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Clinical impact of extended dual antiplatelet therapy after percutaneous coronary interventions in the drug-eluting stent era: a meta-analysis of randomized trials

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Aims The aim of this study was to evaluate benefits and risks of extending dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) in the drug-eluting stent era.

Methods and results We searched electronic databases (Medline, EMBASE, the Cochrane Central Register of Controlled Trials), relevant websites, reference lists, conference abstracts, reviews, chapters in books, and proceedings of advisory panels for the US Food and Drug Administration, for randomized controlled trials investigating the clinical impact of extending DAPT duration in patients undergoing PCI. The primary endpoint was all-cause death. The secondary endpoints were myocardial infarction (MI), stent thrombosis (ST), cerebrovascular accidents (CVAs), and thrombolysis in myocardial infarction (TIMI) major bleeding. We included four trials that randomized 8231 patients (50.2%, extended DAPT duration vs. 49.8%, control duration). A total of 8158 patients (99.1%) were available for final analyses. The median DAPT duration was 16.8 vs. 6.2 months for the extended DAPT and control groups, respectively. At follow-up (median 16.8 months) extending DAPT duration did not reduce all-cause death [odds ratio (95% confidence interval) = 1.15 (0.85–1.54), $P = 0.36$], MI [0.95 (0.66–1.36), $P = 0.77$], ST [0.88 (0.43–1.81), $P = 0.73$], or CVAs [1.51 (0.92–2.47), $P = 0.10$]. Conversely, extended DAPT duration clearly increased the risk of TIMI major bleeding [2.64 (1.31–5.30), $P = 0.006$].

Conclusions The extension of DAPT duration after percutaneous coronary interventions may increase the risk of bleeding without reducing ischaemic events. These results need corroboration from large ongoing trials.

Keywords Drug-eluting stent • Dual antiplatelet therapy • Bleeding

Introduction

Although it is estimated that in excess of 10 million drug-eluting stents (DESs) have been implanted worldwide, the optimal duration of dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) with DESs remains unknown.[1] The guidelines of the American Heart Association/American College of Cardiology recommend that clopidogrel and aspirin therapy should be extended at least to 12 months after DES implantation or longer if a low bleeding risk exists.[2] The guidelines of the European Society of Cardiology suggest 6–12 months DAPT after DES implantation in accordance with published evidence.[3] The lack of concordance between guideline writing authorities reflects the scarcity of randomized trial data[4–6] as well as the inconsistency in observational studies dealing with the issue of DAPT duration.[7–10] In addition, although large-scale randomized trials are ongoing[11,12] their results are not expected to be available for some time. As a consequence, there remains considerable

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uncertainty regarding the safety and efficacy of extended DAPT after PCI.[13]

Against this background, we performed a meta-analysis of existing randomized trials investigating the clinical impact of extending DAPT duration after PCI in the setting of contemporary clinical practice.

Methods

Search strategy and selection criteria

We searched Medline, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), scientific sessions abstracts, and relevant websites (www.cardiosource.com, www.clinicaltrialresults.org, www.escardio.org, www.tctmd.com, and www.theheart.org), starting from 1 January 2002 without language or publication status restrictions. Reference lists of the eligible studies and previous reviews were checked to identify further evaluable articles. The last search was run on 31 March 2012. Search terms included the keywords and the corresponding Medical Subject Headings (MeSH) for: 'dual antiplatelet therapy', 'aspirin', 'clopidogrel', 'stent(s)', 'drug-eluting stent(s)', 'trial', and 'randomized trial'. Inclusion criteria were: (i) randomized design; (ii) intention-to-treat analysis; and (iii) ≥6-month follow-up after treatment allocation. Exclusion criteria were: (i) antiplatelet therapy comparison other than clopidogrel plus aspirin vs. aspirin alone; (ii) irretrievable or duplicated data; and (iii) ongoing trials.

Data collection and assessment of risk of bias

Two investigators (S.C. and R.A.B.) independently assessed reports for eligibility at the title and/or at the abstract level, with divergences resolved by a third investigator (T.T.). Studies that met inclusion criteria were selected for further analysis. Freedom from bias was evaluated by the same two authors, in accordance with the Cochrane Collaboration method[14] based on the following methodological items: adequacy of random sequence generation and allocation concealment, blinding (at participants or outcome assessors level), incomplete outcome data reporting, selective outcome depiction, adequate description of sample size calculation, and detailed funding sources disclosure. Formal quality score adjudication was not used, since previous investigations failed to demonstrate its usefulness.[15]

Outcome variables

The primary outcome of this meta-analysis is all-cause death. Secondary outcomes are: myocardial infarction (MI), stent thrombosis (ST), cerebrovascular accidents (CVAs), and major bleeding [thrombolysis in myocardial infarction (TIMI) classification]. All endpoints were evaluated according to per protocol definitions at the longest available follow-up.

