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Research

Extended dual antiplatelet therapy following percutaneous coronary intervention in clinically important patient subgroups: a systematic review and meta-analysis

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Abstract

Background: Dual antiplatelet therapy (DAPT) is routinely given to patients after percutaneous coronary intervention (PCI) with stenting; however, optimal duration remains uncertain in some situations. We assessed the benefits and harms of extending DAPT beyond 1 year after PCI in clinically important patient subgroups.

Methods: We conducted a systematic review and meta-analysis. We searched electronic databases (Embase, MEDLINE, PubMed, Cochrane Library) and grey literature (from inception to Nov. 5, 2021) and included randomized controlled trials (RCTs) of extended DAPT (> 12 mo) compared with DAPT for 6–12 months following PCI with stenting. The primary outcome was death (all cause, cardiovascular, noncardiovascular); secondary outcomes included major adverse cardiovascular and cerebrovascular events, myocardial infarction (MI), stroke, stent thrombosis and bleeding. Subgroups were based on prespecified patient characteristics (prior MI, acute coronary syndrome [ACS], diabetes mellitus, age, smoking status). Data were analyzed by random-effects pairwise meta-analysis.

Results: We identified 9 RCTs that provided subgroup data. We found that extended DAPT reduced the risk of MI and stent thrombosis but increased the risk of bleeding, compared with standard DAPT, with no difference in the risk of all-cause death (relative risk [RR] 1.07, 95% confidence interval [CI] 0.80–1.42) or cardiovascular death (RR 0.98, 95% CI 0.74–1.30). We found that patients with a prior MI, with ACS at presentation, without diabetes or aged younger than 75 years may derive the most benefit from extended DAPT. Among patients who received extended DAPT, the risk of all-cause death was significantly increased among those with no prior MI (RR 1.64, 95% CI 1.08–2.24), whereas there was no significant difference in the risk of all-cause death between standard and extended DAPT for patients with ACS (RR 1.20, 95% CI 0.51–2.83), with diabetes (RR 1.27, 95% CI 0.86–1.89), aged older than 75 years (RR 1.32, 95% CI 0.39–4.54) or who smoked (RR 0.90, 95% CI 0.42–1.92). Similar results were found for cardiovascular death, where data were available.

Interpretation: Patients with a previous MI with ACS at presentation, without diabetes, or aged younger than 75 years may derive the most benefit from extended DAPT. These findings support the need for careful selection of patients who may benefit most from extended DAPT. **Study registration:** PROSPERO no. CRD42018082587

After percutaneous coronary intervention (PCI) with implantation of drug-eluting or bare-metal stents, patients are given dual antiplatelet therapy (DAPT; P2Y12 inhibitor plus acetylsalicylic acid) with the goal of preventing stent thrombosis and other major adverse cardiac and cerebrovascular events (MACCEs). The optimal duration of DAPT remains uncertain in some situations,[1] and patient characteristics may be important in determining the optimal duration.[2] For some, DAPT for 6-12 months may be appropriate after stenting, whereas others may derive greater benefit from extending DAPT beyond 12 months. Guidelines by the American College of Cardiology–American Heart Association,[3] European Society of Cardiology[4] and the Canadian Cardiovascular Society[5] recommend that extended DAPT be considered for patients at high risk of thrombotic events and low risk of bleeding.

Several randomized controlled trials (RCTs) have assessed the effect of extending DAPT beyond 12 months.[6–11] Previous meta-analyses have provided estimates of the overall relative effect of extended compared with shorter-duration DAPT,[12–22]

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finding that extended DAPT reduces the risk of myocardial infarction (MI) and stent thrombosis, but increases the bleeding risk.[1] However, these meta-analyses have typically pooled all trial participants, despite the importance of individual patient characteristics in the decision to extend DAPT.[23] Therefore, there remains an uncertainty about the relative benefits and harms of extended DAPT among patient subgroups.

To address this gap, we performed a systematic review and meta-analysis of RCTs to assess the relative benefits and harms of extended DAPT (> 12 mo), compared with standard DAPT (6–12 mo), after PCI with stenting in clinically important patient subgroups, including those with previous MI, acute coronary syndrome (ACS) or diabetes, as well as by age and smoking status.

Methods

We undertook a systematic review using the methods of the Cochrane Handbook for Systematic Reviews for Interventions, with reporting guided by the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) checklist for systematic reviews.[24] The review protocol was registered in PROSPERO (CRD42018082587) and published.[25]

Study selection and search strategy

We based our study searching and selection on the Population, Intervention, Comparison, Outcomes and Study (PICOS) design criteria, described in detail in Box 1. An experienced information specialist (B.S.) developed the search strategy in consultation with the review team. Using the Peer Review of Electronic Search Strategies (PRESS) Checklist,[26] the MEDLINE strategy was peer reviewed by another senior information specialist before translation to the other databases. We searched MEDLINE (1947–present) and Embase (1974–present) in multifile on Ovid, the Cochrane Central Register of Controlled Trials (CENTRAL) database of the Cochrane Library (Wiley version) and PubMed from inception to Nov. 5, 2021 (i.e., 2021, Issue 10 of CENTRAL). There were no date or language restrictions on any of the searches. The search strategy used controlled vocabulary appropriate to each database (e.g., MEDLINE medical subject headings "stents," "percutaneous coronary intervention," "purinergic P2Y receptor antagonists") and keywords (e.g., "DES," "PCI," "dual antiplatelet therapy") (Appendix 1, available at www.cmajopen.ca/content/11/1/E118/suppl/DC1). We searched ClinicalTrials.gov and the International Clinical Trials Registry Platform (ICTRP) for ongoing and completed clinical trials. Results were downloaded and deduplicated in Reference Manager (version 12) and uploaded to Distiller SR.

Studies were selected in duplicate by independent reviewers (J.E., Z.B., C.L.) based on title and abstract screening of each identified record. The full text of all abstracts deemed potentially relevant was evaluated for eligibility (J.E., Z.B.), and any disagreements were resolved through discussion among reviewers or in consultation with an additional author (S.E.K.). Study selection was guided by the PICOS criteria (Box 1).

Box 1: Population, Intervention, Comparison, Outcomes and Study (PICOS) design criteria

Population: Adults (≥ 18 yr) who had undergone percutaneous coronary intervention (PCI) with a bare-metal or drug-eluting stent.

Intervention: Dual antiplatelet therapy (DAPT; ≥ 12 mo) following PCI with stenting (extended DAPT).

Comparator: Dual antiplatelet therapy (6–12 mo) following PCI with stenting (standard DAPT) which may involve any type of P2Y12 inhibitor (e.g., clopidogrel, prasugrel, ticagrelor) in combination with acetylsalicylic acid.

Outcomes: The primary outcome was death (all-cause, cardiovascular, noncardiovascular). Secondary outcomes were major adverse cardiac and cerebrovascular event, myocardial infarction (MI), stroke, stent thrombosis, bleeding and urgent target vessel revascularization.

Study design: Randomized controlled trials.

Subgroups of interest: Patients with previous MI, acute coronary syndrome at presentation, type 2 diabetes mellitus (diabetes), age (< 75 yr, ≥ 75 yr) and smoking status.

