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Coronary artery disease

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

Jacob A. Udell[1,2]*, Marc P. Bonaca[3], Jean-Philippe Collet[4], A. Michael Lincoff[5], Dean J. Kereiakes[6], Francesco Costa[7], Cheol Whan Lee[8], Laura Mauri[9], Marco Valgimigli[7,10], Seung-Jung Park[8], Gilles Montalescot[4], Marc S. Sabatine[3], Eugene Braunwald[3], and Deepak L. Bhatt[3]*

[1]Peter Munk Cardiac Centre and Cardiovascular Division, University Health Network, Heart and Stroke Richard Lewar Centre of Excellence, University of Toronto, 76 Grenville Street, Toronto, Canada ON M5S 1B1; [2]Women's College Research Institute and Cardiovascular Division, Department of Medicine, Women's College Hospital, University of Toronto, Toronto, Canada; [3]TIMI Study Group, Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Boston, MA 02115, USA; [4]ACTION Study Group, Institut de Cardiologie Hôpital Pitié-Salpêtrière (APHP), Université Paris 6, INSERM, Paris, France; [5]Department of Cardiovascular Medicine, Cleveland Clinic Coordinating Center for Clinical Research, Cleveland, OH, USA; [6]The Christ Hospital Heart and Vascular Center and The Lindner Center for Research and Education at the Christ Hospital, Cincinnati, OH, USA; [7]Thoraxcenter, Erasmus Medical Center, Rotterdam 3015 CE, The Netherlands; [8]The Heart Institute, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea; [9]Harvard Clinical Research Institute and Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; and [10]University Hospital of Bern, Bern, Switzerland

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Aims Recent trials have examined the effect of prolonged dual antiplatelet therapy (DAPT) in a variety of patient populations, with heterogeneous results regarding benefit and safety, specifically with regard to cardiovascular and non-cardiovascular mortality. We performed a meta-analysis of randomized trials comparing more than a year of DAPT with aspirin alone in high-risk patients with a history of prior myocardial infarction (MI).

Methods and results A total of 33 435 patients were followed over a mean 31 months among one trial of patients with prior MI (63.3% of total) and five trials with a subgroup of patients that presented with, or had a history of, a prior MI (36.7% of total). Extended DAPT decreased the risk of major adverse cardiovascular events compared with aspirin alone (6.4 vs. 7.5%; risk ratio, RR 0.78, 95% confidence intervals, CI, 0.67–0.90; $P = 0.001$) and reduced cardiovascular death (2.3 vs. 2.6%; RR 0.85, 95% CI 0.74–0.98; $P = 0.03$), with no increase in non-cardiovascular death (RR 1.03, 95% CI 0.86–1.23; $P = 0.76$). The resultant effect on all-cause mortality was an RR of 0.92 (95% CI 0.83–1.03; $P = 0.13$). Extended DAPT also reduced MI (RR 0.70, 95% CI 0.55–0.88; $P = 0.003$), stroke (RR 0.81, 95% CI 0.68–0.97; $P = 0.02$), and stent thrombosis (RR 0.50, 95% CI 0.28–0.89; $P = 0.02$). There was an increased risk of major bleeding (1.85 vs. 1.09%; RR 1.73, 95% CI 1.19–2.50; $P = 0.004$) but not fatal bleeding (0.14 vs. 0.17%; RR 0.91, 95% CI 0.53–1.58; $P = 0.75$).

Conclusion Compared with aspirin alone, DAPT beyond 1 year among stabilized high-risk patients with prior MI decreases ischaemic events, including significant reductions in the individual endpoints of cardiovascular death, recurrent MI, and stroke. Dual antiplatelet therapy beyond 1 year increases major bleeding, but not fatal bleeding or non-cardiovascular death.

Keywords Dual antiplatelet therapy • Myocardial infarction • Stable coronary heart disease • Clopidogrel • Prasugrel • Ticagrelor

* Corresponding authors. Tel: +1 416 351 3732, Fax: +1 416 351 3746, Email: jay.udell@utoronto.ca (J. A. U); Tel: +1 857 307 1992, Fax: +1 857 307 1955, Email: dlbhattmd@post.harvard.edu (D. L. B.).