Statistical analysis

Statistical analysis was performed with the RevMan software [Review Manager (RevMan). Version 5.1, The Cochrane Collaboration, Copenhagen, Denmark], and the Stata 11.2 statistical software (STATA Corp, College Station, Texas, USA). The κ-statistic was used to assess agreement between reviewers for study selection. Odds ratio (OR) and 95% confidence interval (95% CI) were used as summary statistics. Treatment effect could not be assessed in trials in which no event was reported within groups. For trials in which only 1 of the treatment groups had no events of interest, the treatment-effect estimate and its standard error (SE) were approximated from 2×2 contingency tables, after adding 0.5 to each cell.[16] The random effects model (DerSimonian and Laird) was used to calculate pooled OR for categorical variables. In case of statistical significance, the number needed to treat or the number needed to harm (NNH) with relative (95% CI) was provided. The Breslow-Day χ^2 test ($P < 0.1$) and the I^2 statistic were calculated to test the statistical evidence of heterogeneity across the studies. As a guide, I^2 values <25% indicated low, 25–50% moderate, and >50% high heterogeneity.[14] Visual inspection of funnel plot asymmetry was performed to address for possible small-study effect, as well as Egger's and Begg's test to address publication bias, over and above any subjective evaluation.[17] Random effects model was used to take into account the mean of a distribution of effects across studies and provides wider confidence intervals for the regression coefficients than fixed effect analysis, if residual heterogeneity exists. The weight used for each trial was the inverse of the sum of the within trial variance and the residual between trial variance. To estimate the additive (between-study) component of variance, tau-2, the restricted maximum likelihood method, was used to take into account the occurrence of residual heterogeneity. A random effect meta-regression analysis was conducted to estimate the extent to which including further covariates—the length of DAPT therapy in the experimental group (12 months or >12 months), the trial size (≤2000 patients or >2000 patients), the geographic area of enrolling countries (Asia or Europe), the use of the Endeavor zotarolimus-eluting stent (ZES, Medtronic, Inc., Santa Rosa, CA, USA), the use of everolimus-eluting stent (EES), the randomization at the time of index PCI, the nature of the study with respect to the publication status (full-length article or grey literature[18])—might have influenced the treatment effect for the endpoints considered. An influence analysis, in which meta-analysis estimates are computed omitting one study at time, was run for all endpoints considered. Finally, we performed exploratory adjusted indirect comparisons, according to the method of Bucher *et al.*[19] and Song *et al.*,[20] aiming at further expanding the observation from direct comparisons. The study was performed in compliance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (Supplementary material online, *Table S1*).[21]

Results

Eligible studies

We screened the title and/or the abstract of 410 potentially eligible publications (*Figure 1*). Of these, 370 citations were excluded since they were not relevant to this study or duplicated. Thus, 40 studies were assessed for eligibility and 36 studies were eliminated as inclusion criteria were not met. Finally, four trials (three full-length manuscripts,[4–6] one meeting presentation[22]) enrolling a total of 8231 patients (4132 randomized to extending DAPT duration and 4099 randomized to control DAPT duration) were included in the meta-analysis. The inter-observer agreement for study selection was good, with a κ-value of 0.91.

The main characteristics of the studies included are reported in Table 1. Briefly, patients with significant coronary artery disease (CAD) undergoing PCI plus stenting were randomized to extended vs. control DAPT duration. In two studies, the randomization to DAPT regimens took place at the time of PCI,[6,22] in one study 1 month after the index procedure[5] and in the remaining trial 12 months after the index procedure.[4] In this latter case, all patients experiencing adverse events after PCI were excluded before subsequent random allocation. Three out of four trials reported that loading doses of clopidogrel (300–600 mg, oral),