Data extraction

Data were extracted by a reviewer and checked by a second reviewer (J.E., Z.B.). Data were extracted from the original, primary publication for each included RCT, with supplementary data obtained from companion reports or clinical trial registration records, all of which were identified as part of database and grey literature searches. Data were extracted based on patient characteristics (prior MI, ACS at presentation, diabetes, age, smoking status). Disagreements were resolved by discussion.

Risk of bias

Two independent reviewers (J.E., Z.B.) assessed the risk of bias using the Cochrane Collaboration's risk of bias tool,[27] with consensus reached through discussion. Additional information was sought from companion publications (e.g., supplements, clinical trial registries, post-hoc analyses). Publication bias was assessed for outcomes with data from at least 10 studies.[27]

Statistical analysis

We present a descriptive summary for study selection, quality assessment and study and patient characteristics. Clinical heterogeneity was assessed by examining participant characteristics. Methodological heterogeneity was assessed by examination of study design characteristics, and data were pooled from studies deemed methodologically similar. Statistical heterogeneity was assessed by use of the I^2 statistic with I^2 greater than 75% considered to represent substantial statistical heterogeneity, and pooled data were not reported above this threshold. Data were analyzed by random-effects pair-wise meta-analysis, with relative risks (RRs) and hazard ratios (HRs) (with 95% confidence intervals [CIs]) presented. Where available, the number of participants randomized was used as the denominator, whereas the number of participants who experienced each outcome formed the numerator; otherwise,

group-level data (RR or HR) are presented, with CIs, as reported in the publication. Bleeding outcomes were analyzed separately by classification type or definition (e.g., Thrombolysis in MI [TIMI], Bleeding Academic Research Consortium [BARC], Global Use of Strategies to Open Occluded Coronary Arteries [GUSTO] classification systems).[28] For MACCE, data were pooled only for studies that used a comparable definition (i.e., including all-cause death, MI, stroke). Although we had intended to perform network meta-analysis to analyze the effects of individual P2Y12 inhibitors, there were insufficient subgroup data to permit such analyses. More details of the analysis plan can be found in the protocol.[25]

Ethics approval

Our systematic review and meta-analysis used publicly available aggregate data; as such, ethics approval was not required.

Results

The initial search identified 7506 records (Figure 1), with an additional 126 records identified by grey literature searching. Among these, 180 records were examined in full text, with 58 meeting the PICOS criteria (Appendix 2, available at www.cmajopen.ca/content/11/1/E118/suppl/DC1). Sixteen RCTs were included, corresponding to 9 unique RCTs reporting data[6–11,29–31] and an additional 7 RCTs[32–38] with no outcome data (e.g., ClinicalTrials.gov record without results).

Among the 9 RCTs reporting data, 4 RCTs[6,8,9,11] randomized participants after completion of at least 12 months (12–18 mo) of DAPT without an adverse event, which excluded participants at high risk of an adverse event immediately after stenting, whereas 5 RCTs[7,10,29–31] randomized participants within the first 30 days after stenting. To ensure consistency across studies, we included 6-month landmark

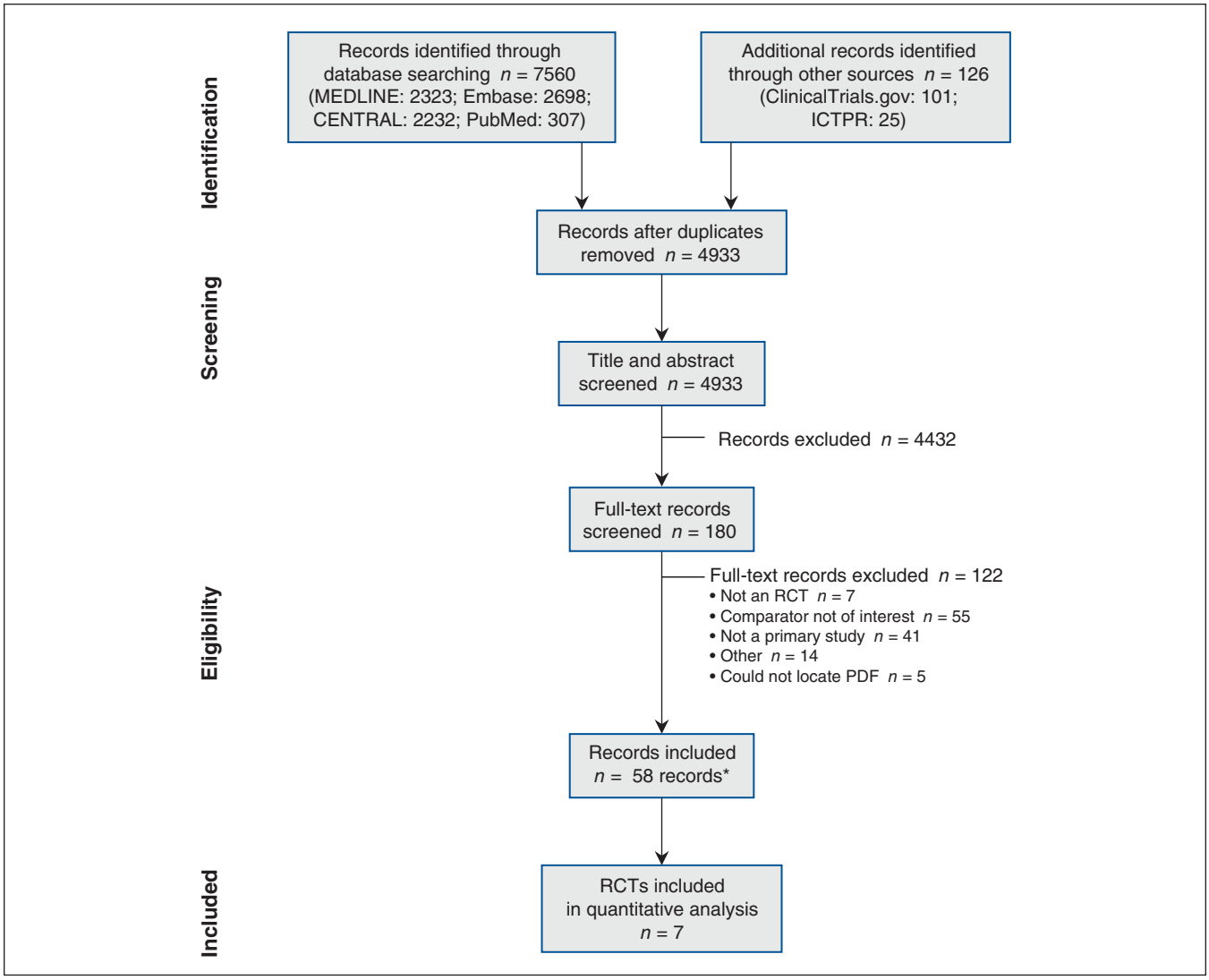

Figure 1: PRISMA flowchart of study selection. *Fifty-eight records corresponded to 16 unique randomized controlled trials (RCTs), of which 9 reported outcome data. Owing to differences in the timing of randomization, 2 RCTs were excluded from quantitative data analyses. Note: CENTRAL = Cochrane Central Register of Controlled Trials, ICTPR = International Clinical Trials Registry Platform, PRISMA = Preferred Reporting Items for Systematic reviews and Meta-Analyses.

data from the Nobori Dual Antiplatelet Therapy as Appropriate Duration (NIPPON) trial,[31] Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study (PRODIGY) trial,[10] and the Is There a Life for DES After Discontinuation of Clopidogrel (ITALIC) trial[7] along with data from trials that randomized participants after at least 6 months of DAPT; thus, the evidence base for this review is formed by 7 RCTs[6–11,31] (Table 1).