Introduction

Patients with myocardial infarction (MI) have heightened platelet activation and aggregation resulting in atherothrombosis following the rupture or fissuring of an unstable atherosclerotic plaque compared with patients with stable ischaemic heart disease (SIHD).[1–3] A higher predisposition to atherothrombosis may persist for years following an MI,[3–6] and SIHD patients with a history of an MI are at high risk for major adverse cardiovascular events (MACE).[7–9] As such, following MI, patients may have a persistent pathobiology that predisposes them to benefit more from therapies that intensely inhibit platelet activation and aggregation than patients following percutaneous coronary intervention (PCI) for stable ischaemia.[10]

However, dual antiplatelet therapy (DAPT) with a platelet adenosine diphosphate (ADP) antagonist in addition to aspirin is strongly recommended for only up to 1 year for reduction of cardiovascular events in patients with a prior MI, with a weak recommendation to continue thereafter in patients who underwent PCI based on expert consensus.[11–15] In the absence of definitive longer-term data, DAPT is often stopped after completion of 1 year of treatment in half of all patients.[16] Recently, two large randomized controlled trials (RCTs) demonstrated that extended duration of DAPT significantly reduced atherothrombotic events in patients 1 year or more following an MI[17] or a PCI[18] at the expense of higher bleeding and, in the case of the PCI trial,[18] potentially a higher risk of death from non-cardiovascular causes. Given these findings, and the heterogeneity in results of other trials testing extended duration DAPT, we sought to better understand the cardiovascular benefits and risks of DAPT beyond 1 year for secondary prevention in high-risk patients with a prior MI.

Methods

Study design

This systematic review and meta-analysis was conducted in accordance with the recommendations of the Cochrane Collaboration and the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines.[19] The previously published study protocol is available at the PROSPERO registry (www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015019657) and Supplementary material online, Appendix.

Eligibility criteria and trial selection

We considered prospective RCTs of secondary prevention eligible for inclusion if they followed patients beyond 1 year that either presented with or had a history of a prior MI and were randomized to a strategy of extended duration (beyond 12 months) DAPT compared with aspirin alone (with or without the use of a placebo for blinding). Eligible RCTs were considered irrespective of language, blinding, and publication status. We excluded observational studies. We excluded trials of DAPT among patients presenting with MI who were followed no longer than 12 months; if such trials followed patients longer, we considered 1-year landmark results of MI patients randomized to DAPT beyond 12 months as a sensitivity analysis. We also excluded trials of patients with SIHD alone undergoing PCI and trials of oral anticoagulant therapies.

Search strategy and data extraction

We conducted a literature search of OVID Medline (1950 to 2 April 2015) and the Cochrane central register of controlled trials databases, utilizing keyword search terms including: 'antiplatelet', 'DAPT', 'thienopyridine', 'secondary prevention', 'MI', 'acute coronary syndrome', 'major adverse cardiovascular events', 'death', 'mortality', and 'survival' (see Supplementary material online, Search Strategy). We reviewed Supplementary material online, Appendices and reference lists of eligible papers, cardiovascular conference abstracts between 2014 and 2015, and clinicaltrials.gov, to ensure identification of relevant published and unpublished studies. If published data were not available, we contacted the study principal investigator (PI) for input to maximize contribution to, and harmonize outcomes.

Baseline characteristics data and outcomes were abstracted for each study from the published manuscripts, appendices, or unpublished data by two investigators (J.A.U. and D.L.B.) independently. Baseline characteristics included patient data and study design characteristics [year, clinical setting (major inclusion and exclusion criteria) sample size, randomized intervention and control, duration of difference in intervention, duration of follow-up, blinding, and primary endpoint]. Results were compared and any disagreements were resolved by consensus.

Quality assessment

Quality was graded based on documentation of trial conduct criteria such as method of randomization, allocation concealment and blinding, blinded outcome adjudication, extent of outcome reporting and ascertainment, participant attrition and adherence metrics.[20] Studies were categorized as high quality if criteria were clearly described and accounted for, low quality if any aspect of the first three criteria was unaccounted for, or otherwise of uncertain risk of bias.

