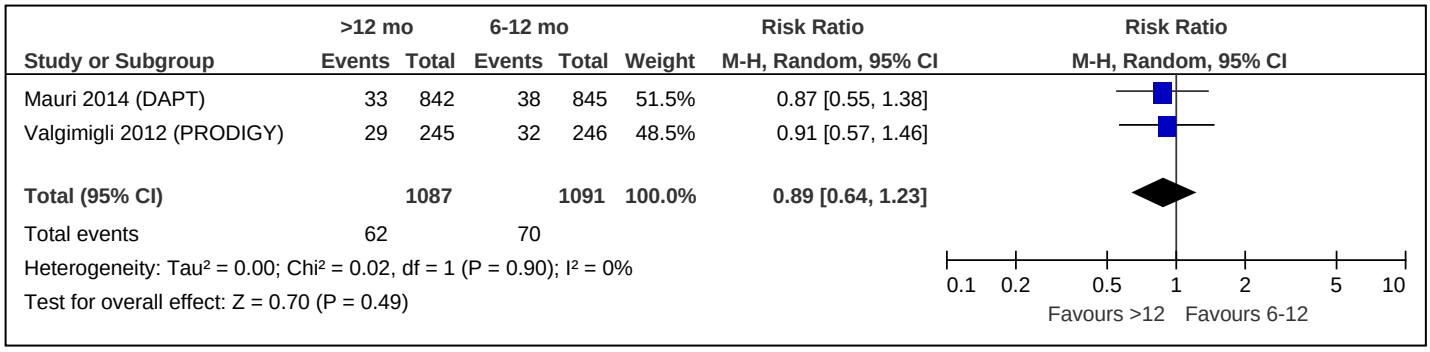
Table 96: Summary of Evidence Available for MACCE Among Patients With a Bare-Metal Stent

Subgroup, RCT	Stent Type	No. of Events/Patients	Outcome Definition	Direction of Estimate	Reported HR (95% CI)
PRODIGY	BMS	6 mo: 32/246 24 mo: 29/245	Death of any cause, nonfatal MI, or cerebrovascular accident	HR < 1 indicates lower risk in extended group	HR 0.89 (0.54 to 1.45)
DAPT	BMS	12 mo: 38/845 30 mo: 33/842	Death, MI, or stroke	HR < 1 indicates a lower risk in the extended group	HR 0.92 (0.57 to 1.47)

BMS = bare-metal stent; CI = confidence interval; HR = hazard ratio; MACCE = major adverse cardiac and cerebrovascular events; MI = myocardial infarction; mo = months; RCT = randomized controlled trial.

The pooled data from the DAPT[34] and PRODIGY[38] trials supports no significant difference in the risk of MACCE between DAPT for more than 12 months compared with DAPT for six to 12 months among patients with a BMS (RR 0.89; 95% CI, 0.64 to 1.23) (Figure 6).

Figure 6: Relative Risk of MACCE Among Patients With a Bare-Metal Stent



CI = confidence interval. mo = months.

Major Bleeding

One RCT (DAPT[34]) reported major bleeding among participants with a BMS.

Participants who received DAPT for 30 months were at higher risk of BARC type 2 bleeding (risk difference 1.88%; 95% CI, 0.56% to 3.21%) and BARC type 3 bleeding (risk difference 1.25%; 95% CI, 0.09% to 2.41%) compared with participants who received DAPT for 12 months (Table 97).

There was no significant difference in the risk of fatal bleeding (type 5) between DAPT for 12 months or for 30 months (risk difference −0.13%; 95% CI. −0.38% to 0.12%) (Table 97).

When considered together, the risk of type 2, 3, or 5 bleeding was significantly higher among patients who received DAPT for 30 months compared with 12 months (risk difference 2.75%; 95% CI, 1.02% to 4.48%) (Table 97).

Table 97: Summary of Evidence Available for Major Bleeding Among Patients With a Bare-Metal Stent

RCT	Bleeding Type	Stent Type	No. of Events/ No. Randomized	Direction of Estimate	Reported Risk Difference (95% CI)
DAPT	BARC type 2, 3 and 5: DAPT	BMS	12 mo: 14/845 30 mo: 36/842	Difference > 0 indicates more events in the extended group	**2.75% (1.02% to 4.48%)**
	BARC type 2: DAPT	BMS	12 mo: 7/845 30 mo: 22/842		**1.88% (0.56% to 3.21%)**
	BARC type 3: DAPT	BMS	12 mo: 6/845 30 mo: 16/842		**1.25% (0.09% to 2.41%)**
	BARC type 5: DAPT	BMS	12 mo: 1/845 30 mo: 0/842		−0.13% (−0.38% to 0.12%)

BARC = Bleeding Academic Research Consortium; BMS = bare-metal stent; CI = confidence interval; mo = months; RCT = randomized controlled trial.

Minor Bleeding

No data were reported for minor bleeding among patients with a BMS.

Gastrointestinal Bleeding

No data were reported for gastrointestinal bleeding among patients with a BMS.

Data Summary: Research Question 4

Is there a rebound effect after withdrawal of P2Y12 inhibitor (clopidogrel, prasugrel, ticagrelor) therapy?

None of the included systematic reviews assessed an outcome of interest after withdrawal of DAPT.

Of the RCTs included in the systematic reviews, only one trial (DAPT[34]) reported outcomes after the discontinuation of DAPT. Data were available for patients with any type of DES from one RCT (DAPT[34]) for all-cause death, stent thrombosis, myocardial infarction, stroke, MACCE, and major bleeding.

The authors of the DAPT trial qualitatively assessed the hazards before and after discontinuation of DAPT following 12 months or 30 months of therapy, and concluded that there was an elevated risk of stent thrombosis and myocardial infarction in the three months following discontinuation of DAPT.

In an inferential analysis, we performed a large sample test to assess for quantitative differences in hazard rate for each outcome before and after discontinuation of DAPT (Table 98).

Among patients who received 12 months of DAPT, there was no significant difference in the risk of all-cause death, myocardial infarction, stent thrombosis, or MACCE after discontinuation of DAPT (Table 98).

Among patients who received DAPT for 30 months, the risk of myocardial infarction and MACCE was higher in the first three months after discontinuation compared with the last three months before discontinuation. There was no significant difference in the risk of all-cause death, stent thrombosis, or stroke after discontinuation of DAPT (Table 98).

Table 98: Summary of Evidence Before and After Withdrawal of DAPT Among Patients With a Drug-Eluting Stent

	3 Months Before Discontinuation		3 Months After Discontinuation		
Duration of DAPT	**No. at Risk**	**Hazard Rate per Day (95% CI)**	**No. at Risk**	**Hazard Rate per day (95% CI)**	***P* value[a]**
All-Cause Death					
12 months	4,659	0.31 (0.14 to 0.48)	4,618	0.28 (0.11 to 0.46)	0.8096
30 months	4,703	0.40 (0.21 to 0.59)	4,663	0.42 (0.21 to 0.64)	0.8913
Myocardial Infarction					
12 months	4,501	0.57 (0.34 to 0.81)	4,440	0.50 (0.26 to 0.74)	0.6829
30 months	4,634	0.43 (0.23 to 0.63)	4,580	1.12 (0.77 to 1.47)	**0.0008**
Stroke					
12 months	4,626	0.14 (0.03 to 0.26)	4,579	0.17 (0.03 to 0.31)	0.7452
30 months	4,670	0.10 (0.00 to 0.19)	4,626	0.26 (0.09 to 0.42)	0.0989
Stent Thrombosis					
12 months	4,603	0.12 (0.01 to 0.23)	4,556	0.11 (0.00 to 0.23)	0.9020
30 months	4,686	0.12 (0.01 to 0.22)	4,642	0.31 (0.13 to 0.50)	0.0793
MACCE					
12 months	4,476	0.92 (0.63 to 1.22)	4,412	0.71 (0.43 to 1.00)	0.3519
30 months	4,611	0.80 (0.53 to 1.07)	4,554	1.59 (1.17 to 2.01)	**0.0019**

CI = confidence interval; DAPT = dual antiplatelet therapy; MACCE = major adverse cardiac and cerebrovascular events.
[a] Hazard rate during the final 3 months before discontinuation compared with the first 3 months following discontinuation.

Patients With Diabetes

One RCT (DAPT[34]) assessed outcomes after discontinuation of DAPT among participants with diabetes with an implanted DES or BMS.

Myocardial infarction: After receiving DAPT for 30 months, in the subsequent three-month period with no DAPT (months 30 to 33), 1.1% of participants with diabetes experienced a myocardial infarction. During the same period, 0.6% of participants who had received only 12 months of DAPT experienced a myocardial infarction (non-significant difference between groups, *P* = 0.12).

Stent thrombosis: After receiving DAPT for 30 months, in the subsequent three-month period with no DAPT (months 30 to 33), 0.3% of participants with diabetes experienced stent thrombosis. During the same period, 0.09% of participants who had received only 12 months of DAPT experienced a stent thrombosis (non-significant difference between groups, *P* = 0.11).

MACCE: After receiving DAPT for 30 months, in the subsequent three-month period with no DAPT (months 30 to 33), 2.1% of participants with diabetes experienced an event. During

the same period, 1.2% of participants who had received only 12 months of DAPT experienced a stent thrombosis (significant difference between groups, *P* = 0.04).

Discussion

Summary of Evidence

Among patients with either a BMS or a DES, extending DAPT beyond 12 months may reduce the risk of myocardial infarction, stent thrombosis, and MACCE but may increase the risk of all-cause and noncardiovascular death and major bleeding. There were no significant differences in the risk of cardiovascular death, stroke, or urgent target revascularization between extended DAPT and shorter-duration DAPT.

Among patients with a DES, extending DAPT beyond 12 months may reduce the risk of myocardial infarction, stent thrombosis, and MACCE but may increase the risk of all-cause and noncardiovascular death and major bleeding. There were no significant differences in the risk of cardiovascular death, stroke, or urgent target revascularization between extended DAPT and shorter-duration DAPT.

Limited data were reported for patients with a BMS. Most of the included systematic reviews focused on patients with a DES, and few of the included RCTs included participants with a BMS. From the available data, DAPT for more than 12 months was associated with an increased risk of major bleeding among patients with a BMS. There were no significant differences in the risk of death, myocardial infarction, stroke, stent thrombosis, or MACCE between extended DAPT and shorter-duration DAPT.

Data were limited for some subgroup analyses. Few of the included systematic reviews examined the effect of extended duration on an outcome of interest, and we extracted data from the RCTs where available. We highlight the differences between groups here, noting the availability of data.

Acute Coronary Syndrome

- Patients with or without ACS may have an increased risk of major bleeding with extended DAPT (one RCT[38]).
- A decreased risk of stent thrombosis among those without ACS was reported in one systematic review[23] (number of included RCTs unclear). One included RCT[38] reported no increased risk of stent thrombosis among patients either with or without ACS.
- There were no significant differences in the risk of MACCE between short DAPT and extended DAPT among patients with or without ACS (one RCT[38]).

Age

- No significant difference in the risk of cardiovascular death for short DAPT or extended DAPT among patients aged more or less than 62.5 years was reported in one systematic review[23] (number of included RCTs unclear).
- A lower risk of myocardial infarction and stent thrombosis with extended DAPT was reported among those aged less than 62.5 years (one systematic review;[23] number of included RCTs unclear).
- Patients aged less than 75 years may have a lower risk of myocardial infarction and stent thrombosis (one RCT[34])

- Patients aged more than 75 years may have a lower risk of MACCE with extended DAPT (one RCT[34]); however, one RCT[35] found no difference in the risk of MACCE in this age group.

Prior Myocardial Infarction

- Patients with a previous myocardial infarction on extended DAPT may have a reduced risk of myocardial infarction, stent thrombosis, and MACCE but an increased risk of major bleeding, with no significant difference in the risk of death (one RCT[34]).
- Patients without a previous myocardial infarction may be at increased risk of all-cause and noncardiovascular death and major bleeding with extended DAPT, but at lower risk of myocardial infarction and stent thrombosis (one RCT[34]).

Diabetes

- Patients with diabetes on extended DAPT may be at increased risk of major bleeding (one RCT[34]).
- There were no significant differences in the risk of all-cause death, noncardiovascular death, cardiovascular death, stroke, stent thrombosis, or MACCE between short DAPT and extended DAPT among those with diabetes (one RCT[34]).
- Patients without diabetes may be at lower risk of myocardial infarction and stent thrombosis. No data were available for major bleeding in patients without diabetes (one RCT[34]).
- Conflicting evidence was reported for MACCE: One RCT[34] reported a reduced risk of MACCE with extended DAPT among patients without diabetes, while three RCTs[35,36,38] reported no significant difference in risk between short DAPT and extended DAPT.

Smoking

- Both smokers and non-smokers may be at reduced risk of myocardial infarction and stent thrombosis with extended DAPT (one RCT[34]).
- One RCT[34] reported a reduced risk of MACCE with extended DAPT among both smokers and non-smokers; however one RCT[35] reported no significant difference between durations.

Lesion Complexity

- There was no difference in the risk of MACCE with extended DAPT among patients with complex or simple lesions (one RCT[38]).

Peripheral Artery Disease

- Patients with peripheral artery disease may be at reduced risk of all-cause and cardiovascular death and MACCE with extended DAPT, with no difference in the risk of myocardial infarction or stent thrombosis (one RCT[38]).
- There was no significant difference in the risk of all-cause or cardiovascular death, myocardial infection, stent thrombosis, or MACCE with extended DAPT among patients with peripheral artery disease (one RCT[38]).

Interpretation of the Results

This systematic review evaluated the evidence from previously published systematic reviews that have investigated the optimal duration of DAPT therapy following PCI with stenting. Where necessary, this review also summarized data from primary studies to address the research questions. The review followed rigorous systematic procedures throughout the review process.

Overall, long-term DAPT of beyond 12 months in patients after PCI was predominantly beneficial in the reduction of stent thrombosis, myocardial infarction, and MACCE; however, this benefit is contrasted by an increase in major bleeding and death, including both noncardiovascular and all-cause.

Subgroups such as those with prior myocardial infarction or age younger than 75 years may derive the most benefit from long-term DAPT; accordingly, individualized risk assessments should be made to determine ideal duration of therapy.

Conflicting data were located for several outcomes. For example, three systematic reviews reported no significant difference in risk between six months and more than12 months of DAPT, while one network meta-analysis reported a significant reduction in risk with 30 months of DAPT compared with six months. The estimate from the network meta-analysis was associated with a wide credible interval, and one should consider whether the assumptions of network meta-analysis are met. This network meta-analysis was published in Chinese, and a full translation of the publication could not be obtained during the review period.

Conflicting data were also reported for the risk of MACCE among participants aged less than 75 years. The DAPT trial[34] reported a significantly reduced risk of MACCE among participants aged less than 75 years, while the ARCTIC-Interruption trial[35] found no significant differences in the risk of MACCE between short DAPT and extended DAPT. These differences are likely due to different definitions of MACCE used in the trials. Of note, ARCTIC-Interruption used a much more inclusive definition of MACCE (Appendix 6).

We also found conflicting data for the risk of MACCE among patients without diabetes. One RCT (DAPT[34]) reported a reduction in the risk of MACCE among patients without diabetes. However DES-LATE and ARCTIC-Interruption both found no significant difference in the risk of MACCE. These differences may be due, in part, to differences in the definition of MACCE used in each trial (Appendix 6). Overall, when the data were pooled from DAPT, DES-LATE, and ARCTIC-Interruption, we found a significant reduction in the risk of MACCE with extended DAPT among participants without diabetes (RR 0.66; 95% CI, 0.55 to 0.79), but not among those with diabetes (RR 1.12; 95% CI, 0.80 to 1.68).