Trial and participant characteristics

The included RCTs were published between 2012 and 2017, and involved 1286–11 648 participants (Table 1). In total, 25 982 participants were randomized, with 13 041 receiving extended DAPT and 12 941 receiving DAPT. Three RCTs[7,10,31] compared extended DAPT with 6 months of DAPT, whereas 4 compared extended DAPT with 12 months of DAPT.[6,8,9,11] Most RCTs involved drug-eluting stents, with

Table 1: Characteristics of included randomized controlled trials

RCT; study name and registry; country	Study design (no. randomized)	Population	Treatments	Timing of randomization	Primary outcome
Mauri et al.[11]; DAPT, NCT00977938; multinational	Multicentre, placebo-controlled, superiority RCT DAPT: 12 mo (5786) v. 30 mo (5862)	≥ 18 yr, PCI with a DES or BMS	ASA + clopidogrel or prasugrel for 12 mo, then continued DAPT or discontinuation of P2Y12 inhibitor (ASA continued) for 18 mo	12 mo post-PCI	Co–primary outcomes: cumulative incidence of definite or probable ST and MACCE (composite of death, MI or stroke)
Valgimigli et al.[10]; PRODIGY, NCT00611286; Italy	Multicentre, open-label, superiority RCT DAPT: 6 mo (723) v. 24 mo (725)	≥ 18 yr; elective, urgent or emergent coronary angioplasty with intended stent implantation; chronic stable CAD or ACS, including non-STEMI and STEMI	ASA + clopidogrel for 6 or 24 mo	30 d ± 5 d post-PCI	Composite: death of any cause, MI, cerebrovascular accident
Collet et al.[6]; ARCTIC-Interruption, NCT00827411; France	Multicentre, open-label, superiority RCT DAPT: 12 mo (641) v. 18–30 mo (645)	≥ 18 yr; DES implantation	ASA alone or + clopidogrel or prasugrel	12 mo post-PCI	Composite: death, MI, ST, stroke, urgent revascularization
Lee et al.[9]; DES-LATE, NCT01186146; Korea	Multicentre, open-label RCT DAPT: 12 mo (2514) v. 24 mo (2531)	≥ 18 yr; DES implanted ≥ 12 mo before enrollment	ASA alone or ASA + clopidogrel	12–18 mo post-PCI	Composite: death resulting from cardiac causes, MI, or stroke
Gilard et al.[7]; ITALIC, NCT01476020; multinational	Multicentre, open-label, noninferiority RCT DAPT: 6 mo (926) v. 24 mo (924)	≥ 18 yr; PCI with a DES for any indication, with the exception of acute MI and treatment of the left main artery, with confirmed nonresistance to ASA	ASA + clopidogrel, prasugrel, or ticagrelor twice daily	During PCI hospitalization	Composite: death, MI, urgent target vessel revascularization, stroke, and major bleeding
Helft et al.[8]; OPTIDUAL, NCT00822536; France	Multicentre, open-label, superiority RCT DAPT: 12 mo (697) v. 18–48 mo (701)	≥ 18 yr with symptoms of stable angina, silent ischemia, or ACS (unstable angina, non-STEMI, or STEMI)	ASA alone or ASA + clopidogrel	12 ± 3 mo post-PCI	Composite: death, MI, stroke, major bleeding
Nakamura et al.[31]; NIPPON, NCT01514227; Japan	Multicentre, noninferiority, open-label RCT DAPT: 6 mo (1654) v. 18 mo (1653)	21–79 yr, with CAD, including acute MI	ASA + clopidogrel or ticlopidine*	During hospitalization for PCI	Composite: all-cause mortality, MI, stroke, major bleeding

Note: ACS = acute coronary syndrome, ASA = acetylsalicylic acid, BMS = bare-metal stent, CAD = coronary artery disease, DAPT = dual antiplatelet therapy, DES = drug-eluting stent, MACCE = major adverse cardiac and cerebrovascular event, MI = myocardial infarction, PCI = percutaneous coronary intervention, RCT = randomized controlled trial, ST = stent thrombosis, STEMI = ST-elevation myocardial infarction.
*Less than 3% of patients received ticlopidine.

the exception of the DAPT and PRODIGY trials, in which 15% to 25% of participants received a bare-metal stent. Clopidogrel was the most frequently used P2Y12 inhibitor, with exclusive use in 3 RCTs (Appendix 3, available at www.cmajopen.ca/content/11/1/E118/suppl/DC1).[8–10]

The mean age of the included participants was 60 years or older (Appendix 4, available at www.cmajopen.ca/content/11/1/E118/suppl/DC1). Most participants were male (69%–82%) and smoking was common (23%–61%). The prevalence of diabetes ranged from 24% to 38%, and between 4% and 31% of participants had a previous MI. There was a wide variation in the prevalence of ACS (0.1%–33% had ST-elevation MI [STEMI]), 2%–23% had non-STEMI and 9%–39% had unstable angina (Appendix 5, available at www.cmajopen.ca/content/11/1/E118/suppl/DC1). These differences may be due, in part, to the eligibility criteria of each RCT (Appendix 6, available at www.cmajopen.ca/content/11/1/E118/suppl/DC1).

Risk of bias assessment

Overall, the RCTs were judged to be at low risk of bias across all domains (Appendix 7, available at www.cmajopen.ca/content/11/1/E118/suppl/DC1). Although all included RCTs employed an open-label design, knowledge of treatment assignment would not be expected to have a substantive effect on the study outcomes. Three RCTs[7,8,31] were at an unclear risk of other sources of bias because of early termination. Publication bias could not be formally assessed for any outcome as less than 10 RCTs were included for all outcomes.

Outcomes

All participants

Compared with standard DAPT, extended DAPT reduced the risk of MI (RR 0.58, 95% CI 0.48–0.70) and probable or definite stent thrombosis (RR 0.38, 95% CI 0.21–0.67) (Table 2). The risk of moderate bleeding was generally higher, although findings differed by classification system (Table 2). There were no significant differences for all-cause death (Figure 2) (RR 1.07, 95% CI 0.80–1.42) or cardiovascular death (RR 0.98, 95% CI 0.74–1.30), stroke, definite stent thrombosis, urgent revascularization or MACCE (see Table 2 for all estimates). Findings related to the risk of noncardiovascular death were inconsistent across RCTs and were not pooled because of high heterogeneity. The DAPT trial[11] reported an increased risk of noncardiovascular death among patients who received extended DAPT, although this finding was not rep-licated in 2 smaller RCTs.[8,31]

Clinically important patient subgroups

Prior MI

Two RCTs[7,11] reported outcome data based on participants' history of MI (Table 3). The DAPT trial[11] reported on participants with a previous MI, prior MI (> 72 h before PCI), index MI (within 72 h of PCI) and both prior and index MI. For consistency, data for any MI from the DAPT trial were pooled with data for participants with a history of MI as reported in the ITALIC trial.