Outcomes

The primary endpoint for this analysis was the incidence of MACE, which was defined as a composite of cardiovascular death, non-fatal MI, and non-fatal stroke. Secondary endpoints included individual components of the composite primary endpoint, all-cause death, non-cardiovascular death, major bleeding events, and when relevant stent thrombosis. All cardiovascular endpoints were adjudicated and defined within the individual trials according to standard criteria. Major bleeding events were considered according to standardized bleeding endpoint definitions reported in each trial (see Supplementary material online, *Table S1* describes individual trial endpoint definitions).[21]

Statistical analysis

Data for patients that either presented with or had a history of a qualifying MI at baseline were extracted and descriptive characteristics were summarized using means (standard deviation), medians (interquartile range), or rates from each study weighted according to individual sample sizes. We extracted the originally reported hazard ratios (HRs) and 95% confidence intervals (CI) from each study when available and otherwise calculated risk ratios (RRs) and 95% CI from the reported number of events and patients at risk per treatment arm. Data from each trial were considered as per the intention-to-treat principle with pooled summary RR and 95% CI derived using a random effects meta-analysis model with weighting based on inverse variance. If a particular endpoint was not reported in a trial, and it could not be deduced from other outcomes or provided by the study PI, it was excluded only from that specific endpoint's pooled analysis. A correction factor of 0.5 was added to values of a treatment arm when no events were observed for calculation of the RR for an endpoint and its variance. We used the Cochran *Q* statistic and the I^2 measure to assess heterogeneity for treatment effects

across trials, with an $I^2 > 75\%$ considered representative of high heterogeneity. We performed sensitivity analyses including sequentially removing studies from the pooled effect estimates and adding studies with applicable 1-year landmark analyses. Heterogeneity among selected subgroups was also explored according to age, sex, DAPT regimen, type of index myocardial event, time from the index MI, and in patients with and without a history of PCI, diabetes, additional MI, stroke or transient ischaemic attack (TIA), or chronic kidney disease. An interaction term representing each category was introduced into the model for MACE and major bleeding to test for differences in treatment effect between subgroups. Publication bias was evaluated by visual inspection of funnel plots, without further statistical testing given these tests have limited specificity and power when <10 studies are analysed.[22] Two-sided *P*-values were calculated with <0.05 considered significant for all analyses. Statistical analyses were performed with Review Manager version 5.3.5 (Nordic Cochrane Centre, Denmark) and Comprehensive Meta-Analysis version 3.0 (Biostat Inc., Englewood, NJ, USA).

Role of the funding source

There was no funding source for this study. J.A.U. and D.L.B. had full access to all the data in the study and had final responsibility for the decision to submit for publication. All included studies complied with the Declaration of Helsinki and individual ethics committees approved the research protocols and informed consent was obtained from subjects in each respective trial.

Results

Among 1342 records screened, we identified 36 RCTs to review in detail (see Supplementary material online, Results and *Figure S1*). After exclusions, the remaining six trials met criteria for eligibility in the primary meta-analysis.[17,18,23–29] These trials, which comprised 33 435 participants randomized to a strategy of extended DAPT ($n = 20\,203$) vs. aspirin alone ($n = 13\,232$), are summarized in *Table 1*. One trial exclusively randomized patients with a history of MI ($n = 21\,162$; 63.3% of the pooled population),[17] one randomized a subgroup of patients with prior MI ($n = 3846$; 11.5%),[23,24] while the remaining four trials randomized patients that recently underwent PCI and included a subgroup whose indication was an acute coronary syndrome ($n = 8427$; 25.2%).[18,25–29] Various ADP antagonists were studied across the six trials as outlined in *Table 1*, including clopidogrel, prasugrel, and ticagrelor.

At baseline, overall, the mean age of participants was 64.0 years, mean weight was 81.4 kg, 7900 (23.6%) were women, 28 064 (83.9%) underwent or had a history of PCI, 9888 (29.6%) had diabetes, 5439 (18.6%) had chronic kidney disease, and 16 340 (48.9%) presented with or had a history of ST-elevation or Q-wave MI (see Supplementary material online, *Table S2*). Enrolled patients infrequently presented with unstable angina ($n = 2384$; 7.1%), with a history of stroke/TIA ($n = 866$; 2.6%), or with a history of revascularization by coronary artery bypass grafting ($n = 2477$; 7.4%). The mean duration of follow-up of 31 months and the mean difference in the achieved duration of DAPT was 30 months (range 17–36 months).