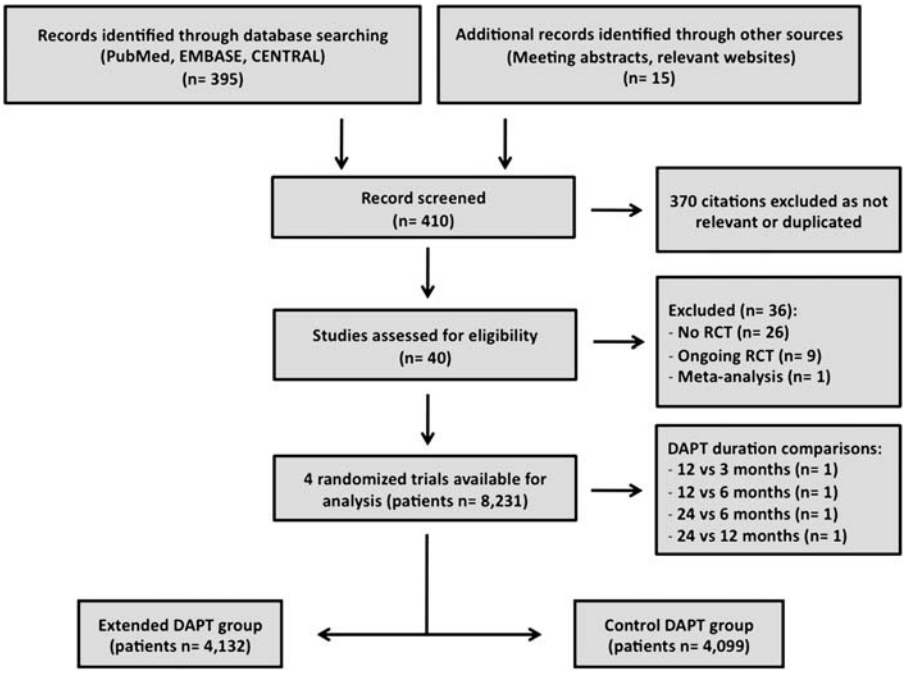

Figure 1 The PRISMA flow chart for the trial selection process. PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses. RCT, randomized controlled trial; DAPT, dual antiplatelet therapy.

as well as aspirin (160–325 mg orally or 500 mg i.v.[5] or at least 300 mg[4,6,22]) were assigned to all patients at the time of index PCI.[4–6] In all cases, aspirin was indefinitely recommended at a dose of 100–200 mg/day[4,6,22] or 80–160 mg/day,[5] while clopidogrel at a dose of 75 mg/day was prescribed for a period of time consistent with randomization assignment. Anticoagulation during coronary interventions was accomplished through the administration of either unfractionated heparin or bivalirudin in all patients. All interventions were performed in accordance with standard care including the administration of glycoprotein IIb/IIIa inhibitors, stent deployment optimization, or use of intravascular imaging techniques, at the operators' discretion. All subjects enrolled received treatments on top of other cardioactive therapies (e.g. beta-blockers, statins, etc.). Stratification to different stent types preceded the random allocation to DAPT groups in all studies. A variety of DESs were used: EES (Xience V, Abbott Vascular, Santa Clara, CA, USA; Promus, Boston Scientific, Natick, MA, USA), paclitaxel-eluting stents (PES, Taxus, Boston Scientific, Natick, MA, USA), sirolimus-eluting stents (SES, Cypher, Cordis, Warren, NJ, USA), and ZES (Endeavor; Resolute, Medtronic, Inc., Santa Rosa, CA, USA). In one study,[5] patients randomly allocated to bare-metal stent therapy were also included. One trial randomized patients with ongoing acute MI and with previous coronary stent implanted in the target vessel.[5] Two trials did not randomize patients with significant left main disease.[6,22] Further common key exclusions criteria among trials were compelling indications for long-term DAPT other than PCI or the need for anticoagulation, a bleeding diathesis or a planned short-term surgery. Per protocol endpoints definitions are listed in detail (Supplementary material online, *Table S2*).

Clinical features among included patients were typical for CAD populations and were well balanced among treatment arms in all studies. The mean age among patients enrolled ranged from 62 to 68 years, the percentage of males from 64 to 77%, the percentage of patients with a diagnosis of diabetes mellitus at admission from 24 to 38%, the percentage of patients with stable CAD from 26 to 48.5%, the percentage of patients undergoing the index procedure for a complex lesion (B2/C type) from 53 to 79.5%. The median DAPT duration was 16.8 (range 12–24) vs. 6.2 (range 3–12) months for the extended duration and control DAPT groups, respectively. The risk of bias among studies is reported in Supplementary material online, *Table S3*.

In each trial, clinical endpoints were adjudicated by independent committees.