Among participants with a previous MI, extended DAPT was associated with a lower risk of MI (RR 0.48, 95% CI 0.36–0.64), probable or definite stent thrombosis (RR 0.29, 95% CI 0.16–0.52) and MACCE (RR 0.67, 95% CI 0.53–0.83), but a higher risk of GUSTO moderate bleeding (RR 2.30, 95% CI 1.28–4.11), GUSTO moderate or severe bleeding (RR 1.89, 95% CI 1.21–2.95) or BARC type 2, 3, 5 bleeding (RR 2.06, 95% CI 1.50–2.82). There were no significant differences for all-cause death (RR 1.04, 95% CI 0.72–1.51) or cardiovascular death (RR 0.52, 95% CI 0.05–5.69), stroke, urgent revascularization or other bleeding outcomes between extended and standard DAPT.

Among participants with no previous MI, data from the DAPT trial suggest that extended DAPT is associated with a lower risk of MI (RR 0.63, 95% CI 0.46–0.87) and probable or definite stent thrombosis (RR 0.32, 95% CI 0.15–0.68), and a higher risk of bleeding (GUSTO moderate, GUSTO moderate or severe, BARC type 2, 3, 5 bleeding; Table 3). In contrast to patients with prior MI, the risk of all-cause death was significantly increased among participants with no prior MI who received extended DAPT (RR 1.64, 95% CI 1.08–2.48). There were no other significant differences (Table 3).

Acute coronary syndrome at presentation

Three RCTs[7,9,11] reported data for participants with ACS (Table 4). Among these, 2 trials[7,9] categorized participants as having ACS or no ACS, whereas 1 RCT reported ACS data for participants with an index MI (occurring < 72 h before the index PCI).[11] Among participants with ACS, extended DAPT was associated with a lower risk of MI (RR 0.49, 95% CI 0.29–0.85), probable or definite stent thrombosis (RR 0.26, 95% CI 0.12–0.54), but a higher risk of bleeding (GUSTO moderate; GUSTO moderate or severe; BARC type 2, 3, 5; Table 4). One RCT[11] reported a significant reduction in MACCE with extended DAPT (RR 0.57, 95% CI 0.43–0.76); however, this finding was not replicated in a second RCT[7] and high statistical heterogeneity precluded pooling. There were no other significant differences (Table 4), including for all-cause death (RR 1.20, 95% CI 0.51–2.83) or cardiovascular death (RR 0.66, 95% CI 0.11–3.91).

Data were limited among participants without ACS. One RCT[9] reported no significant difference in MACCE between extended and shorter DAPT (RR 1.14, 95% CI 0.67–1.95); no data were available for other outcomes.

Diabetes

Three RCTs[7,11,15] reported data for participants with or without diabetes (Table 5). Among participants with diabetes, there was no significant difference in the risk of death (all-cause RR 1.27, 95% CI 0.86–1.89; cardiovascular RR 1.02, 95% CI 0.61–1.71; noncardiovascular RR 1.71, 95% CI 0.79–3.70), MI (RR 0.74, 95% CI 0.54–1.02), stroke (RR 1.01, 95% CI 0.52–1.95), probable or definite stent thrombosis (RR 0.48, 95% CI 0.21–1.06) and urgent revascularization (RR 0.96, 95% CI 0.20–4.74) between extended and standard

DAPT. Two RCTs[10,11] reported MACCE, although the use of different outcome measures (RR, HR) precluded pooling of the data; however, both reported no significant difference in the risk of MACCE between standard and extended DAPT.

Among participants without diabetes, there was no significant difference in all-cause death (RR 1.24, 95% CI 0.86–1.80) (Table 5), although a lower risk of MI (RR 0.44, 95% CI 0.33–0.59) and stent thrombosis (RR 0.29, 95% CI 0.17–0.50) was reported among participants without diabetes who received extended DAPT. Inconsistent findings were noted for the risk of MACCE as 1 RCT[10] reported no significant difference in MACCE (HR 1.06, 95% CI 0.76–1.50), whereas 1 RCT[11] reported a significantly lower risk of MACCE (RR 0.63, 95% CI 0.51–0.78), for a patient who received extended DAPT. No studies assessed cardiovascular or noncardiovascular death, stroke or urgent revascularization.

Table 2: Benefits and harms of extended dual antiplatelet therapy (DAPT; > 12 mo) compared with standard DAPT (6–12 mo) among all trial participants*

Outcome†	RCTs that provided outcome data	No. events (no. participants)		Extended DAPT v. standard DAPT: RR (95% CI); I^2
		> 12 mo	6–12 mo	
All-cause death	ARCTIC-Interruption;[6] ITALIC;[7] OPTIDUAL;[8] DES-LATE;[9] PRODIGY;[10] DAPT;[11] NIPPON[31]	234 (13 041)	205 (12 941)	1.07 (0.80–1.42); 45%
Cardiovascular death	ITALIC;[7] NIPPON;[31] OPTIDUAL;[8] DES-LATE;[9] DAPT[11]	97 (10 829)	98 (10 732)	0.98 (0.74–1.30); 0%
Noncardiovascular death	OPTIDUAL;[8] DAPT;[11] NIPPON[31]	57 (7374)	40 (7292)	NE‡
Myocardial infarction	ARCTIC-Interruption;[6] ITALIC;[7] OPTIDUAL;[8] DES-LATE;[9] DAPT;[11] NIPPON[31]	170 (12 316)	291 (12 218)	0.58 (0.48–0.70); 0%
Stroke	ARCTIC-Interruption;[6] ITALIC;[7] OPTIDUAL;[8] DES-LATE;[9] DAPT;[11] NIPPON[31]	88 (12 316)	92 (12 218)	0.94 (0.70–1.25); 0%
Definite ST	ARCTIC-Interruption;[6] OPTIDUAL;[8] DES-LATE;[9] PRODIGY;[10] DAPT[11]	32 (10 464)	85 (10 361)	0.49 (0.22–1.08); 46%
Probable or definite ST	ARCTIC-Interruption;[6] ITALIC;[7] OPTIDUAL;[8] DAPT;[11] NIPPON[31]	30 (9785)	86 (9704)	0.38 (0.21–0.67); 10%
Urgent revascularization	ITALIC;[7] ARCTIC-INT[6]	11 (1569)	18 (1567)	0.60 (0.24–1.54); 29%
MACCE	ARCTIC-Interruption;[6] ITALIC;[7] DES-LATE;[9] DAPT;[11] PRODIGY[10]	443 (10 687)	506 (10 590)	0.95 (0.76–1.19); 55%
GI bleeding	NIPPON[31]	8 (1887)	9 (1886)	0.89 (0.34–2.30); NA
TIMI major bleeding	ARCTIC-Interruption;[6] ITALIC;[7] OPTIDUAL;[8] DES-LATE[9]	42 (4801)	28 (4778)	1.42 (0.88–2.29); 0%
TIMI minor bleeding	ITALIC;[7] OPTIDUAL[8]	21 (1625)	22 (1623)	0.95 (0.53–1.72); 0%
GUSTO moderate bleeding	DAPT;[11] OPTIDUAL[8]	102 (6563)	60 (6483)	1.68 (1.22–2.30); 0%
GUSTO severe bleeding	DAPT;[11] OPTIDUAL[8]	41 (6553)	33 (6483)	1.41 (0.90–2.20); 0%
GUSTO moderate or severe bleeding	DAPT;[11] OPTIDUAL[8]	148 (6563)	92 (6483)	1.57 (1.17–2.11); 7%
BARC type 3 bleeding	DAPT;[11] OPTIDUAL;[8] NIPPON[31]	161 (8216)	99 (8137)	1.29 (0.76–2.22); 58%
BARC type 5 bleeding	DAPT;[11] OPTIDUAL;[8] NIPPON[31]	10 (8216)	5 (8047)	1.72 (0.62–4.47); 0%
BARC type 2, 3, 5 bleeding	OPTIDUAL[8]	18 (701)	20 (697)	0.89 (0.48–1.68); NA

Note: BARC = Bleeding Academic Research Consortium, CI = confidence interval, GI = gastrointestinal, GUSTO = Global Use of Strategies to Open Occluded Coronary Arteries, MACCE = major adverse cardiovascular and cerebrovascular event, NA = not applicable, NE = not estimable, RCT = randomized controlled trial, RR = relative risk, TIMI = Thrombolysis In Myocardial Infarction, ST = stent thrombosis.