Quality metrics of trial conduct, participant attrition, and therapeutic adherence across trials are summarized (see Supplementary material online, *Table S3*) and were reasonably comparable for trials that varied in length of follow-up, timing of randomization, and type of intervention. Three trials were double blind and placebo-controlled,[17,18,23,24,29] while three were unmasked open-label trials with blinded endpoint adjudication and standard care as the control.[25–28] Forgiving unblinded study designs, all trials were considered high quality. All trials reported or provided results for MACE, CV death, MI, stroke, major bleeding, non-CV death, and all-cause mortality (see Supplementary material online, *Table S1*). Cardiovascular endpoints, cause of death, and major bleeding events were defined in each trial according to standard diagnostic criteria and were adjudicated by a blinded endpoints committee in each trial allowing for comparisons across trials. Four of six trials provided data for stent thrombosis.[18,25–29] Causes of major bleeding events were also provided by all trials (see Supplementary material online, *Table S4*).

Major adverse cardiovascular events

Among the six trials, the individual and pooled HR/RRs for the composite primary endpoint of the 2273 MACE are provided in *Figure 1*. Among the 20 203 participants with a prior MI treated with DAPT beyond 1 year, 1286 (6.37%) patients developed a MACE compared with 987 of 13 232 (7.46%) patients treated with aspirin alone [RR 0.78 (95% CI 0.67–0.90); $P = 0.001$; *Figure 1*]. This risk reduction represented an absolute risk difference (ARD) of 1.09% (95% CI 0.53–1.65) or a number needed to treat (NNT) of 91 (95% CI 61–189) to prevent one MACE over a mean 31 months of follow-up.

Cardiovascular mortality

Extended DAPT for more than a year following an MI significantly reduced cardiovascular death (which comprised 60% of all observed deaths) (*Figure 2*), as 472 of 20 203 patients (2.3%) died from cardiovascular causes while treated with extended DAPT compared with 344 of 13 232 patients (2.6%) treated with aspirin alone [RR 0.85 (95% CI 0.74–0.98); $P = 0.03$; ARD = 0.26%; NNT = 380; see Supplementary material online, *Figure S2*].

Other individual cardiovascular endpoints

Extended DAPT also significantly reduced the risk of MI [RR 0.70 (95% CI 0.55–0.88); $P = 0.003$; ARD = 0.84%; NNT = 120; see Supplementary material online, *Figure S3*] and stroke [RR 0.81 (95% CI 0.68–0.97); $P = 0.02$ ARD = 0.31%; NNT = 324; see Supplementary material online, *Figure S4*]. Among trials that enrolled only PCI-treated patients, definite or probable stent thrombosis events were infrequent. Yet the risk of late stent thrombosis more than a year following an MI was significantly reduced with extended DAPT [RR 0.50 (95% CI 0.28–0.89); $P = 0.02$; ARD = 0.73%; NNT = 137; see Supplementary material online, *Figure S5*].

Major bleeding events and safety

These results occurred in the context of an increased risk of major bleeding events with extended DAPT [1.85 vs. 1.09%; RR 1.73 (95% CI 1.19–2.50); $P = 0.004$; ARD = 0.76%; NNH = 132; *Figure 2* and see Supplementary material online, *Figure S6*]. However, intracranial haemorrhage (ICH) [0.41 vs. 0.31%; RR 1.34 (95% CI 0.89–2.02); $P = 0.17$] and fatal bleeding events [0.14 vs. 0.17%; RR 0.91 (95% CI 0.53–1.58); $P = 0.75$] were infrequent and were not significantly