We found limited data in the included published systematic reviews addressing the benefits and harms of extended DAPT in specific populations. As such, we sought out data from the RCTs that had been included in the systematic reviews. However, data were still limited to address most subgroup questions, and contradictory results were reported between reviews for several outcomes. Because of the limited data and contradictory findings, caution should be used in interpreting these results. The differences between studies and populations have been highlighted in the executive summary and the summaries of findings in section 4.

We found no significant difference in the odds of death (all-cause, cardiovascular or noncardiovascular) among participants with myocardial infarction. This result was based on the findings from one RCT (DAPT), which reported the risk of death among participants with or without a prior acute myocardial infarction randomized to receive either 12 or 36 months of DAPT. In contrast with our findings, a previous meta-analysis[52] reported a reduced risk of death among patients with a prior myocardial infarction with extended DAPT. In their analysis, Udell et al.[52] included participants with a prior myocardial infarction with or without stenting. Two of the RCTs included in their review (CHARISMA MI,[53] PEGASUS-TIMI 54[54]) involved patients with or without PCI (< 85% with PCI), and data were not reported separately for patients with a stent, thus the Udell review did not meet the inclusion criteria

for the present review. Overall, Udell et al.[52] reported that there was a significantly lower risk of cardiovascular death among patients with prior myocardial infarction who received extended DAPT (RR 0.85; 95% CI, 0.74 to 0.98). As well, they also observed a reduced risk of MACCE, myocardial infarction, stroke, and stent thrombosis, with no significant difference in the risk of major bleeding, noncardiovascular death, or all-cause death between short DAPT and extended DAPT.[52]

Udell et al.[52] obtained unpublished data from RCT principal investigators. Thus, they were able to include additional RCTs in their analysis involving patients with a prior myocardial infarction. In an exploratory analysis, we used the reported data from the Udell review[52] (excluding the CHARISMA MI[53] and PEGASUS-TIMI 54[54] trials). In this analysis, we found no significant difference in the risk of cardiovascular death between short DAPT and extended DAPT among patients with a prior myocardial infarction (RR 0.92; 95% CI, 0.66 to 1.29), which was qualitatively consistent with the effect estimate from the DAPT trial[34] (HR 0.67; 95% CI, 0.31 to 1.44).

Strengths and Limitations of the Systematic Review

Strengths

We performed a comprehensive review of the published and grey literature to identify all systematic reviews that aimed to compare extended DAPT (> 12 months) with DAPT for six to 12 months. The review followed an a priori published protocol and used standard approaches for the identification of evidence, data abstraction, quality assessment, and reporting.

Limitations

- The outcome definitions varied among the trials that contributed data to the included systematic reviews. 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 with different bleeding classification scales and did not pool data where they were not deemed to be clinically similar. For MACCE, we have reported the definitions used by each trial, allowing the reader to judge the similarity of the outcome.
- First-generation DESs were used in some of the patients in the DES-LATE,[36] ARCTIC-Interruption,[35] and DAPT[34] trials, which may limit generalizability to current clinical practice. One of the included systematic reviews[16] assessed outcomes among patients with a second-generation DES: Compared with patients who received any type of DES, those with a second-generation DES may not experience a reduction in the risk of stent thrombosis with DAPT beyond 12 months.
- The timing of randomization of patients varied between trials. Two trials randomized patients within the first 30 days after stenting (PRODIGY,[38] ITALIC[37]). In contrast, in four trials (DAPT,[34] DES-LATE,[36] OPTIDUAL,[39] ARCTIC-Interruption[35]), 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 timing of randomization was not reported for one trial (Hu et al.[40]).
- The exclusion of some high-risk patients (e.g., those with STEMI, left main disease, impaired ejection fraction, or cardiogenic shock) from some of the included RCTs may limit the generalizability of these results.

Conclusions

Overall, extending the duration of DAPT beyond 12 months after PCI is predominantly beneficial in reducing stent thrombosis, myocardial infarction, and MACCE but is associated with an increased risk of major bleeding and risk of death. Accordingly, careful selection of DAPT duration following PCI, based on individual cardiovascular and bleeding risk factors, is important to ensure that patients derive net clinical benefits from their treatment.

References

1. Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: A report of the American College of Cardiology / American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2016;133(140):e123-55.
2. Tanguay JF, Bell AD, Ackman ML, Bauer RD, Cartier R, Chan WS, et al. Focused 2012 update of the Canadian Cardiovascular Society Guidelines for the use of antiplatelet therapy. Can J Cardiol. 2013;29:1334-45.
3. The Task Force on Myocardial Revascularization of the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery. 2014 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2014;35:2541-619.
4. Clopidogrel and proton pump inhibitor use: a review of the evidence on safety [Internet]. Ottawa (ON): CADTH; 2017 Mar 14. (CADTH rapid response report: summary with critical appraisal). [cited 2017 Apr 4]. Available from: https://www.cadth.ca/clopidogrel-and-proton-pump-inhibitor-use-review-evidence-safety
5. Dual antiplatelet therapy acetylsalicylic acid dosing: A review of the clinical effectiveness and harms [Internet]. Ottawa (ON): CADTH; 2017 Mar 14. (CADTH rapid response report: summary with critical appraisal). [cited 2017 Apr 4]. Available from: https://www.cadth.ca/dual-antiplatelet-therapy-acetylsalicylic-acid-dosing-review-clinical-effectiveness-and-harms
6. Joanna Briggs Institute Reviewers' manual: Methodology for JBI mixed methods systematic reviews . Adelaide (AUS): Johanna Briggs Institute; 2014.
7. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009;62 (10):1006-12.
8. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer review of electronic search strategies: 2015 guideline statement. J Clin Epidemiol. 2016;75:40-6.
9. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol.2007;7:10.
10. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation. 2011;123 (23):2736-47.
11. Duan HQ, Dong PS, Wang HL, Li ZJ, Du LJ, Zhao YW.. Effect of prolonged dual anti-platelet therapy on reducing myocardial infarction rate after percutaneous coronary intervention. J Biol Regul Homeost Agents. 2015;29 (1):213-9.
12. Giacoppo D, Baber U, Mehran R. Current developments in dual antiplatelet therapy after stenting. Minerva Cardioangiologica. 2014;62 (3):261-76.
13. Fei Y, Tsoi MF, Cheung TT, Cheung BM. Optimal duration of dual antiplatelet therapy after drug-eluting stent implantation: Meta-analysis of randomized controlled trials. Int J Cardiol. 2016;220:895-900.
14. Palla M, Briasoulis A, Siddiqui F, Alesh I, Afonso L. Long (>12 months) and short (<6 months) versus standard duration of dual antiplatelet therapy after coronary stenting: A systematic review and meta-analysis. Am J Ther. 2015:1-9.
15. Sharma A, Lavie CJ, Sharma SK, Garg A, Vallakati A, Mukherjee D, et al. Duration of dual antiplatelet therapy after drug-eluting stent implantation in patients with and without acute coronary syndrome: a systematic review of randomized controlled trials. Mayo Clin Proc. 2016;91(8):1084-93.
16. D'Ascenzo F, Moretti C, Bianco M, Bernardi A, Taha S, Cerrato E, et al. Meta-analysis of the duration of dual antiplatelet therapy in patients treated with second-generation drug-eluting stents. Am J Cardiol. 2016;117(11):1714-23.

17. Tsoi MF, Cheung CL, Cheung TT, Wong ICK, Kumana CR, Tse HF, et al. Duration of dual antiplatelet therapy after drug-eluting stent implantation: Meta-analysis of large randomised controlled trials. Sci.Rep. 2015;5:13204.

18. Verdoia M, Schaffer A, Barbieri L, Montalescot G, Collet JP, Colombo A, et al. Optimal duration of dual antiplatelet therapy after DES implantation: A meta-analysis of 11 randomized trials. Angiology. 2015;67(2):224-38.

19. Cassese S, Byrne RA, Ndrepepa G, Schunkert H, Fusaro M, Kastrati A. Prolonged dual antiplatelet therapy after drug-eluting stenting: meta-analysis of randomized trials. Clin Res Cardiol. 2015;104(10):887-901.

20. Bulluck H, Kwok CS, Ryding AD, Loke YK. Safety of short-term dual antiplatelet therapy after drug-eluting stents: An updated meta-analysis with direct and adjusted indirect comparison of randomized control trials. Int J Cardiol. 2015;181:331-9.

21. Spencer FA, Prasad M, Vandvik PO, Chetan D, Zhou Q, Guyatt G. Longer- versus shorter-duration dual-antiplatelet therapy after drug-eluting stent placement: a systematic review and meta-analysis. Ann Intern Med. 2015;163(2):118-26.

22. Palmerini T, Benedetto U, Bacchi-Reggiani L, Della Riva D, Biondi-Zoccai G, Feres F, et al. Mortality in patients treated with extended duration dual antiplatelet therapy after drug-eluting stent implantation: a pairwise and Bayesian network meta-analysis of randomised trials. Lancet. 2015;385(9985):2371-82.

23. Navarese EP, Andreotti F, Schulze V, Kolodziejczak M, Buffon A, Brouwer M, et al. Optimal duration of dual antiplatelet therapy after percutaneous coronary intervention with drug eluting stents: meta-analysis of randomised controlled trials. BMJ. 2015;350:h1618.

24. Kwok CS, Bulluck H, Ryding AD, Loke YK. Benefits and harms of extending the duration of dual antiplatelet therapy after percutaneous coronary intervention with drug-eluting stents: a meta-analysis. Scientific World J. 2014;2014:794078.

25. Valgimigli M, Park SJ, Kim HS, Park KW, Park DW, Tricoci P, et al. Benefits and risks of long-term duration of dual antiplatelet therapy after drug-eluting stenting: a meta-analysis of randomized trials. Int J Cardiol. 2013;168(3):2579-87.

26. Cassese S, Byrne RA, Tada T, King LA, Kastrati A. Clinical impact of extended dual antiplatelet therapy after percutaneous coronary interventions in the drug-eluting stent era: a meta-analysis of randomized trials. Eur Heart J. 2012;33(24):3078-87.

27. Vandvik PO, Lincoff AM, Gore JM, Gutterman DD, Sonnenberg, Alonso-Coello P, et al. Primary and secondary prevention of cardiovascular disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141(2 suppl):e637S-e68S.

28. Sheyin O, Perez X, Pierre Louis B, Kurian D. The optimal duration of dual antiplatelet therapy in patients receiving percutaneous coronary intervention with drug-eluting stents. Cardiology J.23(3):307-16.

29. Xie C, Ding XL, Miao LY. Different durations of dual anti-platelet therapy after percutaneous coronary intervention with drug-eluting stents in patients with coronary disease: A systematic review. Chinese Pharmaceutical J. 2016;51(9):762-8.

30. Zhang XL, Zhu QQ, Zhu L, Shi SQ, Chen JZ, Xie J, et al. Optimize the duration of DAPT following des implantation: An updated system review and meta-analysis of 10 randomized trials. Clin Trials Regul Sci Cardiol. 2015;6:1-11.

31. You JJ, Singer DE, Howard PA, Lane DA, Eckman MH, Fang MC, et al. Antithrombotic therapy for atrial fibrillation: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141(2 Suppl):e531S-e75S.

32. Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: An update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention, 2011 ACCF/AHA

guideline for coronary artery bypass graft surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease, 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction, 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes, and 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. Circulation. 2016;134:e123-55.

33. Bittl J, Baber U, Bradley S, Wijeysundera DN. Duration of dual antiplatelet therapy: A systematic review for the 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2016;68(10):1116-39.

34. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Schempp 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.

35. Collet JP, Silvain J, Barthélémy O, Range G, Cayla G, Van Belle E, et al. Dual-antiplatelet treatment beyond 1 year after drug-eluting stent implantation (ARCTIC-Interruption): A randomised trial. The Lancet. 2014;384(9954):1577-85.

36. Lee CW, Ahn JM, Park DW, Kang SJ, Lee SW, Kim YK, et al. Optimal duration of dual antiplatelet therapy after drug-eluting stent implantation a randomized, controlled trial. Circulation. 2014;129(3):304-12.

37. 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(8):777-86.

38. 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;12(16)5:2015-26.

39. Helft G, Le Feuvre C, Georges JL, Carrie D, Leclercq F, Eltchainoff 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.

40. Hu T, Wang HC. AS-171 Duration of dual antiplatelet therapy and outcomes after left main percutaneous coronary intervention. Am J Cardiol. 2012;109(7):S85-S6.

41. Colombo A, Chieffo A, Frasheri A, Garbo R, Masotti-Centol M, Salvatella N, et al. Second-generation drug-eluting stent implantation followed by 6- versus 12-month dual antiplatelet therapy: the SECURITY randomized clinical trial. J Am Coll Cardiol. 2014;64(20):2086-97.

42. Feres F, Costa RA, Abizaid A, Leon MB, Marin-Neto JA, Botelho RV, et al. Three vs twelve months of dual antiplatelet therapy after zotarolimus-eluting stents: the OPTIMIZE randomized trial. JAMA. 2013;310(23):2510-22.

43. Gwon HC, Hahn JY, Park KW, Song YB, Chae IH, Han KR et al. Six-month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents: The efficacy of xience/promus versus cypher to reduce late loss after stenting (EXCELLENT) randomized, multicenter study. Circulation. 2012;125(3):505-13.

44. Kim BK, Hong MK, Shin DH, Nam CM, Kim JS, Ko YG, et al. A new strategy for discontinuation of dual antiplatelet therapy: The RESET Trial (REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation). J Am Coll Cardiol. 2012;60(15):1340-8.

45. Schulz-Schupke S, Byrne RA, Ten Berg JM, Neumann FJ, Han Y, Adriaenssens T, et al. ISAR-SAFE: a randomized, double-blind, placebo-controlled trial of 6 vs. 12 months of clopidogrel therapy after drug-eluting stenting. Eur Heart J. 2015;36(20):1252-63.

46. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, et al. Clinical end points in coronary stent trials: A case for standardized definitions. Circulation. 2007;115(17):2344-51.

47. 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):2211-21.

48. Meredith IT, Tanguay JF, Kereiakes DJ, Cutlip D, 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;133:1772-82.

49. Ryan TJ, Faxon DP, Gunnar RM, Kennedy JW, King SB, Peterson KL, et al. Guidelines for percutaneous transluminal coronary angioplasty. A report of the American College of Cardiology/American Heart Association Task Force on assessment of diagnostic and therapeutic cardiovascular procedures. Circulation. 1988;78(2):486-502.

50. Ellis SG, Roubin GS, King SB, Douglas JS Jr, Weintraub WS, Thomas RG, et al. Angiographic and clinical predictors of acute closure after native vessel coronary angioplasty. Circulation. 1988;77(2):372-9.

51. 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):795-803.

52. Udell JA, Bonaca MP, Collet JP, Lincoff AM, Kereiakes DJ, Costa F, et al. Long-term dual antiplatelet therapy for secondary prevention of cardiovascular events in the subgroup of patients with previous myocardial infarction: a collaborative meta-analysis of randomized trials. Eur Heart J. 2016;37(4):390-9.

53. Bhatt DL, Flather MD, Hacke W, Berger PB, Black HR, Boden WE, et al. Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA trial. J Am Coll Cardiol. 2007;49(19):1982-8.

54. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med. 2015;372:1791-800.