*Corresponding forest plots are presented in Appendix 1 and Figure 2.

†MACCE: composite outcome includes all-cause death, myocardial infarction or stroke. Bleeding outcome definitions were obtained from Mehran et al.[28] These include GUSTO moderate bleeding: requiring blood transfusion but not resulting in hemodynamic compromise; GUSTO severe bleed: intracerebral hemorrhage or resulting in substantial hemodynamic compromise requiring treatment; BARC type 3 bleed (3a, 3b, 3c): overt bleeding plus hemoglobin drop of 3 to 5 g/dL, any transfusion with overt bleeding, overt bleeding plus hemoglobin drop of 5 g/dL, cardiac tamponade, bleeding requiring surgical intervention for control (excluding dental, nasal, skin, hemorrhoid), bleeding requiring intravenous vasoactive agents, intracranial hemorrhage, subcategories confirmed by autopsy or imaging or lumbar puncture, intraocular bleed compromising vision. BARC type 5 bleed: fatal bleed. TIMI minor bleed: clinically overt, resulting in hemoglobin drop of 3 to 5 g/dL. TIMI major bleed: any intracranial bleeding (excluding microhemorrhages [10 mm] evident only on gradient-echo MRI), clinically overt signs of hemorrhage associated with a drop in hemoglobin of 5 g/dL, fatal bleeding (bleeding that directly results in death within 7 d).

‡Data not pooled because of high heterogeneity (I^2 > 75), with inconsistent direction of findings across trials.

Study or subgroup	> 12 mo Events	> 12 mo Total	6–12 mo Events	6–12 mo Total	Weight, %	RR M-H, random, 95% CI
Collet et al.[6] (ARCTIC-INT)	7	645	9	641	6.8	0.77 (0.29–2.06)
Gilard et al.[7] (ITALIC)	20	924	11	926	10.6	1.82 (0.88–3.78)
Helft et al.[8] (OPTIDUAL)	16	701	24	697	13.1	0.66 (0.36–1.24)
Lee et al.[9] (DES-LATE)	46	2531	32	2514	18.7	1.43 (0.91–2.23)
Mauri et al.[11] (DAPT)	106	5862	84	5786	25.8	1.25 (0.94–1.65)
Nakamura et al.[31] (NIPPON)	7	1653	16	1654	8.0	0.44 (0.18–1.06)
Valgimigli et al.[10] (PRODIGY)	32	725	29	723	17.1	1.10 (0.67–1.80)
Total (95% CI)		**13 041**		**12 941**	**100.0**	**1.07 (0.80–1.42)**
Total events	234		205			

Test for overall effect: $Z = 0.45$ ($p = 0.65$)
Heterogeneity: $\tau^2 = 0.06$; $\chi^2 = 10.94$, $df = 6$ ($p = 0.09$); $I^2 = 45\%$

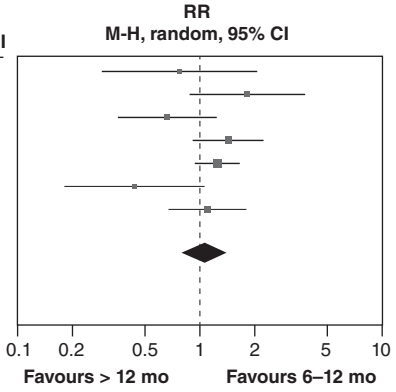

Figure 2: Benefits and harms of extended dual antiplatelet therapy (DAPT) (> 12 mo) compared with standard DAPT (6–12 mo) among all trial participants. Note: CI = confidence interval, M-H = Mantel–Haenszel, RR = relative risk.

Table 3: Benefits and harms of extended dual antiplatelet therapy (DAPT; > 12 mo) compared with standard DAPT (6–12 mo) among participants with or without prior myocardial infarction*

	Previous MI‡				No previous MI			
		No. events (no. participants)				No. events (no. participants)		
Outcome†	RCTs	> 12 mo	6–12 mo	RR (95% CI); I^2	RCTs	> 12 mo	6–12 mo	RR (95% CI); I^2
All-cause death	ITALIC;[7] DAPT[11]	58 (2853)	54 (2769)	1.04 (0.72–1.51); 0%	DAPT	57 (3147)	35 (3161)	1.64 (1.08–2.48); NA
Cardiovascular death	ITALIC[7]	1 (138)	2 (144)	0.52 (0.05–5.69); NA	–	–	–	–
Myocardial infarction	ITALIC;[7] DAPT[11]	69 (2853)	139 (2769)	0.48 (0.36–0.64); 0%	DAPT	60 (3147)	95 (3161)	0.63 (0.46–0.87); NA
Stroke	DAPT[11]	19 (2715)	24 (2625)	0.77 (0.42–1.39); NA	DAPT	25 (3147)	28 (3161)	0.90 (0.52–1.53); NA
Probable or definite ST	DAPT[11]	14 (2715)	47 (2625)	0.29 (0.16–0.52); NA	DAPT	9 (3147)	28 (3161)	0.32 (0.15–0.68); NA
Urgent revascularization	ITALIC[7]	1 (138)	3 (144)	0.35 (0.04–3.30); NA	–	–	–	–
MACCE§	DAPT[11]	128 (2715)	186 (2625)	0.67 (0.53–0.83); NA	DAPT	126 (3147)	145 (3161)	0.87 (0.69–1.10); NA
TIMI minor bleeding	ITALIC[7]	0 (138)	1 (144)	0.35 (0.01–8.46); NA	–	–	–	–
GUSTO moderate bleeding	DAPT[11]	38 (2715)	16 (2625)	2.30 (1.28–4.11); NA	DAPT	57 (3147)	38 (3161)	1.51 (1.00–2.26); NA
GUSTO severe bleeding	DAPT[11]	16 (2715)	13 (2625)	1.19 (0.57–2.47); NA	DAPT	28 (3147)	19 (3161)	1.48 (0.83–2.64); NA
GUSTO moderate or severe bleeding	DAPT[11]	57 (2715)	29 (2615)	1.89 (1.21–2.95); NA	DAPT	85 (3147)	54 (3161)	1.58 (1.13–2.22); NA
BARC type 2, 3, 5 bleeding	DAPT[11]	117 (2715)	55 (2625)	2.06 (1.50–2.82); NA	DAPT	192 (3147)	101 (3161)	1.91 (1.51–2.42); NA

Note: BARC = Bleeding Academic Research Consortium, CI = confidence interval, GUSTO = Global Use of Strategies to Open Occluded Coronary Arteries, MACCE = major adverse cardiovascular and cerebrovascular event, MI = myocardial infarction, NA = not applicable, RCT = randomized controlled trial, RR = relative risk, ST = stent thrombosis, TIMI = Thrombolysis In Myocardial Infarction.
*Corresponding forest plots are presented in Appendix 1 and Figure 2. See Table 2 for bleeding outcome definitions.
†No outcome data available: noncardiovascular death, definite ST, gastrointestinal bleeding, TIMI major bleeding, BARC type 3 bleeding, BARC type 5 bleeding.
‡Prior or index MI.
§Composite outcome: all-cause death, myocardial infarction or stroke.