Table I Characteristics of included trials

Trial	Population included in the present study	*N* (% of total trial enrolment)	Time from MI/ACS to randomization (months)[a]	Study design and time from randomisation to DAPT initiation or continuation (months)[a]	Difference in duration of DAPT (months)[a]	Follow-up (months)[a]	Intervention, *N* Background of aspirin	Control, *N*
CHARISMA MI (2006)[23,24]	Patients ≥45 years of age with documented CAD, CVD, or PAD, or with multiple atherothrombotic risk factors. The subgroup of interest was patients with prior MI. Excluded patients with an existing indication for clopidogrel, including a recent ACS, or at high risk of bleeding, including long-term oral anticoagulation or NSAID use	3846 (24.6)	23.6 (NR)	DAPT initiation, 0	27.6 (NR)	27.6 (NR)	Clopidogrel, 1903	Placebo, 1943
PRODIGY (2012)[25,26]	The subgroup of stabilized patients ≥18 years of age with prior ACS treated with PCI. Excluded patients with a bleeding diathesis, oral anticoagulation, planned surgery, active bleeding, or prior stroke in the past 6 months	1465 (74.4)	1 (NR)	DAPT continuation, 5 (NR)	18 (NR)	24 (NR)	Clopidogrel, 732	No therapy 733
ARCTIC-Interruption (2014)[27]	The subgroup of stabilized patients ≥18 years of age with prior ACS treated with PCI who were free of MACE and major bleeding at 12 months. Excluded patients at physician's discretion, those >15 months from prior randomization, with aspirin resistance, chronic anticoagulation treatment, bleeding diathesis, bleeding GI ulcer, or presentation with STEMI	323 (25.7)	12 (NR)	DAPT continuation, 0	17 (15–18)	17 (15–18)	Clopidogrel or prasugrel, 156	No therapy, 167
DAPT (2014)[18,29]	The subgroup of stabilized patients >18 years of age with prior MI treated with PCI who were free of MACE and major bleeding at 12 months. Excluded patients with a bleeding diathesis, oral anticoagulation, planned surgery, and index PCI with concomitant DES and BMS	3576 (30.7)	12 (NR)	DAPT continuation, 0	18 (NR)	18 (NR)	Clopidogrel or prasugrel, 1805	Placebo, 1771

Continued

Table 1 *Continued*

Trial	Population included in the present study	*N* (% of total trial enrolment)	Time from MI/ACS to randomization (months)[a]	Study design and time from randomisation to DAPT initiation or continuation (months)[a]	Difference in duration of DAPT (months)[a]	Follow-up (months)[a]	Intervention, *N* Background of aspirin	Control, *N*
DES-LATE (2014)[28]	The subgroup of stabilized patients ≥18 years of age with prior ACS treated with PCI who were free of MACE and major bleeding at 12 months. Excluded patients with contraindication to antiplatelet drugs or an indication for long-term clopidogrel	3063 (60.7)	13.3 (12.1–16.1)	DAPT continuation, 0	36 (NR)	42.0 (24.7–50.7)	Clopidogrel, 1512	No therapy, 1551
PEGASUS-TIMI 54 (2015)[17]	Patients ≥50 years of age with prior MI 1–3 years before enrolment with one additional risk factor. Excluded patients with planned DAPT or anticoagulation, patients with a bleeding diathesis or recent (<6 months) GI bleed, recent major surgery (<1 month), and any prior ischaemic or haemorrhagic stroke	21 162 (100)	20.4 (14.4–27.6)	DAPT initiation, 0	33 (28–37)	33 (28–37)	Ticagrelor 90 mg b.i.d., 7050 60 mg b.i.d., 7045	Placebo, 7067
Total		33 435	18		30	31	20 203	13 232

Trial	No. of MACE events	Control group MACE rate	Control group major bleeding rate	Control group annualized MACE rate	Control group annualized major bleeding rate
CHARISMA MI (2006)[23,24]	287	8.3	2.0	3.6	0.87
PRODIGY (2012)[25,26]	132	9.4	0.8	4.7	0.4
ARCTIC-Interruption (2014)[27]	7	2.4	0	1.7	0
DAPT (2014)[18,29]	167	6.3	0.8	4.2	0.53
DES-LATE (2014)[28]	122	4.3	2.0	1.2	0.57
PEGASUS-TIMI 54 (2015)[17]	1558	9.0	1.1	3.3	0.39
Total	2273	7.5	1.1		

ACS, acute coronary syndrome; BMS, bare metal stent; CAD, coronary artery disease; CVD, cerebrovascular disease; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; GI, gastrointestinal; MACE, major adverse cardiovascular events; MI, myocardial infarction; NR, not reported; NSAID, non-steroidal anti-inflammatory drug; PAD, peripheral arterial disease; STEMI, ST-segment elevation MI; TIA, transient ischaemic attack.
[a]Mean (standard deviation) or median (interquartile range).