Appendix 1: Literature Search Strategy

DAPT PCI
Final Strategies
2016 Aug. 12

OVID

Database: Embase <1980 to 2016 Week 32>, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:

---

1 exp Stents/ (190875)
2 (stent or stents or stented or stenting).tw,kw. (201982)
3 (DES or DESs).tw,kw. (70216)
4 (Strecker* or Supremo* or WallFlex* or Wallstent*).tw,kw. (3902)
5 or/1-4 (300274) [STENTS]
6 ((dual or double) adj (antiplatelet* or anti-platelet*)).tw,kw. (9238)
7 (DAPT or DAPTs).tw,kw. (3105)
8 6 or 7 (10825) [DAPT PT 1]
9 Platelet Aggregation Inhibitors/ (61484)
10 (antiplatelet* or anti-platelet*).tw,kw. (62043)
11 (platelet* adj2 inhibit*).tw,kw. (34284)
12 thrombocyte aggregation inhibit*.tw,kw. (264)
13 Purinergic P2Y Receptor Antagonists/ (1565)
14 ((P2Y or P2Y1 or P2Y12 or P2Y2) adj (receptor antagonist* or purinoceptor antagonist*)).tw,kw. (1339)
15 (ADP receptor adj (antagonist* or blocker*)).tw,kw. (665)
16 (adenosine diphosphate receptor adj (antagonist* or blocker*)).tw,kw. (152)
17 clopidogrel*.tw,kw. (28081)
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,kw. (3218)
19 (duocover or duoplavin).tw,kw. (11)
20 clopidogrel.rn. (46154)
21 Prasugrel Hydrochloride/ (6357)
22 (prasugrel or CS 747 or CS747 or effient or efient or LY 640315 or LY640315).tw,kw. (4607)
23 prasugrel.rn. (5348)
24 ticagrelor.tw,kw. (3509)
25 (AZD 6140 or AZD6140 or brilinta or brilique or possia).tw,kw. (691)
26 ticagrelor.rn. (3951)
27 Aspirin/ (201606)
28 asa.tw,kw. (56611)
29 aspirin.tw,kw. (140513)
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,kw. (18867)
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,kw. (22012)
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,kw. (3438)
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,kw. (439)
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,kw. (186)
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,kw. (271)
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,kw. (137)
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,kw. (162)
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,kw. (1718)
39 aspirin.rn. (40892)
40 or/9-39 (379020)
41 Drug Combinations/ (115854)
42 Drug Therapy, Combination/ (200510)
43 Combined Modality Therapy/ (205183)
44 ((combination* or combine* or combining) adj2 (agent or agents or drug or drugs)).tw,kw. (62908)
45 ((combination* or combine* or combining) adj2 (therap* or treatment*)).tw,kw. (262970)
46 ((dual or double) adj2 (therap* or treatment*)).tw,kw. (24189)
47 or/41-46 (734986)
48 40 and 47 (22994) [DAPT PT 2]
49 8 or 48 (25717) DAPT PT 1 & 2]
50 5 and 49 (7359) [STENTS AND DAPT]
51 Adolescent/ not (exp Adult/ and Adolescent/) (1028571)
52 exp Child/ not (exp Adult/ and exp Child/) (2731326)
53 exp Infant/ not (exp Adult/ and exp Infant/) (1507636)
54 or/51-53 (3534744)
55 50 not 54 (7340) [CHILD-ONLY ONLY REMOVED]
56 exp Animals/ not (exp Animals/ and Humans/) (13628610)
57 55 not 56 (4777) [ANIMAL-ONLY REMOVED]
58 (comment or editorial or interview or letter or news or newspaper article).pt. (3189325)
59 57 not 58 (4505) [OPINION PIECES REMOVED]
60 limit 59 to yr="2011-current" (2397) [DATE LIMIT]
61 limit 60 to systematic reviews [Limit not valid in Embase; records were retained] (1126)
62 meta analysis.pt. (72334)
63 exp meta-analysis as topic/ (43504)
64 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw. (231753)

65 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or rapid review* or "review of reviews" or technology assessment* or HTA or HTAs).tw. (271308)
66 exp Technology assessment, biomedical/ (21604)
67 (cochrane or health technology assessment or evidence report).jw. (34056)
68 ((indirect* or mixed or multi-treatment*) adj2 compar*).tw. (8594)
69 ((network* or network-based) adj (MA or MAs)).kw,tw. (11)
70 or/62-69 (502953)
71 60 and 70 (177)
72 61 or 71 (1148) [REVIEWS]
73 exp Guidelines as Topic/ (504541)
74 exp Clinical Protocols/ (219109)
75 Guideline.pt. (15919)
76 Practice Guideline.pt. (21735)
77 standards.fs. (609295)
78 Consensus Development Conference.pt. (10113)
79 Consensus Development Conference, NIH.pt. (756)
80 (guideline* or standards or recommendation*).ti. (239243)
81 (expert consensus or consensus statement* or consensus conference* or practice parameter* or position statement* or policy statement* or CPG or CPGs).tw. (93481)
82 or/73-81 (1404586)
83 60 and 82 (166) [GUIDELINES]
84 72 or 83 (1233) [REVIEWS OR GUIDELINES]
85 84 use ppez (257) [MEDLINE RECORDS]
86 exp stent/ (190875)
87 (stent or stents or stented or stenting).tw,kw. (201982)
88 (DES or DESs).tw,kw. (70216)
89 (Strecker* or Supremo* or WallFlex* or Wallstent*).tw,kw. (3902)
90 or/86-89 (300274) [STENTS]
91 ((dual or double) adj (antiplatelet* or anti-platelet*)).tw,kw. (9238)
92 (DAPT or DAPTs).tw,kw. (3105)
93 acetylsalicylic acid plus clopidogrel/ (322)
94 (duocover or duoplavin).tw,kw. (11)
95 or/91-94 (11094) [DAPT PT 1]
96 antithrombocytic agent/ (34172)
97 (antiplatelet* or anti-platelet*).tw,kw. (62043)
98 (platelet* adj2 inhibit*).tw,kw. (34284)
99 thrombocyte aggregation inhibit*.tw,kw. (264)
100 purinergic P2Y receptor antagonist/ (1720)
101 ((P2Y or P2Y1 or P2Y12 or P2Y2) adj (receptor antagonist* or purinoceptor antagonist*)).tw,kw. (1339)
102 (ADP receptor adj (antagonist* or blocker*)).tw,kw. (665)
103 (adenosine diphosphate receptor adj (antagonist* or blocker*)).tw,kw. (152)
104 clopidogrel/ (45790)
105 (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. (30159)
106 clopidogrel.rn. (46154)
107 prasugrel/ (6357)
108 (prasugrel or CS 747 or CS747 or effient or efient or LY 640315 or LY640315).tw,kw. (4607)
109 prasugrel.rn. (5348)

110 ticagrelor/ (4114)
111 ticagrelor.tw,kw. (3509)
112 (AZD 6140 or AZD6140 or brilinta or brilique or possia).tw,kw. (691)
113 ticagrelor.rn. (3951)
114 acetylsalicylic acid/ (212507)
115 asa.tw,kw. (56611)
116 aspirin.tw,kw. (140513)
117 ("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. (18867)
118 ("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. (22012)
119 (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. (3438)
120 (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. (439)
121 (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. (186)
122 (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. (271)
123 (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. (137)
124 (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. (162)
125 (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. (1718)
126 acetylsalicylic acid.rn. (158374)
127 or/96-126 (374118)
128 acetylsalicylic acid/cb [Drug Combination] (21253)
129 antithrombocytic agent/cb [Drug Combination] (2370)
130 clopidogrel/cb [Drug Combination] (9274)
131 prasugrel/cb [Drug Combination] (533)
132 purinergic P2Y receptor antagonist/cb [Drug Combination] (27)
133 ticagrelor/cb [Drug Combination] (414)
134 drug combination/ (56206)
135 ((combination* or combine* or combining) adj2 (agent or agents or drug or drugs)).tw,kw. (62908)
136 ((combination* or combine* or combining) adj2 (therap* or treatment*)).tw,kw. (262970)
137 ((dual or double) adj2 (therap* or treatment*)).tw,kw. (24189)
138 or/128-137 (401125)
139 127 and 138 (36893) [DAPT PT 2]

140	95 or 139 (39770) [DAPT PTS 1 AND 2]
141	90 and 140 (10221) [STENTS AND DAPT]
142	exp juvenile/ not (exp juvenile/ and exp adult/) (1888506)
143	Adolescent/ not (exp Adult/ and Adolescent/) (1028571)
144	exp Child/ not (exp Adult/ and exp Child/) (2731326)
145	exp Infant/ not (exp Adult/ and exp Infant/) (1507636)
146	or/142-145 (3570214)
147	141 not 146 (10178) [CHILD-ONLY REMOVED]
148	exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (42570215)
149	exp human/ or exp human experimentation/ or exp human experiment/ (33622929)
150	148 not 149 (8948879)
151	147 not 150 (10112) [ANIMAL-ONLY REMOVED]
152	(editorial or letter).pt. (2809807)
153	151 not 152 (9580) [OPINION PIECES REMOVED]
154	journal conference abstract.pt. (2314692)
155	153 not 154 (7714) [CONFERENCE ABSTRACTS REMOVED]
156	limit 155 to yr="2011-current" (3949) [DATE LIMIT]
157	meta-analysis/ (185535)
158	"systematic review"/ (111422)
159	"meta analysis (topic)"/ (28213)
160	(meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw. (231753)
161	(systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews" or technology assessment* or HTA or HTAs).tw. (270915)
162	biomedical technology assessment/ (20495)
163	(cochrane or health technology assessment or evidence report).jw. (34056)
164	((indirect* or mixed or multi-treatment*) adj2 compar*).tw. (8594)
165	((network* or network-based) adj (MA or MAs)).kw,tw. (11)
166	or/157-165 (541812)
167	156 and 166 (383) [REVIEWS]
168	exp practice guideline/ (394445)
169	(guideline* or standards or recommendation*).ti. (239243)
170	(expert consensus or consensus statement* or consensus conference* or practice parameter* or position statement* or policy statement* or CPG or CPGs).tw. (93481)
171	or/168-170 (636803)
172	156 and 171 (288) [GUIDELINES]
173	167 or 172 (618) [REVIEWS OR GUIDELINES]
174	173 use emez (492) [EMBASE RECORDS]
175	85 or 174 (749) [MEDLINE AND EMBASE RECORDS]
176	remove duplicates from 175 (593) [TOTAL UNIQUE RECORDS]
177	176 use ppez (247) [MEDLINE UNIQUE RECORDS]
178	176 use emez (346) [EMBASE UNIQUE RECORDS]

Cochrane Library
Search Name: DAPT PCI
Date Run: 12/08/16 14:47:40.409
Description: 2016 Aug 12 - Ottawa Heart Institute (Final)

ID	Search	Hits
#1	[mh Stents]	4162
#2	(stent or stents or stented or stenting):ti,ab,kw	8289
#3	(DES or DESs):ti,ab,kw	6112
#4	(Strecker* or Supremo* or WallFlex* or Wallstent*):ti,ab,kw	63
#5	{or #1-#4}	13700
#6	((dual or double) next (antiplatelet* or anti-platelet*)):ti,ab,kw	591
#7	(DAPT or DAPTs):ti,ab,kw	146
#8	#6 or #7	606
#9	[mh "Platelet Aggregation Inhibitors"]	3414
#10	(antiplatelet* or (anti next platelet*)):ti,ab,kw	2928
#11	(platelet* near/2 inhibit*):ti,ab,kw	4546
#12	"thrombocyte aggregation" next inhibit*:ti,ab,kw	149
#13	[mh "Purinergic P2Y Receptor Antagonists"]	165
#14	((P2Y or P2Y1 or P2Y12 or P2Y2) next ((receptor next antagonist*) or (purinoceptor next antagonist*))):ti,ab,kw	186
#15	("ADP receptor" next (antagonist* or blocker*)):ti,ab,kw	45
#16	("adenosine diphosphate receptor" next (antagonist* or blocker*)):ti,ab,kw	11
#17	clopidogrel*:ti,ab,kw	2961
#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):ti,ab,kw	43
#19	(duocover or duoplavin):ti,ab,kw	0
#20	[mh "Prasugrel Hydrochloride"]	155
#21	(prasugrel or "CS 747" or CS747 or effient or efient or "LY 640315" or LY640315):ti,ab,kw	433
#22	ticagrelor:ti,ab,kw	345
#23	("AZD 6140" or AZD6140 or brilinta or brilique or possia):ti,ab,kw	21
#24	[mh ^Aspirin]	4755
#25	asa:ti,ab,kw	8945
#26	aspirin:ti,ab,kw	8944
#27	("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):ti,ab,kw	4685
#28	("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"):ti,ab,kw	4896
#29	(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):ti,ab,kw	144
#30	(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):ti,ab,kw	11
#31	(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):ti,ab,kw	9

#32 (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):ti,ab,kw 8
#33 (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):ti,ab,kw 6
#34 (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):ti,ab,kw 3
#35 (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"):ti,ab,kw 19
#36 {or #9-#35} 23203
#37 [mh ^"Drug Combinations"] 10127
#38 [mh ^"Drug Therapy, Combination"] 27392
#39 [mh ^"Combined Modality Therapy"] 13376
#40 ((combination* or combine* or combining) near/2 (agent or agents or drug or drugs)):ti,ab,kw 60119
#41 ((combination* or combine* or combining) near/2 (therap* or treatment*)):ti,ab,kw 54300
#42 ((dual or double) near/2 (therap* or treatment*)):ti,ab,kw 14658
#43 {or #37-#42} 92404
#44 #36 and #43 4556
#45 #8 or #44 4606
#46 #5 and #45 792
#47 [mh Adolescent] not ([mh Adult] and [mh Adolescent]) 85176
#48 [mh Child] not ([mh Adult] and [mh Child]) 145
#49 [mh infant] not ([mh Adult] and [mh Infant]) 14350
#50 {or #47-#49} 98204
#51 #46 not #50 Publication Year from 2011 to 2016 482

DSR - 18
DARE - 20

PubMed (*publisher-supplied and most recent records only*)

Search	Query	Items found
#84	Search #81 OR #83	13
#83	Search #79 AND #82	11
#82	Search publisher[sb]	504950
#81	Search #79 AND #80	2
#80	Search 2016/08/01:2016/08/12[edat]	36590
#79	Search #67 OR #78	344
#78	Search #57 AND #77	116
#77	Search #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76	908040
#76	Search expert consensus[tw] OR consensus statement*[tw] OR consensus conference*[tw] OR practice parameter*[tw] OR position statement*[tw] OR policy statement*[tw] OR CPG[tw] OR CPGs[tw]	43470
#75	Search guideline*[ti] OR standards[ti] OR recommendation*[ti]	105806

Search	Query	Items found
#74	Search Consensus Development Conference, NIH[pt]	745
#73	Search Consensus Development Conference[pt]	10104
#72	Search standards[MeSH Subheading]	599162
#71	Search Practice Guideline[pt]	21687
#70	Search Guideline[pt]	28074
#69	Search Clinical Protocols[mesh]	138912
#68	Search "Guidelines as Topic"[mesh]	129112
#67	Search #57 AND #66	275
#66	Search #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65	745387
#65	Search network MA[tw] OR network MAs[tw] OR network-based MA[tw] OR network-based MAs[tw]	1249
#64	Search (indirect*[tw] OR mixed[tw] OR multi-treatment*[tw]) AND compar*[tw]	144871
#63	Search "Cochrane Database Syst Rev"[Journal:__jrid21711] OR "health technology assessment winchester, england"[Journal] OR "Evid Rep Technol Assess (Full Rep)"[Journal] OR "Evid Rep Technol Assess (Summ)"[Journal] OR "Int J Technol Assess Health Care"[Journal] OR "GMS Health Technol Assess"[Journal] OR "Health Technol Assess (Rockv)"[Journal] OR "Health Technol Assess Rep"[Journal] Schema: nomesh	15782
#62	Search Technology assessment, biomedical[mesh]	9647
#61	Search systematic review*[tw] OR systematic overview*[tw] OR evidence-based review*[tw] OR evidence-based overview*[tw] OR (evidence[tw] AND (review*[tw] OR overview*[tw])) or meta-review*[tw] OR meta-overview*[tw] OR meta-synthes*[tw] OR rapid review*[tw] OR "review of reviews"[tw] OR technology assessment*[tw] OR HTA[tw] OR HTAs[tw]	426817
#60	Search meta-analy*[tw] OR metanaly*[tw] OR metaanaly*[tw] OR met analy*[tw] OR integrative research[tw] OR integrative review*[tw] OR integrative overview*[tw] OR research integration[tw] OR research overview*[tw] OR collaborative review*[tw]	123243
#59	Search meta analysis[pt]	66921
#58	Search systematic[sb]	292597
#57	Search #55 AND #56	1578
#56	Search ("2011"[Date - Publication] : "3000"[Date - Publication])	5764101
#55	Search #53 NOT #54	3218
#54	Search comment[pt] OR editorial[pt] OR interview[pt] OR letter[pt] OR news[pt] OR newspaper article[pt]	1708012
#53	Search #51 NOT #52	3483
#52	Search Animals[mesh] NOT (Animals[mesh] AND Humans[mesh])	4240793
#51	Search #46 NOT #50	3526
#50	Search #47 OR #48 OR #49	1643703
#49	Search Infant[mesh] not (Adult[mesh] and Infant[mesh])	743940