Clinical endpoints

All trials contributed to the analysis either for primary or secondary endpoints. A total of 8158 patients (99.1%) were available for final calculations with a median follow-up of 16.8 months (range 12–24). All-cause death occurred in 187 patients (2.2%). No significant benefit in terms of all-cause death risk reduction was found with extended vs. control DAPT duration [2.4 vs. 2.1%; OR (95% CI) = 1.15 (0.85–1.54), $P = 0.36$; $I^2 = 0\%$, P for heterogeneity—phet = 0.56; *Figure 2*]. Myocardial infarction occurred in 123 patients (1.5%). No significant benefit in terms of MI risk reduction was found with extended vs. control DAPT duration [1.4 vs. 1.5%; 0.95 (0.66–1.36), $P = 0.77$; $I^2 = 0\%$, phet = 0.41; *Figure 3A*). Stent thrombosis occurred in 48 patients (0.5%). No significant benefit in terms of ST risk reduction was found with extended vs. control DAPT duration [0.5% vs. 0.6%; 0.88 (0.43–

Table I Main characteristics of included trials

Trial	EXCELLENT[6]	PRODIGY[5]	REAL/ZEST-LATE[4]	RESET[22]
Patients, *n*	1443	1970	2701	2148
Age, years	68	64	62	62
Male (%)	64.5	77	70	64
BMI, kg/m^2	25	26.6[a]	n/r	25
Diabetes (%)	38	24	26	29
Dyslipidaemia (%)	76	55	43	59
Hypertension (%)	73	72	58.5	62
Current smoker (%)	27	24	31	24
Ejection fraction (%)	61	52.5[a]	59.5	64
Previous PCI (%)	9	18	12	3
Stable CAD (%)	48.5	26	37.5	45
Multivessel disease (%)	52	66	48	n/r
Lesion Type B2/C (%)	53	66	79.5	68.5
LAD treated (%)	50	53	49	53
Stent/lesion	1.2	1.9	1.2	n/r
Stent length/lesion (mm)	28	30[a]	31	23
Clopidogrel LD	Yes	Yes	Yes	n/r
Glycoprotein IIb/IIIa inhibitors use (%)	1.7	n/r	n/r	1.9
Type of DES used	EES, SES	EES, PES, ZES	PES, SES, ZES	EES, SES, ZES[b]
Main inclusion criteria	≥1 de novo lesion; native coronary vessel; RVD ≥2.25 to 4.25 mm; >50% DS; stable angina, unstable angina, recent MI, silent ischaemia, positive functional study, or reversible changes on ECG consistent with ischaemia	≥18 years; ≥1 coronary artery lesion; ≥50% DS; PCI suitability; RVD ≥2.25 mm; chronic stable coronary artery disease or ACS (NSTEMI or STEMI)	<12 months DES implantation; no MACE (MI, stroke, repeat PCI) or major bleeding since PCI; DAPT on board	20–85 years; ≥50% DS; RVD ≥2.5 to 4.0 mm; elective PCI; stable angina, unstable angina, or acute MI
Main exclusion criteria	<72 h MI; <25% LVEF or cardiogenic shock; any stent implantation in the target vessel before enrolment; major bleeding <3 months; major surgery <2 months; elective surgery planned <12 months; >50% DS on the LM; CTO; true bifurcation lesions requiring a planned 2-stent strategy	Elective surgery planned <24 months after index PCI (unless DAPT could be maintained throughout the peri-surgical period); bleeding diathesis; major surgery <15 days; active bleeding or previous stroke <6 months; concomitant or foreseeable need for anticoagulants	DAPT contraindications due to bleeding diathesis or major bleeding history; long-term DAPT indication due to concomitant vascular disease or recent ACS	Cerebral/peripheral atherosclerotic arterial disease, thrombo-embolic disease or ST history; <40% LVEF; restenotic lesion; CTO; LM disease requiring intervention; cardiogenic shock; <48 h STEMI
Primary endpoint	Target vessel failure (composite of cardiac death, MI, or ID-TVR)	Composite of all-cause death, MI or CVAs	MI or cardiac death	Composite of cardiac death, MI, ST, ID-TVR and TIMI major or minor bleeding

Continued

Table 1 *Continued*

Trial	EXCELLENT[6]	PRODIGY[5]	REAL/ZEST-LATE[4]	RESET[22]
Secondary endpoint	Cardiac death; MI; ID-TVR; all-cause death; death or MI; ST; TIMI major bleeding; MACCE (a composite of death, MI, stroke, or any revascularization); safety endpoint (a composite of death, MI, stroke, ST or TIMI major bleeding)	All-cause death; MI; CVAs; cardiac death; ST; bleeding	All-cause death; MI, stroke; ST; repeat revascularization; composite of MI or all-cause death; a composite of MI, stroke or all-cause death; a composite of MI, stroke or cardiac death; TIMI major bleeding	-
Time to randomization	At index PCI	1 month after index PCI	12 months after index PCI	At index PCI
DAPT duration				
Extended DAPT group	12 months	24 months	24 months	12 months
Control DAPT group	6 months	6 months	12 months	3 months
Longest FU	12 months	24 months	24 months	12 months
Year	2012	2012	2010	2012
Registration number	NCT00698607	NCT00611286	NCT00484926 NCT00590174	NCT01145079