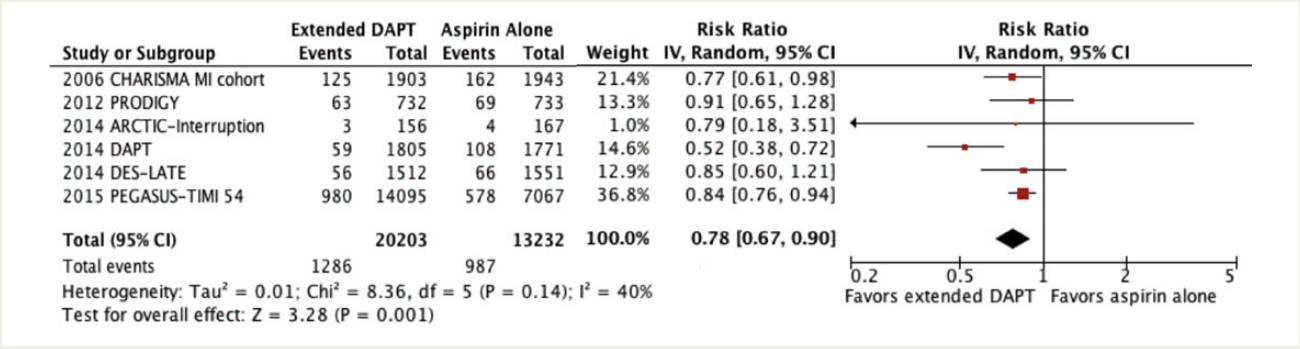

Figure 1 Risk of major adverse cardiovascular events comparing extended dual antiplatelet therapy vs. aspirin alone. Square data markers represent risk ratios and horizontal lines the 95% confidence intervals with marker size reflecting the statistical weight of the study using inverse variance random effects meta-analysis. A diamond data marker represents the overall risk ratios and 95% confidence intervals for major adverse cardiovascular events. There was no significant between-trial heterogeneity (Q statistic = 8.36, d.f. = 5; $P = 0.14$; $I^2 = 40\%$).

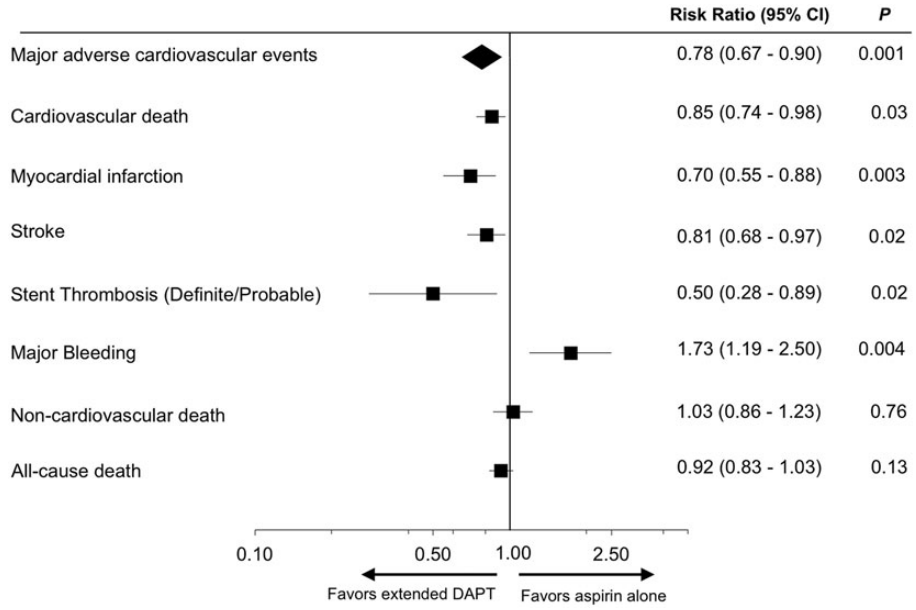

Figure 2 Risk of individual cardiovascular and bleeding endpoints comparing extended dual antiplatelet therapy vs. aspirin alone. Square data markers represent risk ratios and horizontal lines the 95% confidence intervals using inverse variance random effects meta-analysis.

different between extended DAPT-treated patients and aspirin alone. Treatment with extended DAPT had no significant effect on non-CV death [RR 1.03 (95% CI 0.86–1.23); $P = 0.76$; see Supplementary material online, *Figure S7*]. The net effect was a non-significant RR of 0.92 (95% CI 0.83–1.03; $P = 0.13$; see Supplementary material online, *Figure S8*) for all-cause mortality.