Search	Query	Items found
#48	Search Child[mesh] not (Adult[mesh] and Child[mesh])	1051770
#47	Search Adolescent[mesh] not (Adult[mesh] and Adolescent[mesh])	516995
#46	Search #5 and #45	3534
#45	Search #8 or #44	26956
#44	Search #36 and #43	26352
#43	Search #37 OR #38 OR #39 OR #40 OR #41 OR #42	1224394
#42	Search (dual[tw] OR double[tw]) AND (therap*[tw] OR treatment*[tw])	241590
#41	Search (combination*[tw] OR combine*[tw] OR combining[tw]) AND (therap*[tw] OR treatment*[tw])	872093
#40	Search (combination*[tw] OR combine*[tw] OR combining[tw]) AND (agent[tw] OR agents[tw] OR drug[tw] OR drugs[tw])	732690
#39	Search Combined Modality Therapy[mesh:noexp]	152069
#38	Search Drug Therapy, Combination[mesh:noexp]	147121
#37	Search Drug Combinations[mesh:noexp]	63994
#36	Search #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35	158701
#35	Search tapal[tw] OR temagin[tw] OR tevapirin[tw] OR "th 2152"[tw] OR "thrombo-aspilets"[tw] OR treupahlin[tw] OR treuphalin[tw] OR tromalyt[tw] OR tromcor[tw] OR turivital[tw] OR verin[tw] OR vitalink[tw] OR xaxa[tw] OR "zero-order release"[tw]	641
#34	Search reumyl[tw] OR rhodine[tw] OR rhonal[tw] OR ronal[tw] OR salacetin[tw] OR salacetogen[tw] OR saletin[tw] OR salisalido[tw] OR sargepirine[tw] OR soldral[tw] OR solpyron[tw] OR solucetyl[tw] OR solupsa[tw] OR spren[tw]	16
#33	Search naspro[tw] OR novasen[tw] OR "nu seal"[tw] OR "nu seals"[tw] OR nuseal[tw] OR nuseals[tw] OR "ortho acetoxybenzoate"[tw] OR "ortho acetoxybenzoic"[tw] OR ostoprin[tw] OR pancemol[tw] OR paracin[tw] OR paynocil[tw] OR pengo[tw] OR "platet 300 cleartab"[tw] OR plewin[tw] OR polopiryna[tw] OR premaspin[tw] OR primaspan[tw] OR proprin[tw] OR pyronoval[tw]	21
#32	Search genasprin[tw] OR globentyl[tw] OR godamed[tw] OR gotosan[tw] OR helicon[tw] OR idotyl[tw] OR infatabs[tw] OR istopirin[tw] OR istopyrine[tw] OR ivepirine[tw] OR juvepirine[tw] OR keypo[tw] OR kilios[tw] OR "mcn r 358"[tw] OR measurin[tw] OR mejoral[tw] OR melabon[tw] OR micropyrin[tw] OR mikristin[tw] OR miniasal[tw] OR mycristin[tw]	103
#31	Search darosal[tw] OR dispirin[tw] OR dolean[tw] OR dolean[tw] OR dusil[tw] OR ecasil[tw] OR ecosprin[tw] OR egalgic[tw] OR emocin[tw] OR empirin[tw] OR encaprin[tw] OR encine[tw] OR endosprin[tw] OR entaprin[tw] OR entericin[tw] OR enteroprin[tw] OR enterosarine[tw] OR enterospirine[tw] OR entrophen[tw] OR eskotrin[tw] OR euthermine[tw] OR extren[tw]	12
#30	Search bebesan[tw] OR biprin[tw] OR bokey[tw] OR boxazin[tw] OR breoprin[tw] OR bufferin[tw] OR cafenol[tw] OR caprin[tw] OR cardioaspirina[tw] OR	68

Search	Query	Items found
	caspirin[tw] OR catalgine[tw] OR catalgix[tw] OR cemerit[tw] OR cemirit[tw] OR claradin[tw] OR claragine[tw] OR comoprin[tw] OR contrheuma[tw]	
#29	Search actorin[tw] OR acylpyrine[tw] OR acytosal[tw] OR adiro[tw] OR alabukun[tw] OR alasil[tw] OR "albyl-e"[tw] OR "alka seltzer"[tw] OR alkaspirin[tw] OR anasprin[tw] OR andol[tw] OR anopyrin[tw] OR ansin[tw] OR anthrom[tw] OR aptor[tw] OR arthralgyl[tw] OR asaflow[tw] OR asaphen[tw] OR asapor[tw] OR asatard[tw] OR asawin[tw] OR aspec[tw] OR aspent[tw] OR aspex[tw] OR aspilets[tw] OR aspirem[tw] OR aspirgran[tw] OR aspirina[tw] OR aspirine[tw] OR aspirinine[tw] OR aspirisucre[tw] OR aspisol[tw] OR aspo cid[tw] OR aspro[tw] OR asrina[tw] OR asrivo[tw] OR asta[tw] OR asteric[tw] OR astrix[tw]	718
#28	Search "2 acetoxybenzoate"[tw] OR "8-hour bayer"[tw] OR acenterine[tw] OR acesal[tw] OR acetan[tw] OR acetard[tw] OR aceticil[tw] OR aceticyl[tw] OR acetonyl[tw] OR acetophen[tw] OR acetosal[tw] OR "acetosalicylic acid"[tw] OR acetosalin[tw] OR acetosalum[tw] OR "acetyl salicylate"[tw] OR "acetyl salicylic acid"[tw] OR "acetylic salicylic acid"[tw] OR acetylin[tw] OR acetylo[tw] OR acetylon[tw] OR "acetylosalicylic acid"[tw] OR acetylsal[tw] OR "acetylsalicyclic acid"[tw] OR acetylsalicyl[tw] OR acetylsalicylate[tw] OR "acetylsalicylic acid"[tw] OR "acetylsalycic acid"[tw] OR "acetylsalycylic acid"[tw] OR acetysal[tw] OR acidulatum[tw] OR "acidum acetyl salicylicum"[tw] OR "acidum acetylosalicylicum"[tw] OR "acidum acetylsalicylicum"[tw]	10173
#27	Search "2-(Acetyloxy)benzoic Acid"[tw] OR "acetylsalicylic acid"[tw] OR acetysal[tw] OR acylpyrin[tw] OR aloxiprimum[tw] OR colfarit[tw] OR dispril[tw] OR easprin[tw] OR ecotrin[tw] OR endosprin[tw] OR magnecyl[tw] OR micristin[tw] OR polopirin[tw] OR polopiryna[tw] OR solprin[tw] OR solupsan[tw] OR zorprin[tw]	8794
#26	Search aspirin[tw]	58693
#25	Search asa[tw]	20726
#24	Search Aspirin[mesh:noexp]	40309
#23	Search "AZD 6140"[tw] OR AZD6140[tw] OR brilinta[tw] OR brilique[tw] OR possia[tw]	89
#22	Search ticagrelor[tw]	1330
#21	Search prasugrel[tw] OR "CS 747"[tw] OR CS747[tw] OR effient[tw] OR efient[tw] OR "LY 640315"[tw] OR LY640315[tw]	1656
#20	Search Prasugrel Hydrochloride[mesh]	888
#19	Search duocover[tw] OR duoplavin[tw]	0
#18	Search clopilet[tw] OR grepid[tw] OR iscover[tw] OR "PCR 4099"[tw] OR PCR4099[tw] OR plavix[tw] OR "SC 25989C"[tw] OR "SC 25990C"[tw] OR "SR 25989"[tw] OR zopya[tw] OR zylagren[tw] OR zyllt[tw]	264
#17	Search clopidogrel*[tw]	11225
#16	Search adenosine diphosphate receptor antagonist*[tw] or adenosine diphosphate receptor blocker*[tw]	69
#15	Search ADP receptor antagonist*[tw] or ADP receptor blocker*[tw]	256
#14	Search ((P2Y[tw] OR P2Y1[tw] OR P2Y12[tw] OR P2Y2[tw]) AND (receptor	2616

Search	Query	Items found
	antagonist*[tw] OR purinoceptor antagonist*[tw]))	
#13	Search Purinergic P2Y Receptor Antagonists[mesh]	1127
#12	Search thrombocyte aggregation inhibit*[tw]	78
#11	Search platelet*[tw] AND inhibit*[tw] Schema: nomesh	83230
#10	Search antiplatelet*[tw] OR anti-platelet*[tw]	23489
#9	Search Platelet Aggregation Inhibitors[mesh]	29783
#8	Search #6 OR #7	3661
#7	Search DAPT[tw] OR DAPTs[tw]	1020
#6	Search dual antiplatelet*[tw] OR dual anti-platelet*[tw] OR double antiplatelet*[tw] OR double anti-platelet*[tw]	3101
#5	Search #1 OR #2 OR #3 OR #4	108007
#4	Search Strecker*[tw] OR Supremo*[tw] OR WallFlex*[tw] OR Wallstent*[tw]	1554
#3	Search DES[tw] OR DESs[tw]	22435
#2	Search stent[tw] OR stents[tw] OR stented[tw] OR stenting[tw]	88856
#1	Search Stents[mesh]	60825

DAPT – PCI Add-On
Overlap with Previous Search, Removed
2016 Aug 13

MEDLINE

Database: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:

---

1 exp Stents/ (62028)
2 (stent or stents or stented or stenting).tw,kw. (77864)
3 (DES or DESs).tw,kw. (19836)
4 (Strecker* or Supremo* or WallFlex* or Wallstent*).tw,kw. (1565)
5 or/1-4 (106535)
6 ((dual or double) adj (antiplatelet* or anti-platelet*)).tw,kw. (3060)
7 (DAPT or DAPTs).tw,kw. (1046)
8 6 or 7 (3642)
9 Platelet Aggregation Inhibitors/ (30286)
10 (antiplatelet* or anti-platelet*).tw,kw. (23852)
11 (platelet* adj2 inhibit*).tw,kw. (14919)
12 thrombocyte aggregation inhibit*.tw,kw. (83)
13 Purinergic P2Y Receptor Antagonists/ (1180)
14 ((P2Y or P2Y1 or P2Y12 or P2Y2) adj (receptor antagonist* or purinoceptor antagonist*)).tw,kw. (469)
15 (ADP receptor adj (antagonist* or blocker*)).tw,kw. (258)
16 (adenosine diphosphate receptor adj (antagonist* or blocker*)).tw,kw. (70)

17 clopidogrel*.tw,kw. (9874)
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,kw. (270)
19 (duocover or duoplavin).tw,kw. (0)
20 clopidogrel.rn. (7187)
21 Prasugrel Hydrochloride/ (917)
22 (prasugrel or CS 747 or CS747 or effient or efient or LY 640315 or LY640315).tw,kw. (1542)
23 prasugrel.rn. (917)
24 ticagrelor.tw,kw. (1246)
25 (AZD 6140 or AZD6140 or brilinta or brilique or possia).tw,kw. (87)
26 ticagrelor.rn. (659)
27 Aspirin/ (40894)
28 asa.tw,kw. (20853)
29 aspirin.tw,kw. (42191)
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,kw. (8194)
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,kw. (9735)
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,kw. (695)
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,kw. (71)
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,kw. (12)
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,kw. (101)
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,kw. (21)
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,kw. (15)
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,kw. (648)
39 aspirin.rn. (40894)
40 or/9-39 (119277)
41 Drug Combinations/ (64989)
42 Drug Therapy, Combination/ (149637)
43 Combined Modality Therapy/ (154632)
44 ((combination* or combine* or combining) adj2 (agent or agents or drug or drugs)).tw,kw. (26941)
45 ((combination* or combine* or combining) adj2 (therap* or treatment*)).tw,kw. (110788)

46	((dual or double) adj2 (therap* or treatment*)).tw,kw. (9301)
47	or/41-46 (455154)
48	40 and 47 (11764)
49	8 or 48 (12602)
50	5 and 49 (2863)
51	Adolescent/ not (exp Adult/ and Adolescent/) (530953)
52	exp Child/ not (exp Adult/ and exp Child/) (1078580)
53	exp Infant/ not (exp Adult/ and exp Infant/) (760098)
54	or/51-53 (1681845)
55	50 not 54 (2858)
56	exp Animals/ not (exp Animals/ and Humans/) (4299057)
57	55 not 56 (2835)
58	(comment or editorial or interview or letter or news or newspaper article).pt. (1732215)
59	57 not 58 (2587)
60	limit 59 to yr="2011-current" (1422)
61	limit 60 to systematic reviews (150)
62	meta analysis.pt. (72368)
63	exp meta-analysis as topic/ (15295)
64	(meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw. (103844)
65	(systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or rapid review* or "review of reviews" or technology assessment* or HTA or HTAs).tw. (125756)
66	exp Technology assessment, biomedical/ (9795)
67	(cochrane or health technology assessment or evidence report).jw. (18216)
68	((indirect* or mixed or multi-treatment*) adj2 compar*).tw. (3521)
69	((network* or network-based) adj (MA or MAs)).kw,tw. (3)
70	or/62-69 (230882)
71	60 and 70 (116)
72	61 or 71 (172)
73	exp Guidelines as Topic/ (131858)
74	exp Clinical Protocols/ (142115)
75	Guideline.pt. (15920)
76	Practice Guideline.pt. (21740)
77	standards.fs. (609373)
78	Consensus Development Conference.pt. (10115)
79	Consensus Development Conference, NIH.pt. (756)
80	(guideline* or standards or recommendation*).ti. (107308)
81	(expert consensus or consensus statement* or consensus conference* or practice parameter* or position statement* or policy statement* or CPG or CPGs).tw. (41038)
82	or/73-81 (920792)
83	60 and 82 (110)
84	72 or 83 (257)
85	exp Percutaneous Coronary Intervention/ (42311)
86	(percutaneous coronary adj3 (intervention? or revascular* or re-vascular*)).tw,kw. (23498)
87	(PCI or PCIs or PPCI or PPCIs).tw,kw. (18670)
88	(coronary adj2 balloon adj (dilation* or dilatation*)).tw,kw. (29)
89	(coronary angioplast* adj2 balloon).tw,kw. (246)
90	PTCA.tw,kw. (6370)

91 Angioplasty, Balloon, Laser-Assisted/ (358)
92 (laser-assisted adj2 angioplast*).tw,kw. (171)
93 (laser balloon* adj2 angioplast*).tw,kw. (37)
94 percutaneous transluminal laser angioplast*.tw,kw. (25)
95 PTLA.tw,kw. (44)
96 or/85-95 (57794)
97 96 and 49 (2726)
98 97 not 54 (2724)
99 98 not 56 (2713)
100 99 not 58 (2501)
101 limit 100 to yr="2011-current" (1194)
102 limit 101 to systematic reviews (129)
103 101 and 70 (92)
104 101 and 82 (107)
105 102 or 103 or 104 (229)
106 105 not 84 (83)