Age group

Three RCTs[7,10,11] reported outcome data by age group (≥ 75 yr, < 75 yr; Table 6). Among participants aged older than 75 years, a single RCT[10] reported an increased risk of stroke among those who received extended DAPT (RR 8.59, 95% CI 1.08–68.28). The risk of bleeding was also increased in this subgroup (GUSTO moderate to severe, RR 5.01, 95% CI 1.46–17.26); however, this finding was not replicated in the larger DAPT trial[11] (HR 1.03, 95% CI 0.54–1.98). There were no significant differences in the risks of all-cause death (RR 1.32, 95% CI 0.39–4.54) or cardiovascular death (RR 0.98, 95% CI 0.24–4.04), MI, stent thrombosis, urgent revascularization, MACCE or minor bleeding between extended and standard DAPT among participants aged 75 years and older (Table 6).

Two RCTs reported outcomes for participants aged younger than 75 years.[10,11] Owing to reporting differences (i.e., HR v. RR), the findings reported by the DAPT and PRODIGY trials could not be pooled, and are presented separately in Table 6. The DAPT trial[11] reported a reduction in the risk of MI, probable and stent thrombosis and MACCE among participants aged younger than 75 years. These findings were not replicated in the smaller PRODIGY trial.[10]

Smoking

Limited subgroup data were available by smoking status. In total, 3 RCTs[6,10,11] reported outcome data by smoking status. One RCT[10] categorized participants as smokers or nonsmokers, 1 RCT[11] categorized smoking status as current tobacco use and no current tobacco use, and 1 RCT[6]

Table 4: Benefits and harms of extended dual antiplatelet therapy (DAPT; > 12 mo) compared with standard DAPT (6–12 mo) among participants with or without acute coronary syndrome at presentation*

	Acute coronary syndrome				No acute coronary syndrome			
		No. events (no. participants)				No. events (no. participants)		
Outcome†	RCTs	> 12 mo	6–12 mo	RR (95% CI); I^2	RCTs	> 12 mo	6–12 mo	RR (95% CI); I^2
All-cause death	ITALIC;[7] DAPT[11]	34 (2211)	32 (2171)	1.20 (0.51–2.83); 50%	–	–	–	–
Cardiovascular death	ITALIC[7]	2 (406)	3 (400)	0.66 (0.11–3.91); NA	–	–	–	–
Myocardial infarction	ITALIC;[7] DAPT[11]	46 (2211)	99 (2171)	0.49 (0.29–0.85); 27%	–	–	–	–
Stroke	DAPT[11]	13 (1805)	12 (1771)	1.06 (0.49–2.32); NA	–	–	–	–
Probable or definite ST	DAPT[11]	9 (1805)	34 (1771)	0.26 (0.12–0.54); NA	–	–	–	–
Urgent revascularization	ITALIC[11]	0 (406)	6 (400)	0.08 (0–1.34); NA	–	–	–	–
MACCE‡	DES-LATE;[9] DAPT[11]	108 (3317)	157 (3322)	NE§	DES-LATE	29 (1019)	24 (963)	1.14 (0.67–1.95); NA
TIMI minor bleeding	ITALIC[7]	4 (406)	2 (400)	1.97 (0.36–10.70); NA	–	–	–	–
GUSTO moderate bleeding	DAPT[11]	22 (1805)	5 (1771)	4.23 (1.64–11.37); NA	–	–	–	–
GUSTO severe bleeding	DAPT[11]	13 (1805)	9 (1771)	1.42 (0.61–3.31); NA	–	–	–	–
GUSTO moderate or severe bleeding	DAPT[11]	34 (1805)	14 (1771)	2.38 (1.28–4.42); NA	–	–	–	–
BARC type 2, 3, 5 bleeding	DAPT[11]	78 (1805)	37 (1771)	2.07 (1.41–3.04); NA	–	–	–	–

Note: BARC = Bleeding Academic Research Consortium, CI = confidence interval, GUSTO = Global Use of Strategies to Open Occluded Coronary Arteries, MACCE = major adverse cardiovascular and cerebrovascular event, NA = not applicable, NE = not estimable, RCT = randomized controlled trial, RR = relative risk, ST = stent thrombosis, TIMI = Thrombolysis In Myocardial Infarction.
*Corresponding forest plots are presented in Appendix 1 and Figure 2. See Table 2 for bleeding outcome definitions.
†No outcome data available: noncardiovascular death, definite ST, gastrointestinal bleeding, TIMI major bleeding, BARC type 3 bleeding, BARC type 5 bleeding.
‡Composite outcome: all-cause death, myocardial infarction or stroke.
§Data not pooled because of high heterogeneity (I^2 > 75).

Table 5: Benefits and harms of extended dual antiplatelet therapy (DAPT) compared with DAPT for 6–12 months among participants with or without diabetes*

	Diabetes				No diabetes			
		No. events (no. participants)				No. events (no. participants)		
Outcome†	RCTs	> 12 mo	6–12 mo	RR (95% CI)‡; I^2	RCTs	> 12 mo	6–12 mo	RR (95% CI)‡; I^2
All-cause death	ITALIC;[7] DAPT[11]	56 (2086)	42 (1990)	1.27 (0.86–1.89); 0%	DAPT	62 (4125)	50 (4132)	1.24 (0.86–1.80); NA
Cardiovascular death	ITALIC;[7] DAPT[11]	30 (2086)	28/1990	1.02 (0.61–1.71); 0%	–	–	–	–
Noncardiovascular death	DAPT[11]	18 (1737)	10/1654	1.71 (0.79–3.70); NA	–	–	–	–
Myocardial infarction	ITALIC;[7] DAPT[11]	63 (2086)	81/1990	0.74 (0.54–1.02); 0%	DAPT	66 (4125)	149 (4132)	0.44 (0.33–0.59); NA
Stroke	DAPT[11]	18 (1737)	17/1654	1.01 (0.52–1.95); NA	–	–	–	–
Definite ST	DAPT[11]	6 (1737)	14/1654	0.41 (0.16–1.06); NA	–	–	–	–
Probable or definite ST	DAPT[11]	9 (1737)	18/1654	0.48 (0.21–1.06)	DAPT	17 (4125)	58 (4132)	0.29 (0.17–0.50); NA
Urgent revascularization	ITALIC[7]	3 (349)	3/336	0.96 (0.20–4.74)	–	–	–	–
MACCE§	DAPT;[11] PRODIGY[10]	DAPT: 111 (1737)	DAPT: 113 (1654)	PRODIGY: HR 0.85 (0.53–1.38); NA DAPT: 0.94 (0.73–1.20); NA	DAPT, PRODIGY	DAPT: 136 (4125)	DAPT: 215 (4132)	PRODIGY: HR 1.06 (0.76–1.50); NA DAPT: 0.63 (0.51–0.78); NA
Gastrointestinal bleeding	–	–	–	–	–	–	–	–
TIMI major bleeding	–	–	–	–	–	–	–	–
TIMI minor bleeding	ITALIC[7]	2 (349)	3 (336)	0.64 (0.11–3.82); NA	–	–	–	–
GUSTO moderate bleeding	DAPT[11]	32 (1737)	20 (1654)	1.52 (0.87–2.65); NA	–	–	–	–
GUSTO severe bleeding	DAPT[11]	9 (1737)	6 (1654)	1.43 (0.51–4.00); NA	–	–	–	–
GUSTO moderate or severe bleeding	DAPT[11]	41 (1737)	26 (1654)	1.50 (0.92–2.44); NA	DAPT	99 (4125)	58 (4132)	1.71 (1.24–2.36); NA
BARC type 3 bleeding	DAPT[11]	44 (1737)	24 (1654)	1.75 (1.07–2.86); NA	–	–	–	–
BARC type 5 bleeding	DAPT[11]	1 (1737)	2 (1654)	0.48 (0.04–5.25); NA	–	–	–	–
BARC type 2, 3, 5 bleeding	DAPT[11]	95 (1737)	57 (1654)	1.59 (1.15–2.19); NA	–	–	–	–