Sensitivity analyses

There was no meaningful heterogeneity in results across trials for either the primary or the secondary endpoints. No evidence of publication bias was suggested by visual inspection of the funnel plots for MACE (see Supplementary material online, *Figure S9*) or secondary endpoints. Results for the primary endpoint analysis remained significant after removal of any one trial from the pooled result (see Supplementary material online, *Table S5*). More so, after simultaneous removal of both the PEGASUS-TIMI 54 and DAPT results, the primary endpoint remained significant among the remaining four trials [RR 0.82 (95% CI 0.70–0.97); $P = 0.02$; ARD = 1.11% (95% CI 0.09–2.13)]. The addition of 1-year landmark results from two trials testing other strategies of more intensive antiplatelet therapy for secondary prevention among stabilized patients >1 year from an MI,[30,31] also did not materially change the results [RR 0.79 (95% CI 0.72–0.87); $P < 0.00001$; see Supplementary material online, Appendix *Figure S10*]. Finally, results did not significantly differ among any subgroup for MACE or major bleeding (all P-interactions ≥0.09; see Supplementary material online, *Tables S6 and S7*).

Discussion

Our meta-analysis of >33 000 high-risk patients stabilized following an MI found that, overall compared with aspirin alone, extended DAPT beyond 1 year resulted in a 22% relative and 1.1% absolute risk reduction for major adverse cardiovascular events over a mean 31 months of follow-up. The magnitude of this relative risk reduction was consistent, with no significant heterogeneity, or sensitivity to removing any one trial from the pooled results. The pooled data in our meta-analysis show for the first time that there is a significant 15% reduction in cardiovascular death in post-MI patients receiving long-term DAPT. There was a 0.8% absolute increase in the risk of major bleeding, but without significant excess of ICH or fatal bleeding and no impact on non-cardiovascular causes of death.

This meta-analysis differs in important ways from prior reports.[32–36] We elected to focus on stabilized patients with a history of prior MI since these patients are known to be at higher atherothrombotic risk compared with patients with SIHD treated with elective PCI.[9,24,37,38] As such, we reasoned that these patients would be expected to demonstrate a more favourable benefit-to-risk profile when treated with long-term DAPT compared with patients without a prior MI. We also focused on trials that randomized at least one arm of this population to a strategy of DAPT >1 year following a qualifying MI vs. aspirin alone. We did this in order to address the unresolved question of whether treatment of patients with a history of MI with DAPT beyond the currently recommended 1-year duration results in significant and clinically meaningful reductions in atherothrombotic events. As well, we leveraged the power of a larger population to better quantify the magnitude of bleeding risk with this strategy and refine risk estimates for cardiovascular and non-cardiovascular causes of death. Finally, we analysed eligible trials irrespective of whether, when, and how patients were treated with PCI, since data support up to a year of DAPT post-MI regardless of whether patients underwent PCI. Patients with MI treated with PCI have stent-related factors that may modify the benefit–risk trade-off of extended DAPT, including the timing and propensity for late stent thrombosis[39,40]; however, the benefit of extended DAPT was consistent regardless of whether trials exclusively enrolled patients undergoing PCI or not.

Our findings of reduced atherothrombotic risk with extended DAPT irrespective of whether trials enrolled only PCI-treated patients support prior research that suggests the mechanism of long-term cardiovascular benefit with extended DAPT in patients with a history of prior MI is likely an extension of the benefits seen following early treatment of an MI, and distinct from simply preventing stent thrombosis in patients with prior PCI. For instance, long term, the majority of ruptured coronary plaques that result in recurrent MI appear to occur in lesions other than earlier culprits treated with PCI in patients with coronary heart disease.[18,29,41] After an infarction, patients have a more susceptible coronary milieu and are more prone to recurrent plaque rupture with prolonged platelet activation and aggregation[1–3,42] and higher circulating markers of myonecrosis and inflammation[43] compared with stable patients which may mediate a preferential benefit from extended DAPT. Furthermore, prolonged DAPT in patients with a history of prior MI appeared to reduce ischaemic events in other arterial territories, in accordance with our observed results for stroke.