Embase

Database: Embase <1980 to 2016 Week 33>
Search Strategy:

---

1 exp stent/ (129038)
2 (stent or stents or stented or stenting).tw,kw. (124348)
3 (DES or DESs).tw,kw. (50438)
4 (Strecker* or Supremo* or WallFlex* or Wallstent*).tw,kw. (2337)
5 or/1-4 (194067)
6 ((dual or double) adj (antiplatelet* or anti-platelet*)).tw,kw. (6191)
7 (DAPT or DAPTs).tw,kw. (2065)
8 acetylsalicylic acid plus clopidogrel/ (324)
9 (duocover or duoplavin).tw,kw. (11)
10 or/6-9 (7469)
11 antithrombocytic agent/ (34232)
12 (antiplatelet* or anti-platelet*).tw,kw. (38259)
13 (platelet* adj2 inhibit*).tw,kw. (19390)
14 thrombocyte aggregation inhibit*.tw,kw. (182)
15 purinergic P2Y receptor antagonist/ (544)
16 ((P2Y or P2Y1 or P2Y12 or P2Y2) adj (receptor antagonist* or purinoceptor antagonist*)).tw,kw. (872)
17 (ADP receptor adj (antagonist* or blocker*)).tw,kw. (407)
18 (adenosine diphosphate receptor adj (antagonist* or blocker*)).tw,kw. (82)
19 clopidogrel/ (45883)
20 (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. (20240)
21 clopidogrel.rn. (39065)
22 prasugrel/ (5462)
23 (prasugrel or CS 747 or CS747 or effient or efient or LY 640315 or LY640315).tw,kw. (3083)
24 prasugrel.rn. (4453)
25 ticagrelor/ (4138)
26 ticagrelor.tw,kw. (2274)

27 (AZD 6140 or AZD6140 or brilinta or brilique or possia).tw,kw. (604)
28 ticagrelor.rn. (3318)
29 acetylsalicylic acid/ (171800)
30 asa.tw,kw. (35803)
31 aspirin.tw,kw. (98397)
32 ("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. (10681)
33 ("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. (12286)
34 (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. (2744)
35 (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. (370)
36 (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. (174)
37 (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. (170)
38 (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. (116)
39 (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. (147)
40 (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. (1071)
41 acetylsalicylic acid.rn. (158494)
42 or/11-41 (264320)
43 acetylsalicylic acid/cb [Drug Combination] (21271)
44 antithrombocytic agent/cb [Drug Combination] (2371)
45 clopidogrel/cb [Drug Combination] (9282)
46 prasugrel/cb [Drug Combination] (537)
47 purinergic P2Y receptor antagonist/cb [Drug Combination] (27)
48 ticagrelor/cb [Drug Combination] (419)
49 drug combination/ (56245)
50 ((combination* or combine* or combining) adj2 (agent or agents or drug or drugs)).tw,kw. (36034)
51 ((combination* or combine* or combining) adj2 (therap* or treatment*)).tw,kw. (152504)
52 ((dual or double) adj2 (therap* or treatment*)).tw,kw. (14919)
53 or/43-52 (261321)
54 42 and 53 (31983)
55 10 or 54 (33975)
56 5 and 55 (8179)

57 exp juvenile/ not (exp juvenile/ and exp adult/) (1890385)
58 Adolescent/ not (exp Adult/ and Adolescent/) (498271)
59 exp Child/ not (exp Adult/ and exp Child/) (1654439)
60 exp Infant/ not (exp Adult/ and exp Infant/) (748230)
61 or/57-60 (1890385)
62 56 not 61 (8140)
63 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (22610326)
64 exp human/ or exp human experimentation/ or exp human experiment/ (17396865)
65 63 not 64 (5214417)
66 62 not 65 (8083)
67 (editorial or letter).pt. (1459362)
68 66 not 67 (7667)
69 journal conference abstract.pt. (2315598)
70 68 not 69 (5801)
71 limit 70 to yr="2011-current" (2713)
72 meta-analysis/ (113483)
73 "systematic review"/ (111926)
74 "meta analysis (topic)"/ (28357)
75 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw. (128482)
76 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews" or technology assessment* or HTA or HTAs).tw. (146050)
77 biomedical technology assessment/ (11812)
78 (cochrane or health technology assessment or evidence report).jw. (15869)
79 ((indirect* or mixed or multi-treatment*) adj2 compar*).tw. (5087)
80 ((network* or network-based) adj (MA or MAs)).kw,tw. (8)
81 or/72-80 (319711)
82 71 and 81 (282)
83 exp practice guideline/ (373455)
84 (guideline* or standards or recommendation*).ti. (132218)
85 (expert consensus or consensus statement* or consensus conference* or practice parameter* or position statement* or policy statement* or CPG or CPGs).tw. (52534)
86 or/83-85 (484850)
87 71 and 86 (266)
88 82 or 87 (496)
89 exp percutaneous coronary intervention/ (75723)
90 (percutaneous coronary adj3 (intervention? or revascular* or re-vascular*)).tw,kw. (41969)
91 (PCI or PCIs or PPCI or PPCIs).tw,kw. (41738)
92 (coronary adj2 balloon adj (dilation* or dilatation*)).tw,kw. (38)
93 (coronary angioplast* adj2 balloon).tw,kw. (285)
94 PTCA.tw,kw. (8371)
95 laser angioplasty/ (900)
96 (laser-assisted adj2 angioplast*).tw,kw. (209)
97 (laser balloon* adj2 angioplast*).tw,kw. (42)
98 percutaneous transluminal laser angioplast*.tw,kw. (30)
99 PTLA.tw,kw. (55)
100 or/88-99 (97434)
101 100 and 55 (7118)

102 101 not 61 (7105)
103 102 not 65 (7093)
104 103 not 67 (6744)
105 104 not 69 (5373)
106 limit 105 to yr="2011-current" (2486)
107 81 and 106 (365)
108 86 and 106 (370)
109 "201633".em. (28279) [UPDATE WEEK]
110 88 and 109 (4)
111 88 not 110 (492)
112 108 not 111 (106) [UNIQUE EMBASE RECORDS]

Cochrane Library

Search Name: DAPT PCI - PCI Additions (overlap with original search, removed)
Date Run: 13/08/16 22:57:17.407
Description: 2016 Aug 13 - Ottawa Heart Institute (Final)

ID	Search	Hits
#1	[mh Stents]	4162
#2	(stent or stents or stented or stenting):ti,ab,kw	8289
#3	(DES or DESs):ti,ab,kw	6112
#4	(Strecker* or Supremo* or WallFlex* or Wallstent*):ti,ab,kw	63
#5	{or #1-#4}	13700
#6	((dual or double) next (antiplatelet* or anti-platelet*)):ti,ab,kw	591
#7	(DAPT or DAPTs):ti,ab,kw	146
#8	#6 or #7	606
#9	[mh "Platelet Aggregation Inhibitors"]	3414
#10	(antiplatelet* or (anti next platelet*)):ti,ab,kw	2928
#11	(platelet* near/2 inhibit*):ti,ab,kw	4546
#12	"thrombocyte aggregation" next inhibit*:ti,ab,kw	149
#13	[mh "Purinergic P2Y Receptor Antagonists"]	165
#14	((P2Y or P2Y1 or P2Y12 or P2Y2) next ((receptor next antagonist*) or (purinoceptor next antagonist*))):ti,ab,kw	186
#15	("ADP receptor" next (antagonist* or blocker*)):ti,ab,kw	45
#16	("adenosine diphosphate receptor" next (antagonist* or blocker*)):ti,ab,kw	11
#17	clopidogrel*:ti,ab,kw	2961
#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):ti,ab,kw	43
#19	(duocover or duoplavin):ti,ab,kw	0
#20	[mh "Prasugrel Hydrochloride"]	155
#21	(prasugrel or "CS 747" or CS747 or effient or efient or "LY 640315" or LY640315):ti,ab,kw	433
#22	ticagrelor:ti,ab,kw	345
#23	("AZD 6140" or AZD6140 or brilinta or brilique or possia):ti,ab,kw	21
#24	[mh ^Aspirin]	4755
#25	asa:ti,ab,kw	8945
#26	aspirin:ti,ab,kw	8944
#27	("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):ti,ab,kw	4685

#28	("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"):ti,ab,kw 4896
#29	(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):ti,ab,kw 144
#30	(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):ti,ab,kw 11
#31	(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):ti,ab,kw 9
#32	(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):ti,ab,kw 8
#33	(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):ti,ab,kw 6
#34	(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):ti,ab,kw 3
#35	(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"):ti,ab,kw 19
#36	{or #9-#35} 23203
#37	[mh ^"Drug Combinations"] 10127
#38	[mh ^"Drug Therapy, Combination"] 27392
#39	[mh ^"Combined Modality Therapy"] 13376
#40	((combination* or combine* or combining) near/2 (agent or agents or drug or drugs)):ti,ab,kw 60119
#41	((combination* or combine* or combining) near/2 (therap* or treatment*)):ti,ab,kw 54300
#42	((dual or double) near/2 (therap* or treatment*)):ti,ab,kw 14658
#43	{or #37-#42} 92404
#44	#36 and #43 4556
#45	#8 or #44 4606
#46	#5 and #45 792
#47	[mh Adolescent] not ([mh Adult] and [mh Adolescent]) 85176
#48	[mh Child] not ([mh Adult] and [mh Child]) 145
#49	[mh infant] not ([mh Adult] and [mh Infant]) 14350
#50	{or #47-#49} 98204
#51	#46 not #50 Publication Year from 2011 to 2016 482
#52	[mh "Percutaneous Coronary Intervention"] 4599
#53	("percutaneous coronary" near/3 (intervention* or revascular* or re-vascular*)):ti,ab,kw 5125
#54	(PCI or PCIs or PPCI or PPCIs):ti,ab,kw 3563
#55	(coronary near/2 balloon next (dilation* or dilatation*)):ti,ab,kw 11
#56	(coronary next angioplast* near/2 balloon):ti,ab,kw 70
#57	PTCA:ti,ab,kw 924

#58 [mh "Angioplasty, Balloon, Laser-Assisted"] 31
#59 ("laser-assisted" near/2 angioplast*):ti,ab,kw 36
#60 (laser next balloon* near/2 angioplast*):ti,ab,kw 7
#61 ("percutaneous transluminal laser" next angioplasty*):ti,ab,kw 2
#62 PTLA:ti,ab,kw 4
#63 {or #52-#62} 8226
#64 #63 and #45 826
#65 #64 not #50 Publication Year from 2011 to 2016 437
#66 #65 not #51 151

DARE - 9

PubMed
(*publisher-supplied and most recent records only*)

Search	Query	Items found
#109	Search #108 NOT #84	3
#108	Search #106 or #107	9
#107	Search #104 AND #82	8
#106	Search #104 AND #105	2
#105	Search 2016/08/01:2016/08/13[edat]	36590
#104	Search #102 OR #103	322
#103	Search (#101 AND #77)	116
#102	Search #101 AND #66	247
#101	Search #100 AND #56	1452
#100	Search #99 NOT #54	3436
#99	Search #98 NOT #52	3685
#98	Search #97 NOT #50	3707
#97	Search #96 and #45	3710
#96	Search #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95	58977
#95	Search PTLA[tw]	44
#94	Search percutaneous transluminal laser angioplast*[tw]	24
#93	Search laser balloon*[tw] AND angioplast*[tw]	45
#92	Search laser-assisted[tw] AND angioplast*[tw]	513
#91	Search Angioplasty, Balloon, Laser-Assisted[mesh]	356
#90	Search PTCA[tw]	6350
#89	Search coronary angioplast*[tw] AND balloon[tw] Schema: syn	9693
#88	Search coronary balloon[tw] AND (dilation*[tw] OR dilatation*[tw])	76
#87	Search PCI[tw] OR PCIs[tw] OR PPCI[tw] OR PPCIs[tw]	18691
#86	Search percutaneous coronary[tw] AND (intervention*[tw] OR revascular*[tw] OR	26746

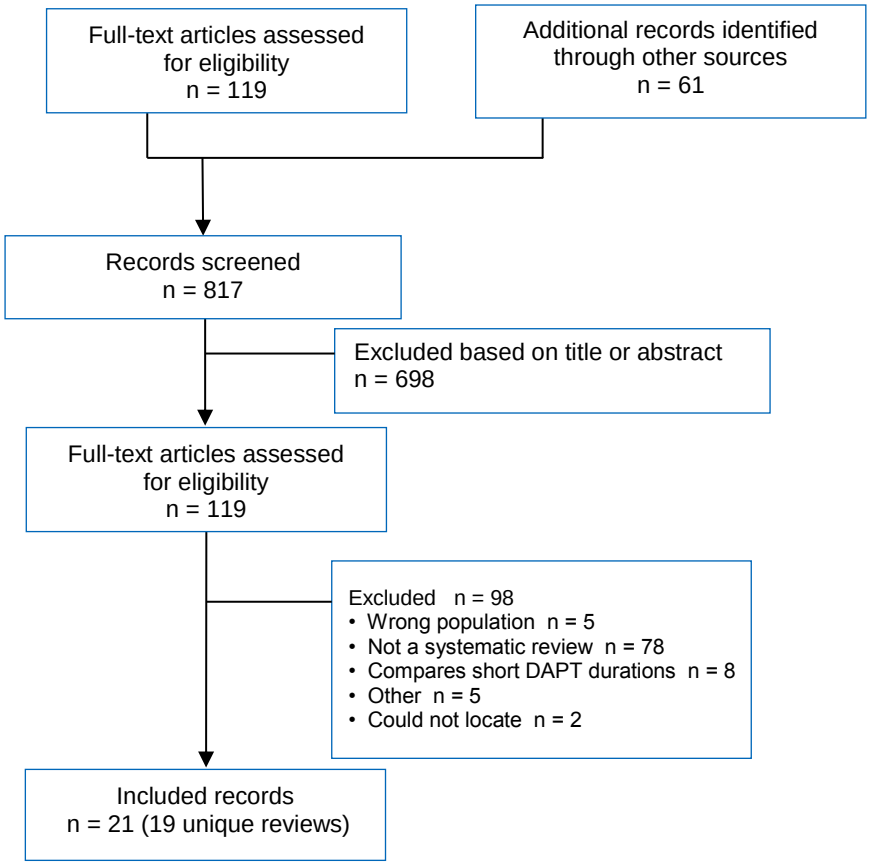
Search	Query	Items found
	re-vascular*[tw])	
#85	Search Percutaneous Coronary Intervention[mesh]	41523
#84	Search #81 OR #83	13
#83	Search #79 AND #82	11
#82	Search publisher[sb]	504950
#81	Search #79 AND #80	2
#80	Search 2016/08/01:2016/08/12[edat]	36590
#79	Search #67 OR #78	344
#78	Search #57 AND #77	116
#77	Search #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76	908040
#76	Search expert consensus[tw] OR consensus statement*[tw] OR consensus conference*[tw] OR practice parameter*[tw] OR position statement*[tw] OR policy statement*[tw] OR CPG[tw] OR CPGs[tw]	43470
#75	Search guideline*[ti] OR standards[ti] OR recommendation*[ti]	105806
#74	Search Consensus Development Conference, NIH[pt]	745
#73	Search Consensus Development Conference[pt]	10104
#72	Search standards[MeSH Subheading]	599162
#71	Search Practice Guideline[pt]	21687
#70	Search Guideline[pt]	28074
#69	Search Clinical Protocols[mesh]	138912
#68	Search "Guidelines as Topic"[mesh]	129112
#67	Search #57 AND #66	275
#66	Search #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65	745387
#65	Search network MA[tw] OR network MAs[tw] OR network-based MA[tw] OR network-based MAs[tw]	1249
#64	Search (indirect*[tw] OR mixed[tw] OR multi-treatment*[tw]) AND compar*[tw]	144871
#63	Search "Cochrane Database Syst Rev"[Journal:__jrid21711] OR "health technology assessment winchester, england"[Journal] OR "Evid Rep Technol Assess (Full Rep)"[Journal] OR "Evid Rep Technol Assess (Summ)"[Journal] OR "Int J Technol Assess Health Care"[Journal] OR "GMS Health Technol Assess"[Journal] OR "Health Technol Assess (Rockv)"[Journal] OR "Health Technol Assess Rep"[Journal]	15782
#62	Search Technology assessment, biomedical[mesh]	9647
#61	Search systematic review*[tw] OR systematic overview*[tw] OR evidence-based review*[tw] OR evidence-based overview*[tw] OR (evidence[tw] AND (review*[tw] OR overview*[tw])) or meta-review*[tw] OR meta-overview*[tw] OR meta-synthes*[tw] OR rapid review*[tw] OR "review of reviews"[tw] OR technology assessment*[tw] OR HTA[tw] OR HTAs[tw]	426817
#60	Search meta-analy*[tw] OR metanaly*[tw] OR metaanaly*[tw] OR met analy*[tw]	123243