Note: BARC = Bleeding Academic Research Consortium, CI = confidence interval, GUSTO = Global Use of Strategies to Open Occluded Coronary Arteries, HR = hazard ratio, MACCE = major adverse cardiovascular and cerebrovascular event, NA = not applicable, RCT = randomized controlled trial, RR = relative risk, ST = stent thrombosis, TIMI = Thrombolysis In Myocardial Infarction.
*Corresponding forest plots are presented in Appendix 1 and Figure 2. See Table 2 for bleeding outcome definitions.
†No outcome data available: gastrointestinal bleeding, TIMI major bleeding.
‡Unless otherwise stated.
§Composite outcome: all-cause death, myocardial infarction or stroke.

categorized smoking as current smoking and no smoking. For this analysis, we considered smoking, current tobacco use, and current smoking to include participants who smoke.

Among smokers and nonsmokers, extended DAPT significantly decreased the risk of MI and probable or definite stent thrombosis (Table 7). Differential effects between subgroups were noted for MACCE (significantly reduced among smokers) and bleeding (increased among nonsmokers) with extended DAPT. One additional RCT[6] assessed MACCE among smokers and nonsmokers using an

Table 6: Benefits and harms of extended dual antiplatelet therapy (DAPT; > 12 mo) compared with standard DAPT (6–12 mo) among participants aged younger than 75 years or 75 years and older*

	≥ 75 yr				< 75 yr			
		No. events (no. participants)				No. events (no. participants)		
Outcome†	RCTs	> 12 mo	6–12 mo	RR (95% CI)‡; I^2	RCTs	> 12 mo	6–12 mo	RR (95% CI)‡; I^2
All-cause death	ITALIC;[7] PRODIGY[10]	33 (420)	35 (428)	1.32 (0.39–4.54); 61%	PRODIGY	17 (704)	10 (679)	1.64 (0.76–3.56); NA
Cardiovascular death	ITALIC;[7] PRODIGY[10]	15 (420)	20 (428)	0.98 (0.24–4.04); 29%	PRODIGY	5 (704)	2 (679)	2.41 (0.47–12.39); NA
Myocardial infarction	ITALIC;[7] PRODIGY;[10] DAPT[11]	ITALIC, PRODIGY: 20 (420); DAPT: NR	ITALIC, PRODIGY: 14 (428); DAPT: NR	ITALIC, PRODIGY: 1.48 (0.63–3.47); 6% DAPT: HR 0.76 (0.38–1.54); NA	PRODIGY, DAPT	PRODIGY: 10 (704); DAPT: NR	PRODIGY: 9 (679); DAPT: NR	PRODIGY: 1.07 (0.44–2.62); NA DAPT; HR 0.46 (0.36–0.60); NA
Stroke	PRODIGY[10]	8 (283)	1 (304)	8.59 (1.08–68.28); NA	PRODIGY	9 (704)	3 (679)	2.89 (0.79–10.64); NA
Definite ST	PRODIGY[10]	1 (283)	2 (304)	0.54 (0.05–5.89); NA	PRODIGY	4 (704)	4 (679)	0.96 (0.24–3.84); NA
Probable or definite ST	PRODIGY;[10] DAPT[11]	PRODIGY: 4 (283); DAPT: NR	PRODIGY: 6 (304); DAPT: NR	PRODIGY 0.72 (0.20–2.51); NA DAPT: HR 0.23 (0.03–2.06); NA	PRODIGY, DAPT	PRODIGY: 4 (704); DAPT: NR	PRODIGY: 4 (679); DAPT: NR	PRODIGY: 0.96 (0.24–3.84); NA DAPT: HR 0.29 (0.17–0.49); NA
Urgent revascularization	ITALIC[7]	1 (137)	1 (124)	0.91 (0.06–14.32); NA	–	–	–	–
MACCE§	PRODIGY;[10] DAPT[11]	PRODIGY: 28 (283); DAPT: NR	PRODIGY: 31 (304); DAPT: NR	PRODIGY: 0.97 (0.60–1.58); NA DAPT: HR 0.95 (0.59–1.52); NA	PRODIGY, DAPT	PRODIGY: 33 (704); DAPT: NR	PRODIGY: 20 (679); DAPT: NR	PRODIGY: 1.59 (0.92–2.75); NA DAPT: HR 0.69 (0.57–0.83); NA
TIMI minor bleeding	ITALIC[7]	1 (137)	3 (124)	0.30 (0.03–2.86); NA	–	–	–	–
GUSTO moderate or severe bleeding	PRODIGY;[10] DAPT[11]	PRODIGY: 14 (283); DAPT: NR	PRODIGY: 3 (304); DAPT: NR	PRODIGY: 5.01 (1.46–17.26); NA DAPT: HR 1.03 (0.54–1.98); NA	PRODIGY, DAPT	PRODIGY: 8 (704); DAPT: NR	PRODIGY: 5 (679); DAPT: NR	PRODIGY: 1.54 (0.51–4.69); NA DAPT: HR 1.78 (1.29–2.47); NA
BARC type 3 bleeding	PRODIGY[10]	9 (283)	4 (304)	2.42 (0.75–7.76); NA	PRODIGY	9 (704)	5 (679)	1.74 (0.58–5.15); NA
BARC type 2, 3, 5 bleeding	PRODIGY[10]	23 (283)	9 (304)	2.75 (1.29–5.83); NA	PRODIGY	30 (704)	11 (679)	2.63 (1.33–5.21); NA

Note: BARC = Bleeding Academic Research Consortium, CI = confidence interval, HR = hazard ratio, GUSTO = Global Use of Strategies to Open Occluded Coronary Arteries, MACCE = major adverse cardiovascular and cerebrovascular event, NA = not applicable, NR = not reported, RCT = randomized controlled trial, RR = relative risk, ST = stent thrombosis, TIMI = Thrombolysis In Myocardial Infarction.
*Corresponding forest plots are presented in Appendix 1 and Figure 2. See Table 2 for bleeding outcome definitions.
†No outcome data available: noncardiovascular death, gastrointestinal bleeding, TIMI major bleeding, GUSTO moderate bleeding, GUSTO severe bleeding, BARC type 5 bleeding.
‡Unless otherwise stated.
§Composite outcome: all-cause death, myocardial infarction or stroke.

alternative definition (including all-cause death, MI, stent thrombosis, stroke, urgent revascularization), finding a nonsignificant difference in risk between DAPT durations for both smokers (RR 0.86, 95% CI 0.27–2.76) and nonsmokers (RR 0.88, 95% CI 0.48–1.61).