Coronary heart disease treatment guidelines recommend 1 year of DAPT in patients following MI, based simply on the original duration of pivotal secondary prevention RCTs,[11–15] although landmark analyses from these trials suggested continued divergence of event curves with time.[44–46] This recommendation was extended to patients treated with coronary revascularization by PCI,[15,47] based on expert consensus and observational studies suggesting a delayed propensity for complete endothelialization and subsequent risk of late stent thrombosis following discontinuation of DAPT in patients treated with early generation drug-eluting stents.[48,49] Subsequently, a number of small RCTs have randomized patients treated with PCI to shorter durations of DAPT and concluded that 1-year duration of DAPT may offer no benefit compared with shorter courses of therapy.[50–55] However, none of these prior trials were powered to study this question, each enrolled limited numbers of subjects with MI, and prior meta-analyses have not distinguished treatment effects between acute and stable coronary patients.[32–36] To the best of our knowledge, there are at least eight ongoing outcomes trials comparing experimental with traditional DAPT strategies enrolling patients following PCI (see Supplementary material online, *Table S8*). These trials will greatly inform the care of patients receiving stents. However, each of these trials is primarily focused on PCI, whereas our meta-analysis results pertain to the patient's underlying history of MI irrespective of PCI status.

Considering the inclusion and exclusion criteria of the trials we studied certain characteristics that may define stabilized high-risk patients with previous MI at low risk of bleeding that benefit from extended DAPT. The majority of patients studied were considered high risk for recurrent atherothrombotic events with 93% having a history of biomarker positive acute coronary syndrome often in the presence of additional risk factors such as older age, diabetes, or established atherosclerosis. Studies typically excluded patients with a bleeding diathesis such as a coagulation disorder or long-term anticoagulation therapy, recent (within 6–12 months) or active major bleeding such as gastrointestinal bleeding, recent (within 1 month) major surgery, or any history of ICH. In addition, very few patients enrolled had a history of a prior stroke or TIA (<3%). As such, our findings may not be generalizable to all acute coronary syndrome patients,[56] such as patients with unstable angina or a history of stroke, but may be most accurately applied to patients with a prior history of MI who have tolerated 1 year of DAPT without development of, or ongoing risk for, significant bleeding.

There are certain limitations to this study. First, we pooled trials with heterogeneous populations that varied in treatment strategy, study design, intended primary outcome, and major bleeding definitions. For logistical reasons, we did not evaluate individual patient-level data, but unpublished data for several endpoints were provided by individual PIs to compare standard endpoints among similar patients across trials. Second, some of the RCTs were unblinded, which may bias reporting of non-fatal adverse cardiovascular and bleeding events. However, these unblinded trials provided <15% of the total population studied and all trials utilized blinded central committee endpoint adjudication. Third, five of the six included trials focused on subgroups, as they were not prospectively designed to determine whether extended DAPT was beneficial in

post-MI patients. However, meta-analysis of randomized comparisons within each subgroup of patients with a history of MI remain valid. Finally, although three-quarters of the primary outcome events analysed were contributed from the PEGASUS-TIMI 54 and DAPT trials, our primary endpoint results were robust and remained significant after removal of both trials from the pooled result. Additionally, for the first time, pooling of these trials allowed detection of a significant reduction in cardiovascular death.

In summary, compared with aspirin alone, extended DAPT beyond 1 year among stabilized high-risk patients with previous MI decreased the risk of MACE, including cardiovascular death alone, as well as recurrent MI and stroke. There was an increase in the risk of major bleeding, but not fatal bleeding, with no excess of non-cardiovascular causes of death. These findings now clarify that in patients with prior MI who are at low risk of bleeding, continuation of DAPT beyond a year offers a substantial reduction in important cardiovascular outcomes and should be considered.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Authors' contributions

J.A.U., E.B., and D.L.B. conceived and designed the study; J.A.U. performed the literature search, statistical analysis, and wrote the first draft of the manuscript; all authors analysed the data, interpreted the findings; and provided critical revision of the manuscript for important intellectual content; J.A.U., E.B., and D.L.B. provided administrative, technical, and material support and supervised the study.

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