Search	Query	Items found
	OR integrative research[tw] OR integrative review*[tw] OR integrative overview*[tw] OR research integration[tw] OR research overview*[tw] OR collaborative review*[tw]	
#59	Search meta analysis[pt]	66921
#58	Search systematic[sb]	292597
#57	Search #55 AND #56	1578
#56	Search ("2011"[Date - Publication] : "3000"[Date - Publication])	5764101
#55	Search #53 NOT #54	3218
#54	Search comment[pt] OR editorial[pt] OR interview[pt] OR letter[pt] OR news[pt] OR newspaper article[pt]	1708012
#53	Search #51 NOT #52	3483
#52	Search Animals[mesh] NOT (Animals[mesh] AND Humans[mesh])	4240793
#51	Search #46 NOT #50	3526
#50	Search #47 OR #48 OR #49	1643703
#49	Search Infant[mesh] not (Adult[mesh] and Infant[mesh])	743940
#48	Search Child[mesh] not (Adult[mesh] and Child[mesh])	1051770
#47	Search Adolescent[mesh] not (Adult[mesh] and Adolescent[mesh])	516995
#46	Search #5 and #45	3534
#45	Search #8 or #44	26956
#44	Search #36 and #43	26352
#43	Search #37 OR #38 OR #39 OR #40 OR #41 OR #42	1224394
#42	Search (dual[tw] OR double[tw]) AND (therap*[tw] OR treatment*[tw])	241590
#41	Search (combination*[tw] OR combine*[tw] OR combining[tw]) AND (therap*[tw] OR treatment*[tw])	872093
#40	Search (combination*[tw] OR combine*[tw] OR combining[tw]) AND (agent[tw] OR agents[tw] OR drug[tw] OR drugs[tw]) Schema: syn	732690
#39	Search Combined Modality Therapy[mesh:noexp]	152069
#38	Search Drug Therapy, Combination[mesh:noexp]	147121
#37	Search Drug Combinations[mesh:noexp]	63994
#36	Search #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35	158701
#35	Search tapal[tw] OR temagin[tw] OR tevapirin[tw] OR "th 2152"[tw] OR "thrombo-aspilets"[tw] OR treupahlin[tw] OR treuphalin[tw] OR tromalyt[tw] OR tromcor[tw] OR turivital[tw] OR verin[tw] OR vitalink[tw] OR xaxa[tw] OR "zero-order release"[tw]	641
#34	Search reumyl[tw] OR rhodine[tw] OR rhonal[tw] OR ronal[tw] OR salacetin[tw] OR salacetogen[tw] OR saletin[tw] OR salisalido[tw] OR sargepirine[tw] OR soldral[tw] OR solpyron[tw] OR solucetyl[tw] OR solupsa[tw] OR spren[tw]	16

Search	Query	Items found
#33	Search naspro[tw] OR novasen[tw] OR "nu seal"[tw] OR "nu seals"[tw] OR nuseal[tw] OR nuseals[tw] OR "ortho acetoxybenzoate"[tw] OR "ortho acetoxybenzoic"[tw] OR ostoprin[tw] OR pancemol[tw] OR paracin[tw] OR paynocil[tw] OR pengo[tw] OR "platet 300 cleartab"[tw] OR plewin[tw] OR polopiryna[tw] OR premaspin[tw] OR primaspan[tw] OR proprin[tw] OR pyronoval[tw]	21
#32	Search genasprin[tw] OR globentyl[tw] OR godamed[tw] OR gotosan[tw] OR helicon[tw] OR idotyl[tw] OR infatabs[tw] OR istopirin[tw] OR istopyrine[tw] OR ivepirine[tw] OR juvepirine[tw] OR keypo[tw] OR kilios[tw] OR "mcn r 358"[tw] OR measurin[tw] OR mejoral[tw] OR melabon[tw] OR micropyrin[tw] OR mikristin[tw] OR miniasal[tw] OR mycristin[tw]	103
#31	Search darosal[tw] OR dispirin[tw] OR dolean[tw] OR dolean[tw] OR dusil[tw] OR ecasil[tw] OR ecosprin[tw] OR egalgic[tw] OR emocin[tw] OR empirin[tw] OR encaprin[tw] OR encine[tw] OR endosprin[tw] OR entaprin[tw] OR entericin[tw] OR enteroprin[tw] OR enterosarine[tw] OR enterospirine[tw] OR entrophen[tw] OR eskotrin[tw] OR euthermine[tw] OR extren[tw]	12
#30	Search bebesan[tw] OR biprin[tw] OR bokey[tw] OR boxazin[tw] OR breoprin[tw] OR bufferin[tw] OR cafenol[tw] OR caprin[tw] OR cardioaspirina[tw] OR caspirin[tw] OR catalgine[tw] OR catalgix[tw] OR cemerit[tw] OR cemirit[tw] OR claradin[tw] OR claragine[tw] OR comoprin[tw] OR contrheuma[tw]	68
#29	Search actorin[tw] OR acylpyrine[tw] OR acytosal[tw] OR adiro[tw] OR alabukun[tw] OR alasil[tw] OR "albyl-e"[tw] OR "alka seltzer"[tw] OR alkaspirin[tw] OR anasprin[tw] OR andol[tw] OR anopyrin[tw] OR ansin[tw] OR anthrom[tw] OR aptor[tw] OR arthralgyl[tw] OR asaflow[tw] OR asaphen[tw] OR asapor[tw] OR asatard[tw] OR asawin[tw] OR aspec[tw] OR aspent[tw] OR aspex[tw] OR aspilets[tw] OR aspirem[tw] OR aspirgran[tw] OR aspirina[tw] OR aspirine[tw] OR aspirinine[tw] OR aspirisucre[tw] OR aspisol[tw] OR aspo cid[tw] OR aspro[tw] OR asrina[tw] OR asrivo[tw] OR asta[tw] OR asteric[tw] OR astrix[tw]	718
#28	Search "2 acetoxybenzoate"[tw] OR "8-hour bayer"[tw] OR acenterine[tw] OR acesal[tw] OR acetan[tw] OR acetard[tw] OR aceticil[tw] OR aceticyl[tw] OR acetonyl[tw] OR acetophen[tw] OR acetosal[tw] OR "acetosalicylic acid"[tw] OR acetosalin[tw] OR acetosalum[tw] OR "acetyl salicylate"[tw] OR "acetyl salicylic acid"[tw] OR "acetylic salicylic acid"[tw] OR acetylin[tw] OR acetylo[tw] OR acetylon[tw] OR "acetylosalicylic acid"[tw] OR acetylsal[tw] OR "acetylsalicyclic acid"[tw] OR acetylsalicyl[tw] OR acetylsalicylate[tw] OR "acetylsalicylic acid"[tw] OR "acetylsalycic acid"[tw] OR "acetylsalycylic acid"[tw] OR acetysal[tw] OR acidulatum[tw] OR "acidum acetyl salicylicum"[tw] OR "acidum acetylosalicylicum"[tw] OR "acidum acetylsalicylicum"[tw]	10173
#27	Search "2-(Acetyloxy)benzoic Acid"[tw] OR "acetylsalicylic acid"[tw] OR acetysal[tw] OR acylpyrin[tw] OR aloxiprimum[tw] OR colfarit[tw] OR dispril[tw] OR easprin[tw] OR ecotrin[tw] OR endosprin[tw] OR magnecyl[tw] OR micristin[tw] OR polopirin[tw] OR polopiryna[tw] OR solprin[tw] OR solupsan[tw] OR zorprin[tw]	8794
#26	Search aspirin[tw]	58693
#25	Search asa[tw]	20726
#24	Search Aspirin[mesh:noexp]	40309

Search	Query	Items found
#23	Search "AZD 6140"[tw] OR AZD6140[tw] OR brilinta[tw] OR brilique[tw] OR possia[tw]	89
#22	Search ticagrelor[tw]	1330
#21	Search prasugrel[tw] OR "CS 747"[tw] OR CS747[tw] OR effient[tw] OR efient[tw] OR "LY 640315"[tw] OR LY640315[tw]	1656
#20	Search Prasugrel Hydrochloride[mesh]	888
#19	Search duocover[tw] OR duoplavin[tw]	0
#18	Search clopilet[tw] OR grepid[tw] OR iscover[tw] OR "PCR 4099"[tw] OR PCR4099[tw] OR plavix[tw] OR "SC 25989C"[tw] OR "SC 25990C"[tw] OR "SR 25989"[tw] OR zopya[tw] OR zylagren[tw] OR zyllt[tw]	264
#17	Search clopidogrel*[tw]	11225
#16	Search adenosine diphosphate receptor antagonist*[tw] or adenosine diphosphate receptor blocker*[tw]	69
#15	Search ADP receptor antagonist*[tw] or ADP receptor blocker*[tw]	256
#14	Search ((P2Y[tw] OR P2Y1[tw] OR P2Y12[tw] OR P2Y2[tw]) AND (receptor antagonist*[tw] OR purinoceptor antagonist*[tw]))	2616
#13	Search Purinergic P2Y Receptor Antagonists[mesh]	1127
#12	Search thrombocyte aggregation inhibit*[tw]	78
#11	Search platelet*[tw] AND inhibit*[tw]	83230
#10	Search antiplatelet*[tw] OR anti-platelet*[tw]	23489
#9	Search Platelet Aggregation Inhibitors[mesh]	29783
#8	Search #6 OR #7	3661
#7	Search DAPT[tw] OR DAPTs[tw]	1020
#6	Search dual antiplatelet*[tw] OR dual anti-platelet*[tw] OR double antiplatelet*[tw] OR double anti-platelet*[tw]	3101
#5	Search #1 OR #2 OR #3 OR #4	108007
#4	Search Strecker*[tw] OR Supremo*[tw] OR WallFlex*[tw] OR Wallstent*[tw]	1554
#3	Search DES[tw] OR DESs[tw]	22435
#2	Search stent[tw] OR stents[tw] OR stented[tw] OR stenting[tw]	88856
#1	Search Stents[mesh]	60825

Appendix 2: Selection of Included Studies



Appendix 3: List of Included Studies

1. Fei Y, Tsoi MF, Cheung TT, et al. Optimal duration of dual antiplatelet therapy after drug-eluting stent implantation: Meta-analysis of randomized controlled trials. Int J Cardiol. 2016;220:895-900.

2. Palla M, Briasoulis A, Siddiqui F, et al. Long (>12 months) and short (<6 months) versus standard duration of dual antiplatelet therapy after coronary stenting: A systematic review and meta-analysis. Am J Ther. 2015:1-9.

3. Sharma A, Lavie CJ, Sharma SK, et al. Duration of dual antiplatelet therapy after drug-eluting stent implantation in patients with and without acute coronary syndrome: A systematic review of randomized controlled trials. Mayo Clin Proc. 2016;91:1084-93.

4. Ascenzo FD, Moretti C, Bianco M, et al. Meta-analysis of the duration of dual antiplatelet therapy in patients treated with second-generation drug-eluting stents. Am J Cardiol. 2016;117:1714-23.

5. Tsoi MF, Cheung CL, Cheung TT, et al. Duration of dual antiplatelet therapy after drug-eluting stent implantation: Meta-analysis of large randomised controlled trials. Sci.Rep. 2015;5:13204.

6. Verdoia M, Schaffer A, Barbieri L, et al. Optimal duration of dual antiplatelet therapy after DES implantation: A meta-analysis of 11 randomized trials. Angiology. 2015;67:224-38.

7. Cassese S, Byrne RA, Ndrepepa G, et al. Prolonged dual antiplatelet therapy after drug-eluting stenting: meta-analysis of randomized trials. Clin Res Cardiol. 2015;104:887-901.

8. Bulluck H, Kwok CS, Ryding AD, et al. Safety of short-term dual antiplatelet therapy after drug-eluting stents: An updated meta-analysis with direct and adjusted indirect comparison of randomized control trials. Int J Cardiol. 2015;181:331-9.

9. Spencer FA, Prasad M, Vandvik PO, et al. Longer- versus shorter-duration dual-antiplatelet therapy after drug-eluting stent placement: A systematic review and meta-analysis. Ann Intern Med. 2015;163:118-26.

10. Palmerini T, Benedetto U, Bacchi-Reggiani L, et al. Mortality in patients treated with extended duration dual antiplatelet therapy after drug-eluting stent implantation: A pairwise and Bayesian network meta-analysis of randomised trials. Lancet. 2015;385:2371-82.

11. Navarese EP, Andreotti F, Schulze V, et al. Optimal duration of dual antiplatelet therapy after percutaneous coronary intervention with drug eluting stents: Meta-analysis of randomised controlled trials. BMJ. 2015;350:h1618.

12. Kwok CS, Bulluck H, Ryding AD, et al. Benefits and harms of extending the duration of dual antiplatelet therapy after percutaneous coronary intervention with drug-eluting stents: a meta-analysis. Scientific World J. 2014;2014:794078.

13. Valgimigli M, Park SJ, Kim HS, et al. Benefits and risks of long-term duration of dual antiplatelet therapy after drug-eluting stenting: a meta-analysis of randomized trials. Int J Cardiol. 2013;168:2579-87.

14. Cassese S, Byrne RA, Tada T, et al. Clinical impact of extended dual antiplatelet therapy after percutaneous coronary interventions in the drug-eluting stent era: a meta-analysis of randomized trials. Eur Heart J. 2012;33:3078-87.

15. Vandvik PO, Lincoff AM, Gore JM, et al. Primary and secondary prevention of cardiovascular disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141:e637S-e68S.

16. Sheyin O, Perez X, Pierre Louis B, Kurian D. The optimal duration of dual antiplatelet therapy in patients receiving percutaneous coronary intervention with drug-eluting stents. Cardiol J.23:307-16.

17. Xie C, Ding XL, Miao LY. Different durations of dual anti-platelet therapy after percutaneous coronary intervention with drug-eluting stents in patients with coronary disease: A systematic review. Chinese Pharmaceutical J. 2016;51:762-8.

18. Zhang XL, Zhu QQ, Zhu L, et al. Optimize the duration of DAPT following des implantation: An updated system review and meta-analysis of 10 randomized trials. Clin Trials Reg Science Cardiol. 2015;6:1-11.

19. You JJ, Singer DE, Howard PA, et al. Antithrombotic therapy for atrial fibrillation: Antithrombotic therapy and prevention of thrombosis, 9th ed: American college of chest physicians evidence-based clinical practice guidelines. Chest. 2012;141:e531S-e75S.

20. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: An update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention, 2011 ACCF/AHA guideline for coronary artery bypass graft surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease, 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction, 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes, and 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. Circulation. 2016;134(10):e123-55.

21. Bittl J, Baber U, Bradley S, et al. Duration of dual antiplatelet therapy: A systematic review for the 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2016;68:1116

Appendix 4: List of Excluded Studies

1. Park Y, Franchi F, Rollini F, et al. Dual Antiplatelet Therapy after Coronary Stenting. Expert Opin Pharmacother. 2016 Jun 16.
2. Zeymer U, Becher A, Jennings E, et al. Systematic review of the clinical impact of dual antiplatelet therapy discontinuation after acute coronary syndromes. Europ Heart J Acute Cardiovasc Care. 2016 May 3.
3. Palmerini T, Stone GW. Optimal duration of dual antiplatelet therapy after drug-eluting stent implantation: conceptual evolution based on emerging evidence. Eur Heart J. 2016;37:353-64.
4. Udell JA, Bonaca MP, Collet JP, et al. Long-term dual antiplatelet therapy for secondary prevention of cardiovascular events in the subgroup of patients with previous myocardial infarction: a collaborative meta-analysis of randomized trials. Eur Heart J. 2016;37:390-9.
5. Ziada KM, Abdel-Latif A, Charnigo R, et al. Safety of an abbreviated duration of dual antiplatelet therapy (<6 months) following second-generation drug-eluting stents for coronary artery disease: A systematic review and meta-analysis of randomized trials. Catheter Cardiovasc Interv. 2016;87:722-32.
6. Eisen A, Giugliano RP. Antiplatelet and anticoagulation treatment in patients with non-ST-segment elevation acute coronary syndrome: comparison of the updated North American and European guidelines. Cardiol Rev. 2016;24:170-6.
7. Mastoris I, Mathias PM, Dangas GD. Dual antiplatelet therapy duration: A review of current available evidence. Clin Ther. 2016;38:961-73.
8. Basaraba JE, Barry AR. What is the optimal duration of dual antiplatelet therapy after percutaneous coronary intervention with drug-eluting stent implantation? Am J Health-Syst Pharm. 2016:73:e229-e37.
9. Calcagno S, Lucisano L, Mancone M, et al. Bleeding versus thrombosis: role of short DAPT in complex lesions. Minerva Cardioangiologica. 2015;63:533-46.
10. Suwita BM, Laksmi PW, Wijaya IP. Extended dual antiplatelet for diabetic elderly patients after drug-eluting stent implantation: an evidence-based clinical review. Acta Med.Indones. 2015;47:253-64.
11. Summaria F, Giannico MB, Talarico GP, et al. Antiplatelet therapy in hemodialysis patients undergoing percutaneous coronary interventions. Nephrourol Mon. 2015;7:e28099.
12. Yang J, Fan ZX, Yang CJ, et al. A meta-analysis of randomized clinical trials comparing shorter (less or equal than 6 months) and longer (more or equal than 12 months) dual anti-platelet therapy following drug-eluting coronary stents. Iran Red Crescent Med J. 2015;17:e26904.
13. Liou K, Nagaraja V, Jepson N, et al. Optimal duration of dual antiplatelet therapy following drug-eluting stents implantation: A meta-analysis of 7 randomised controlled trials. Int J Cardiol. 2015:578-80.
14. Abo-Salem E, Alsidawi S, Jamali H, et al. Optimal duration of dual antiplatelet therapy after drug-eluting stents: meta-analysis of randomized trials. Cardiovasc Ther. 2015;33:253-63.
15. Liu C, Liu M, Chen D, et al. Effectiveness of prolonged clopidogrel-based dual antiplatelet therapy after drug-eluting stent implantation: Evidence-based meta-analysis. Herz. 2015;40:795-802.

16. Ascenzo FD, Colombo F, Barbero U, et al. Discontinuation of dual antiplatelet therapy over 12 months after acute coronary syndrome increases risk for adverse events in patients treated with percutaneous coronary intervention: systematic review and meta-analysis. J Interv Cardiol. 2014;27:233-41.
17. Ariotti S, Costa F, Valgimigli M. Coronary stent selection and optimal course of dual antiplatelet therapy in patients at high bleeding or thrombotic risk: navigating between limited evidence and clinical concerns. Curr Opin Cardiol. 2015;30:325-32.
18. Montalescot G, Brieger D, Dalby AJ, et al. Duration of Dual Antiplatelet Therapy After Coronary Stenting: A Review of the Evidence. J Am Coll Cardiol. 2015;66:832-47.
19. Giustino G, Baber U, Sartori S, et al. Duration of dual antiplatelet therapy after drug-eluting stent implantation: a systematic review and meta-analysis of randomized controlled trials. J Am Coll Cardiol.2015;65:1298-310.
20. Palmerini T, Sangiorgi D, Valgimigli M, et al. Short- versus long-term dual antiplatelet therapy after drug-eluting stent implantation: an individual patient data pairwise and network meta-analysis. J Am Coll Cardiol. 2015;65:1092-102.
21. Elmariah S, Mauri L, Doros G, et al. Extended duration dual antiplatelet therapy and mortality: a systematic review and meta-analysis. Lancet.2015;385:792-8.
22. Pandit A, Giri S, Hakim FA, Fortuin FD. Shorter (<6 months) versus longer (>12 months) duration dual antiplatelet therapy after drug eluting stents: a meta-analysis of randomized clinical trials.2015;85:34-40.
23. Scheller B. Antithrombocytic therapy and PCI. Duration of therapy after DCB/stents/scaffolds. Herz.2014;39:819-21.
24. Zeymer U, Zahn R. Antithrombotic therapy and atrial fibrillation. Dual or triple therapy after acute coronary syndrome and stent? Herz.2014;39:814-8.
25. Pilgrim T, Windecker S. Antiplatelet therapy for secondary prevention of coronary artery disease. Heart.2014;100:1750-6.
26. Liu M, Chen J, Huang D, et al. Optimal duration of dual antiplatelet therapy after drug-eluting stent implantation: a meta-analysis of 3 randomized controlled trials. J Cardiovasc Pharmacol. 2014; 64:41-6.
27. El-Hayek G, Messerli F, Bangalore S, et al. Meta-analysis of randomized clinical trials comparing short-term versus long-term dual antiplatelet therapy following drug-eluting stents. Am J Cardiol. 2014; 114:236-42.
28. Park SJ, Kang SM, Park DW. Dual antiplatelet therapy after drug-eluting stents: defining the proper duration. Coronary Artery Disease. 2014; 25:83-9.
29. Tanguay JF, Bell AD, Ackman ML, et al. Focused 2012 update of the Canadian Cardiovascular Society guidelines for the use of antiplatelet therapy. Can J Cardiol. 2013;29:1334-45.
30. Norgard NB, DiNicolantonio JJ. Clopidogrel, prasugrel, or ticagrelor? A practical guide to use of antiplatelet agents in patients with acute coronary syndromes. Postgrad Med.2013;125:91-102.
31. Zhang T, Shen L, Hu L, et al. Optimal duration of dual-antiplatelet therapy following drug-eluting stent implantation: a meta-analysis. J Clin Pharmacol.2013;53:345-51.
32. Shin DH, Hong MK. Optimal duration of dual antiplatelet therapy after drug-eluting stent implantation. Expert Rev Cardiovasc Ther. 2012;10:1273-85.

33. Alonso-Coello P, Bellmunt S, McGorrian C, et al. Antithrombotic therapy in peripheral artery disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012; 141:e669S-e90S.
34. Musumeci G, Lorenzo ED, Valgimigli M. Dual antiplatelet therapy duration: what are the drivers? Curr Opin Cardiol.2011; 26 Suppl 1:S4-14.
35. Lemesle G, Paparoni F, Delhaye C, Bonello L, Lablanche JM. Duration of dual antiplatelet therapy after percutaneous coronary intervention with drug-eluting stent implantation: a review of the current guidelines and literature. Hosp Pract (Minneap). 2011;39:32-40.
36. Faxon DP, Eikelboom JW, Berger PB, et al. Consensus document: antithrombotic therapy in patients with atrial fibrillation undergoing coronary stenting. A North-American perspective. Thromb Haemost. 2011;106:572-84.
37. Moseley AD, Collado FM, Volgman AS, , et al. Duration of dual antiplatelet therapy in coronary artery disease: A review article. Curr Atherosclero Rep.2016;18.
38. Bagai A, Bhatt DL, Eikelboom JW, et al. Individualizing duration of dual antiplatelet therapy after acute coronary syndrome or percutaneous coronary intervention. Circulation.2016;133:2094-8.
39. Stone GW. DAPT duration after coronary stenting: assessing risk-benefit tradeoffs in individual patients. J Am Coll Cardiol.2016;67:2503-5.
40. Huang H, Li Y, Sun M. Shorter (<6 months) vs. longer (>12 months) dual antiplatelet therapy after second-generation drug-eluting stents implantation: A meta-analysis of randomized controlled trials. Eur Heart J(Suppl). 2016;18:A54-A62.
41. Bang VV, Levy MS. Duration of dual anti-platelet therapy following drug eluting stents: Less is more? Catheter Cardiovasc Interv. 2016;87:733-4.
42. Bondar M, Ilia M, Fletcher H. Dual antiplatelet therapy duration in patients with drug-eluting stents. US Pharm. 2016:HS2-HS5.
43. Holmes DR, Rihal CS. Is prolonged DAPT apt or a study in zero-sum games? JACC: Cardiovasc Interv. 2016;9:148-50.
44. Bittl JA. The tradeoff between shorter and longer courses of dual antiplatelet therapy after implantation of newer generation drug-eluting stents. Curr Cardiol Rep.2016;18:1-6.
45. Sahebjalal M, Curzen N. Twelve month dual antiplatelet therapy after drug-eluting stents-too long, too short or just right? Int Cardiol Rev.2015;10:136-8.
46. Schurtz G, Manchuelle A, Lemesle G. Stent length as a potential indicator to select patients who may benefit from long-term dual antiplatelet therapy. Interv Cardiol. 2015;7:419-26.
47. Chang L, Yeh RW. Assessing the optimal strategy for dual antiplatelet therapy. Expert Rev Cardiovasc Ther. 2015;13:1067-9.
48. Eisen A, Bhatt DL. Antiplatelet therapy: Defining the optimal duration of DAPT after PCI with DES. Nat Rev Cardiol.2015;12:445-6.
49. 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;131:2001-9.
50. Ruparelia N, Chieffo A. Dual antiplatelet therapy following drug-eluting stent implantation: How long is long enough? Expert Rev Cardiovasc Ther. 2015;13:585-7.
51. Kirtane AJ, King SB. Should all stent patients have prolonged dual antiplatelet therapy? JACC: Cardiovasc Interv. 2015;8:873-5.

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

53. Warren J, Baber U, Mehran R. Antiplatelet therapy after drug-eluting stent implantation. J Cardiol. 2015;65:98-104.

54. Messori A, Fadda V, Maratea D, et al.. Outcomes with short-term versus long-term antiplatelet dual therapy after drug-eluting stenting: quantifying the equivalence margins. Int J Cardiol. 2014;172:469-70.

55. Chang M, Park DW. Optimal duration of dual antiplatelet therapy after implantation of drug-eluting stents: shorter or longer? Cardiol Ther. 2014;3:2.

56. Christodoulidis G, Baber U, Mehrana R. Should P2Y12 inhibitors be given for 12 months in acute coronary syndrome? Curr Opin Cardiol. 2014;29:301-6.

57. Cerrato E, Ascenzo FD, Biondi-Zoccai GG, et al. Dual antiplatelet therapy after drug-eluting stent implantation: When is "enough" enough? J Cardiovasc Pharmacol. 2014;64:38-40.

58. Rha SW. Duration of dual antiplatelet treatment in the era of next generation drug-eluting stents. World J Cardiol. 2014;6:148-53.

59. Cully M. Antiplatelet therapy: DAPT for 3 months is sufficient. Nat Rev Cardiol. 2014;11:3.

60. Tomey M, Mehran R. Dual antiplatelet therapy dilemmas: Duration and choice of antiplatelets in acute coronary syndromes topical collection on management of acute coronary syndromes. Curr Cardiol Rep. 2013;15.

61. Brott TG, Halperin JL, Abbara S, et al. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR /CNS /SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: Executive summary. Catheter Cardiovasc Interv. 2013;81:E75-E123.

62. El-Deeb MH, Riyami AMA, Riyami AAA, et al. 2012 Oman heart association simplified guidelines for the management of patients with unstable angina/Non-ST-elevation myocardial infarction. Crit Pathw Cardiol.2012;11:139-46.

63. Guyatt GH, Akl EA, Crowther M, et al. Executive summary: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141:7S-47S.

64. Kirchhof P, Lip GYH, Gelder ICV, et al. Comprehensive risk reduction in patients with atrial fibrillation: Emerging diagnostic and therapeutic options report from the 3rd Atrial Fibrillation Competence NETwork/European Heart Rhythm Association Consensus Conference. Europace.2012;14:8-27.

65. Jr S, Benjamin EJ, Bonow RO, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update. J Am Coll Cardiol. 2011;58:2432-46.

66. Smith SC, Benjamin EJ, Bonow RO, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: A guideline from the American Heart Association and American College of Cardiology Foundation. Circulation. 2011;124:2458-73.

67. 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;4:1129-32.

68. Bell AD, Roussin A, Cartier R, et al. The use of antiplatelet therapy in the outpatient setting: Canadian cardiovascular society guidelines. Can J Cardiol. 2011; 27:S1-S59.

69. Bell AD, Roussin A, Cartier R, et al. The use of antiplatelet therapy in the outpatient setting: Canadian Cardiovascular Society Guidelines executive summary. Can J Cardiol. 2011; 27:208-21.

70. Wright RS, Anderson JL, Adams CD, et al. 2011 ACCF/AHA focused update of the guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction (Updating the 2007 Guideline): A report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation.2011; 123:2022-60.

71. Ghattas A, Shantsila E, Lip GYH. Antithrombotic therapy after percutaneous coronary intervention in anticoagulated patients: A fine balance between thrombosis and bleeding. Ther Adv Cardiovasc Dis. 2011;5:5-9.

72. Fuster V, Ryden LE, Cannom DS, et al. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2011;123:e269-e367.

73. Ba B, Ma YT, Yu ZX, et al. Optimal duration of dual antiplatelet therapy in patients undergoing percutaneous coronary intervention: A meta-analysis. Chinese J Evidence-Based Med. 2012;12:577-82.

74. Fihn SD, Gardin JM, Abrams J, et al. 2012 Accf/aha/acp/aats/pcna/scai/sts guideline for the diagnosis and management of patients with stable ischemic heart disease. J Am Coll Cardiol. 2011; 60:e44-e164.

75. Camm AJ, Lip GYH, Caterina RD, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation. Eur Heart J. 2012;33:2719-47.

76. Serebruany VL, Cherepanov V, Golukhova EZ, et al. The Dual Antiplatelet Therapy Trial after the FDA update: noncardiovascular deaths, cancer and optimal treatment duration. Cardiology. 2015;132:74-80.

77. Fanari Z, Malodiya A, Weiss SA, et al. Long-term use of dual antiplatelet therapy for the secondary prevention of atherothrombotic events: Meta-analysis of randomized controlled trials. Cardiovasc Revasc Med. 2015;Jul 20.

78. Keach JW, Yeh RW, Maddox TM. Dual antiplatelet therapy in patients with stable ischemic heart disease. Curr Atherosclero Rep.2016;18:5.

79. Levine GN, Jeong YH, Goto S, et al. Expert consensus document: World Heart Federation expert consensus statement on antiplatelet therapy in East Asian patients with ACS or undergoing PCI. Nat Rev Cardiol.2014;11:597-606.