Interpretation

Dual antiplatelet therapy is required after coronary revascularization; however, the optimal duration of treatment requires balancing the potential benefits and harms, which may depend on individual patient characteristics. In this systematic review of clinically important patient subgroups, we found that patients with a prior MI, with ACS at presentation, without diabetes, or aged younger than 75 years, may derive the most benefit from extended DAPT. The findings of this review support individualizing DAPT based on patient-specific risk factors.

Many systematic reviews have attempted to elucidate the optimal duration of extended DAPT after PCI with stenting; however, few have taken individual patient characteristics into account,[1] despite guideline recommendations to tailor the duration of DAPT to patient characteristics.[3–5] To address this evidence gap, we undertook a systematic review to address the question of the optimal duration of DAPT among such subgroups. Our review includes the same core set of RCTs included in most previous systematic reviews (PRODIGY trial,[10] Drug-Eluting Stents to Reduce Late Coronary Arterial Thrombotic Event [DES-LATE] trial,[9] Assessment by a Double Randomization of a Conventional Antiplatelet Strategy Versus a Monitoring-Guided Strategy for Drug-Eluting Stent Implantation and, of Treatment Interruption Versus Continuation One Year After Stenting [ARCTIC-Interruption] trial,[6] ITALIC trial,[7] DAPT trial,[11] OPTImal DUAL Antiplatelet Therapy [OPTIDUAL] trial[8]). We used companion trial reports and additional analyses to provide data for these subgroups. Our findings, when not stratified by subgroup, are consistent with previous reviews that have reported a lower risk of MI and stent thrombosis with extended DAPT, compared with standard DAPT; however, we identified important differences in outcomes based on patient characteristics.

This review also serves to identify important gaps for future research. Notably, there was little available evidence for some clinically important subgroups (e.g., by smoking status, age group). Although the question of the optimal duration of DAPT treatment is not new, relatively few trials have assessed the continuation of DAPT beyond 12 months after stenting, and the majority of the evidence for most subgroups is from the DAPT trial, the largest RCT to assess the question of the optimal duration of DAPT. However, important differences have been noted between the findings of the DAPT trial and other trials, including an increased risk of all-cause death in the DAPT trial that was not replicated in other

Table 7: Benefits and harms of extended dual antiplatelet therapy (DAPT; > 12 mo) compared with standard DAPT (6–12 mo), by smoking status*

	Smokers				Nonsmokers			
		No. events (no. participants)				No. events (no. participants)		
Outcome†	RCTs	> 12 mo	6–12 mo	RR (95% CI); I^2	RCTs	> 12 mo	6–12 mo	RR (95% CI); I^2
All-cause death	PRODIGY[10]	NR	NR	HR 0.90 (0.42–1.92); NA	PRODIGY	NR	NR	HR 0.99 (0.67–1.47); NA
Myocardial infarction	DAPT[11]	25 (1222)	65 (1210)	0.38 (0.24–0.60); NA	DAPT	74 (3743)	133 (3683)	0.55 (0.41–0.72); NA
Probable or definite ST	DAPT[11]	6 (1222)	29 (1210)	0.20 (0.09–0.49); NA	DAPT	13 (3743)	36 (3683)	0.36 (0.19–0.67); NA
MACCE‡	DAPT;[11] PRODIGY[10]	74 (1444)	109 (1457)	0.69 (0.52–0.91); 0%	DAPT, PRODIGY	236 (4505)	274 (4414)	0.87 (0.64–1.20); 68%
GUSTO moderate or severe bleeding	DAPT[11]	15 (1222)	17 (1210)	0.87 (0.44–1.74); NA	DAPT	104 (3743)	73 (4893)	1.83 (1.32–2.52); NA
BARC type 2, 3, 5 bleeding	PRODIGY[10]	12 (222)	10 (247)	1.34 (0.59–3.03); NA	PRODIGY	61 (762)	24 (731)	2.44 (1.54–3.87); NA

Note: BARC = Bleeding Academic Research Consortium, CI = confidence interval, GUSTO = Global Use of Strategies to Open Occluded Coronary Arteries, HR = hazard ratio, MACCE = major adverse cardiovascular and cerebrovascular event, NA = not applicable, NR = not reported, RCT = randomized controlled trial, RR = relative risk, ST = stent thrombosis.
*Corresponding forest plots are presented in Appendix 1 and Figure 2. See Table 2 for bleeding outcome definitions.
†No outcome data available: cardiovascular death, noncardiovascular death, stroke, definite ST, urgent revascularization, gastrointestinal bleeding, TIMI major bleeding, TIMI minor bleeding, GUSTO moderate bleeding, GUSTO severe bleeding, BARC type 3 bleeding, BARC type 5 bleeding.
‡Composite outcome: all-cause death, myocardial infarction or stroke.

studies. We noted other such differences in findings between the DAPT trial and other RCTs, including the risk of MI, stent thrombosis and MACCE among patients aged younger than 75 years and those without diabetes.

The importance of patient characteristics has long been recognized in determining the optimal duration of DAPT. The DAPT score,[23] a prediction tool for estimating the benefits and harms of extending DAPT for more than 12 months after PCI, incorporates many of the characteristics considered in this review, including a history of MI, diabetes, age and smoking. The original DAPT score showed modest accuracy in predicting which patients would be at higher risk of late ischemic and bleeding events with extended DAPT,[23] whereas subsequent studies have shown that the DAPT score is a more accurate predictor of benefits and harms among patients with a prior MI, owing to a higher risk of adverse outcomes in this group. This further highlights the importance of considering individual patient characteristics in the decision to extend DAPT.[39]

Limitations

This review has several limitations that merit consideration. All included trials were open label. However, knowledge of treatment assignment would not be expected to have a substantive effect on the effect estimates for the outcomes of interest. Initial randomization may not hold in subgroups, potentially leading to imbalances between treatment groups, and we did not formally assess effect modification by patient characteristics. Further, the findings may not be generalizable to all patients in clinical practice, as some high-risk patients may have been excluded based on trial eligibility or owing to randomization after the completion of an initial event-free period in most trials. Outcome definitions for MACCE and major bleeding varied across trials. We reported data separately that were assessed by using different bleeding classification scales, and, for MACCE, we pooled only data from trials that used a comparable definition of the composite outcome, to increase homogeneity. Limited data were available for some patient subgroups, limiting the power of these analyses to detect differences between DAPT durations and increasing the probability of a false-negative finding. Finally, given the large number of comparisons and limited power for some, we cannot exclude the possibility of type I and type II errors.

Conclusion

Individual patient characteristics are important in determining the benefits and harms of extending DAPT beyond 12 months after stenting. Patients with prior MI and those with ACS at presentation, as well as patients without diabetes or aged younger than 75 years, may derive the most benefit from extended DAPT provided that the increased risk of bleeding is accounted for. These findings support the need for the careful selection of patients who may benefit most from extending the duration of DAPT beyond 12 months.

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