80. Cayla G, Silvain J, Collet JP, et al. Updates and current recommendations for the management of patients with non-ST-elevation acute coronary syndromes: What it means for clinical practice. Am J Cardiol.2015;115:10A-22A.

81. Levine GN, Jeong YH, Goto S, et al. World Heart Federation expert consensus statement on antiplatelet therapy in east Asian patients with ACS or undergoing PCI. Glob Heart. 2014; 9:457-67.

82. Olivier CB, Diehl P, Bode C, et al. Antiplatelet therapy after acute coronary syndrome. Therapeutic strategies and treatment duration. Herz. 2014;39:808-13.

83. Tomey M, Mehran R. Dual antiplatelet therapy dilemmas: duration and choice of antiplatelets in acute coronary syndromes. Curr Cardiol Rep.2013;15:405, 2013.

84. Sadanandan S, Singh IM. Clopidogrel: The data, the experience, and the controversies. Am J Cardiovasc Drugs. 2012;12:361-74.

85. Wenger NK. 2011 ACCF/AHA focused update of the guidelines for the management of patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction (updating the 2007 Guideline): Highlights for the clinician. Clin Cardiol. 2012;35:3-8.

86. Fitchett DH, Theroux P, Brophy JM, et al. Assessment and management of acute coronary syndromes (ACS): a Canadian perspective on current guideline-recommended treatment-part 1: Non-ST-segment elevation ACS. Can J Cardiol. 2011;27 Suppl A:S387-401.

87. Rodriguez F, Mahaffey KW. Management of patients with NSTE-ACS: A comparison of the recent AHA/ACC and ESC guidelines. J Am Coll Cardiol. 2016;68:313-21.

88. Huo Y, Thompson P, Buddhari W, et al. Challenges and solutions in medically managed ACS in the Asia-Pacific region: Expert recommendations from the Asia-Pacific ACS Medical Management Working Group. Int J Cardiol.2015;183:63-75.

89. Ackman ML, Bucci C, Callaghan M, et al. A pharmacist's guide to the 2012 update of the Canadian Cardiovascular Society Guidelines for the use of antiplatelet therapy. Can Pharm J. 2015;148:71-81.

90. Patrono C, Andreotti F. Antithrombotic therapy for patients with atrial fibrillation and atherothrombotic vascular disease striking the right balance between efficacy and safety. Circulation. 2013;128:684-6.

91. Guidelines for elective percutaneous coronary intervention in patients with stable coronary artery disease (JCS 2011) published in 2012: Digest version. Circulation J. 2013;77:1590-607.

92. Li YH, Yeh HI, Tsai CT, et al. 2012 Guidelines of the Taiwan Society of Cardiology (TSOC) for the management of ST-segment elevation myocardial infarction. Acta Cardiologica Sinica. 2012;28:63-89.

93. Weitz JI, Eikelboom JW, Samama MM. New antithrombotic drugs - Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141:e120S-e51S.

94. 2011 ACCF/AHA focused update of the guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction (updating the 2007 guideline). J Am Coll Cardiol. 2011;57:1920-59.

95. Hamm CW, Bassand JP, Agewall S, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2011;32:2999-3054.

96. Wenger NK. What's new in antiplatelet and anticoagulant therapy recommendations for unstable angina/non-ST-elevation myocardial infarction: 2012 focused update from the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Clin Cardiol. 2012;35:669-72.

COULD NOT LOCATE

1. Giacoppo D, Baber U, Mehran R. Current developments in dual antiplatelet therapy after stenting. Minerva Cardioangiologica.2014;62:261-76.

2. Duan HQ, Dong PS, Wang HL, Li ZJ, Du LJ, Zhao YW. Effect of prolonged dual anti-platelet therapy on reducing myocardial infarction rate after percutaneous coronary intervention. J Biol Regul Homeost Agents.2015;29:213-9.

Appendix 5: AMSTAR Rating for Included Systematic Reviews

Table 99: AMSTAR[9] Rating for Systematic Reviews Included in the Evidence Synthesis

Systematic Review	A priori Research Design	Duplicate Selection/Extraction	Comprehensive Literature Search	Publication Status	List of Included/ Excluded Studies	Characteristics Reported	Quality Assessed	Quality Used Appropriately	Methods Appropriate	Publication Bias Assessed	Conflicts Disclosed	AMSTAR Rating
Fei 2016	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	7
Palla 2015	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	7
D'Ascenzo 2016	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	9
Tsoi 2015	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	7
Verdoia 2016	No	Yes	Yes	Yes	No	Yes	Can't answer	No	Yes	Yes	No	5
Cassese 2015	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	7
Palmerini 2015	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Can't answer	Yes	No	7
Navarese 2015	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	7
Xie 2016	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	No	6
Zhang 2015	No	Yes	Yes	Yes	No	Yes	Yes	No	Can't answer	Yes	No	6
Bittl 2016	No	Yes	Can't answer	Can't answer	No	Yes	Yes	Yes	Yes	No	No	5

Appendix 6: Definitions Used in Randomized Controlled Trials

Adapted from Spencer et al. 2015[21]

PRODIGY[38]

Myocardial Infarction

The diagnosis of acute myocardial infarction was based on the universal definition of myocardial infarction. The term “myocardial infarction” should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Under these conditions, any one of the following criteria meets the diagnosis of myocardial infarction:

1. Detection of an increase or decrease in the levels of cardiac biomarkers (preferably troponin) with at least 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 electrocardiography, 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, or evidence of fresh thrombus by coronary angiography 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 myocardial infarction. A subtype related to a documented stent thrombosis is recognized.
4. For coronary artery bypass grafting (CABG) in patients with normal baseline troponin values, elevations of cardiac biomarker levels above the 99th percentile are indicative of periprocedural myocardial necrosis. By convention, increases of biomarkers greater than 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 myocardial infarction.
5. Pathologic findings of acute myocardial infarction.

Major Bleeding

This was defined per the thrombolysis in myocardial infarction (TIMI) criteria.

Stroke

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

Death

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

DES-LATE[36]

Myocardial Infarction

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

Major Bleeding

This was defined per the TIMI criteria.

Stroke

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

Death

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

ARCTIC-Interruption[35]

Myocardial Infarction

Periprocedural myocardial infarction was defined as follows:

1. In patients with elevated biomarker levels before PCI, a positive diagnosis of reinfarction is made when all of the following criteria are present: documentation that the troponin level (or CK level in the absence of CK-MB) is decreasing, troponin (or CK-MB) measured six hours after PCI is greater than three times upper limit of normal, and the peak troponin (or CK-MB) level measured within 24 hours after the event is elevated by at least 50% above the previous level.
2. In patients in whom biomarker levels are normal or have returned to normal before PCI, periprocedural myocardial infarction is defined when the troponin (or CK- MB) level measured six hours after PCI is greater than three times upper limit of normal. Measurements of biomarkers are requested before and six hours after PCI and at discharge.

Major Bleeding

The STEEPLE definition was used:

1. Fatal bleeding
2. Retroperitoneal, intracranial, or intraocular bleeding
3. Bleeding that requires intervention (surgical or endoscopic) or decompression of an enclosed place to stop or control the event
4. Clinically overt bleeding, requiring transfusion of one or more units of packed red cells or whole blood

5. Clinically overt bleeding, causing a decrease in the hemoglobin level of 30 g/L (3 g/dL) or greater (or if hemoglobin level is not available, a decrease in hematocrit of 10% or more).

Stroke

This event was not described.

Death

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

DAPT[34]

Myocardial Infarction

Periprocedural myocardial infarction: Troponin or CK-MB level greater than three times the upper reference limit within 48 hours of the procedure.

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

1. New pathologic Q waves or LBBB
2. New native or graft vessel occlusion
3. Imaging evidence of loss of viable myocardium.

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

1. Symptoms of ischemia
2. Electrocardiography changes indicative of new ischemia (new ST-T changes or new LBBB)
3. Development of pathologic Q waves
4. Imaging evidence of a new loss of viable myocardium or a new regional wall-motion abnormality

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

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

1. New ST-elevation or LBBB
2. Documented thrombus by angiography or autopsy
3. Reinfarction, spontaneous, and periprocedural.

Myocardial infarction: Stable or decreasing values on two samples obtained more than six hours apart and a 20% increase three to six hours after the second sample was obtained.

Major Bleeding

Major bleeding was defined by using the GUSTO (Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries) classification; severe and moderate bleeding were combined.

Severe or life-threatening: Either intracranial hemorrhage or bleeding that causes hemodynamic compromise and requires intervention.

Moderate: Bleeding that requires blood transfusion but does not result in hemodynamic compromise.

Stroke

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

1. Persists more than 24 hours or results in death in less than 24 hours or
2. Persists less than 24 hours if pharmacologic therapy (a thrombolytic drug) or nonpharmacologic therapy (a neurointerventional procedure, such as intracranial angioplasty) is used or
3. Persists less than 24 hours, but has neuroradiologic (magnetic resonance imaging or computed tomography) diagnostic changes suggestive of acute tissue injury.

Death

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

ITALIC[37]

Myocardial Infarction

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

Major Bleeding

This was defined according to the TIMI classification as intracranial hemorrhage, a 50 g/L (5 g/dL) decrease in hemoglobin concentration, or a 15% absolute decrease in hematocrit.

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 death versus noncardiovascular death were provided.

OPTIDUAL[39]

Major Adverse Cardiac and Cerebrovascular Event (MACCE)

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

Myocardial Infarction

Classified and adjudicated according to the Academic Research Consortium definition

Major Bleeding

Classified as fatal bleeding, intracranial bleeding (assessed by magnetic resonance imaging, computed tomography, or autopsy), hemorrhagic shock, a need for transfusion of at least two units of packed red blood cells, reductions in hemoglobin greater than 3 g/dl, intraocular bleeding that leads to visual loss, or bleeding that requires surgery. Classified via TIMI (major and minor) and Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 classification.

Appendix 7: Rapid Reviews

The following text summarizes information from two rapid reviews commissioned to complement information from this health technology assessment.

Impact of ASA Dosage

TITLE: Dual Antiplatelet Therapy Acetylsalicylic Acid Dosing: A Review of the Clinical Effectiveness and Harms[5]

Context and Policy Issues

Acute coronary syndromes (ACS) continue to be the worldwide leading cause of adult mortality and morbidity. Patients with ACS or stable angina are commonly treated with percutaneous coronary intervention (PCI) and stenting to slow coronary artery disease progression and prevent major cardiac events. The risks of PCI with stenting include thrombotic complications of acute closure and stent thrombosis. Antiplatelet therapeutics have become an integral part of this management approach to prevent activation of the thrombotic cascade and these subsequent complications.

Dual antiplatelet therapy (DAPT) is the most common therapeutic option for patients following PCI. DAPT consists of ASA in combination with clopidogrel (an irreversible P2Y12 inhibitor), prasugrel (an irreversible P2Y12 inhibitor), or ticagrelor (a reversible P2Y12 receptor antagonist). In particular, ASA with clopidogrel has demonstrated prevention of thrombotic events in patients undergoing PCI and has represented the standard of care for many years. ASA itself has been a cornerstone of antiplatelet therapy for many years, offering cardioprotective effects through irreversible inhibition of cyclooxygenase-1 and subsequent downstream reduction of thrombus formation.

Clinically effective and safe DAPT dosing requires a balance between thrombotic risk with inadequate inhibition and bleeding risk with potent inhibition for this patient population. A previously published CADTH technology report, from November 2010, reviewed the evidence for different ASA dosages as part of DAPT as one objective. The purpose of this report is to retrieve and review current existing evidence on the clinical effectiveness and safety of a range of ASA dosages as a component of DAPT for patients following PCI with stenting.

Research Question

What is the comparative clinical benefit and harm of different dosages of ASA as part of dual antiplatelet therapy following PCI?

Key Findings

A limited quantity of evidence was identified on aspirin dosages as part of DAPT; however, one large, well-conducted randomized controlled trial included in this report directly addressed this research question. This international trial reported no differences in the outcomes of cardiovascular death, myocardial infarction, stroke, stent thrombosis, or major bleeding outcomes between high-dose (300 mg to 325 mg per day) and low-dose (75 mg to 100 mg per day) aspirin in DAPT regimens with clopidogrel. During the three-month follow-up, evidence of a statistically significant increase in recurrent ischemia was reported for patients receiving the low aspirin dose as part of the DAPT regimens. A retrospective observational study also did not observe statistically significant differences for DAPT

patients in cardiovascular death, myocardial infarction, stroke or major bleeding outcomes between high-dose (325 mg per day) and low-dose (81 mg per day) aspirin. Both studies observed a significant increase in minor bleeding outcomes for patients in this population receiving the high-dose aspirin regimens following PCI management. A third study, with important methodological limitations, was consistent with the large randomized controlled trial and did not observe a statistically significant difference in the occurrence of stent thrombosis between patients receiving a moderate-dose or high-dose (162 mg to 325 mg per day) or a low-dose (81 mg per day) aspirin as part of a DAPT regimen. The evidence presented in this report was therefore consistent in that low-dose aspirin as part of DAPT did not increase incidence of cardiovascular death, myocardial infarction, stroke, or stent thrombosis; however, higher-dose aspirin increased the frequency of bleeding complications without any clear benefit.

Impact of Clopidogrel: Proton Pump Inhibitor

TITLE: Clopidogrel and Proton Pump Inhibitor Use: A Review of the Evidence on Safety[4]

Context and Policy Issues

Clopidogrel is a thienopyridine prodrug that is commonly prescribed in conjunction with ASA (aspirin) as DAPT for patients who are at high risk of acute and potentially fatal cardiovascular events following PCI. PCI involves coronary revascularization through stent implantation or coronary artery bypass grafting (CABG). Acute cardiovascular events associated with PCI include angina, myocardial infarction, stroke, and major or minor thrombolysis in myocardial infarction (TIMI) bleeding. Clopidogrel, when metabolized to its active form 2-oxo-clopidogrel, inhibits oral adenosine diphosphate–induced platelet aggregation by blocking the P2Y12 receptor on the surface of platelets.

Proton pump inhibitors are commonly used to mitigate a number of adverse gastrointestinal effects that are linked to clopidogrel. Proton pump inhibitors include omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole. There is emerging, though uncertain, evidence suggesting that proton pump inhibitors may interfere with clopidogrel metabolism, and as a result attenuate its P2Y12 receptor–based platelet inhibition function, resulting in increased incidence or risks of acute CV events relative to clopidogrel DAPT or clopidogrel monotherapy (i.e., the use of clopidogrel without aspirin).

Of note, the DAPT trial published in December 2014 compared the use of ASA + P2Y12 inhibitor for 12 months versus 30 months post-PCI with stenting and found some potential clinical benefits (i.e., reduced risk of stent thrombosis and major adverse cardiovascular and cerebrovascular events) of the longer treatment duration; an increased risk of bleeding, however, was also observed.

Since it may be anticipated that some patients, with lower risk of bleeding, may stay on DAPT for a longer time period post-PCI with stenting, there may be a possibility that the co-prescription of a proton pump inhibitor to reduce the risk of gastrointestinal complications increases. Given the potential drug interaction between proton pump inhibitors and clopidogrel, an assessment of the impact of this regimen on cardiovascular outcomes is needed to inform policy and clinical decisions.

Objective

The objective of this report is to assess the current evidence on the impact of proton pump inhibitors on adverse events in adults being treated with clopidogrel DAPT or monotherapy following PCI involving stents.

Research Question

What are the harms of proton pump inhibitors used concomitantly with clopidogrel for patients requiring antiplatelet therapy following PCI?

Key Findings

Although the findings across the studies were mixed, overall, the evidence favours clopidogrel antiplatelet therapy without proton pump inhibitors. The evidence suggests that there are still some serious safety risks associated with the use of proton pump inhibitors with clopidogrel antiplatelet therapy (with or without aspirin) in patients following PCI stent implantation.