BMI, body mass index; PCI, percutaneous coronary intervention; CAD, coronary artery disease; LAD, left anterior descending artery; LD, loading dose (300–600 mg); DES, drug-eluting stents; FU, follow-up; EES, everolimus-eluting stent; PES, paclitaxel-eluting stent; SES, sirolimus-eluting stent; ZES, eluting stent; RVD, reference vessel diameter; DS, diameter stenosis; ACS, acute coronary syndrome; NSTEMI/STEMI, non-ST-elevation/ST-elevation myocardial infarction; MAC(C)E, major adverse cardiac (cerebrovascular) events; DAPT, dual antiplatelet therapy; MI, myocardial infarction; LVEF, left ventricular ejection fraction; LM, left main; CTO, chronic total occlusion; ST, stent thrombosis; ID-TVR, ischaemia-driven target vessel revascularization; CVAs, cerebrovascular accidents; TIMI, thrombolysis in myocardial infarction; NCT, national clinical trial.
Trial acronyms: EXCELLENT, Efficacy of Xience/Promus vs. Cypher to Reduce Late Loss After Stenting; PRODIGY, Prolonging Dual antiplatelet treatment after Grading stent-induced Intimal hyperplasia study; REAL/ZEST-LATE, Correlation of Clopidogrel Therapy Discontinuation in Real-World Patients Treated with Drug-Eluting Stent Implantation/Evaluation of the Long-Term Safety after Zotarolimus-Eluting Stent, Sirolimus-Eluting Stent, or Paclitaxel-Eluting Stent Implantation for Coronary Lesions—Late Coronary Arterial Thrombotic Events; RESET, Real Safety and Efficacy of a 3-month Dual Antiplatelet Therapy Following Zotarolimus-eluting Stents Implantation.
Overall mean values are reported.
[a]Median.
[b]Only Endeavor ZES (Medtronic, Santa Clara, CA, USA) was used in the control DAPT arm.

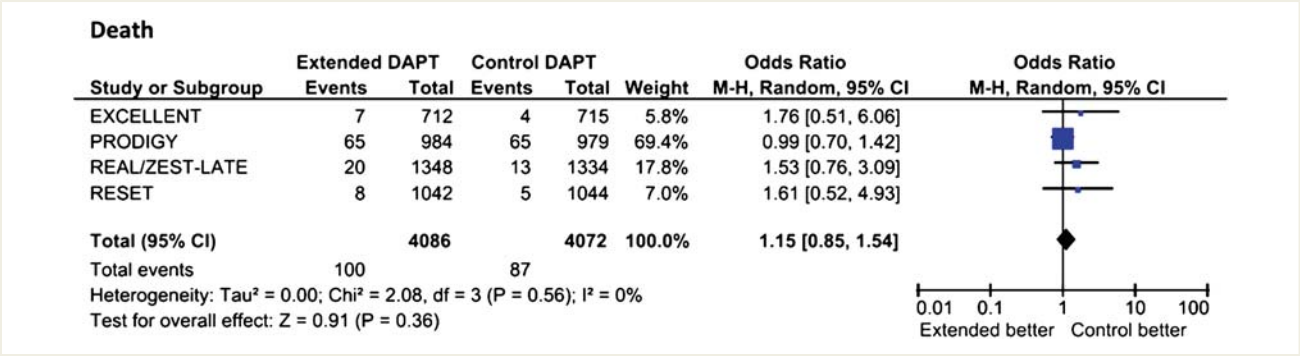

Figure 2 All-cause death in patients extending dual antiplatelet therapy (DAPT) after percutaneous coronary interventions. (*A*) Odds ratio with (95% confidence interval) of all-cause death associated with extended dual antiplatelet therapy vs. control group. The squares and the horizontal lines indicate the odds ratio and the (95% CI) for each trial included; the size of each square is proportional to the statistical weight of a trial in the meta-analysis; diamond indicates the effect estimate derived from meta-analysis, with the centre indicating the point estimate and the left and the right ends of the (95% CI).

1.81), $P = 0.73$; $I^2 = 16\%$, phet = 0.31; *Figure 3B*]. Cerebrovascular accidents occurred in 68 patients (0.8%). No significant benefit in terms of CVAs risk reduction was observed with extended vs. control DAPT duration [1.0 vs. 0.6%; 1.51 (0.92–2.47), $P = 0.10$; $I^2 = 11\%$, phet = 0.81; *Figure 3C*]. Thrombolysis in myocardial infarction major bleeding occurred in 40 patients (0.5%). A significant risk increase in TIMI major bleeding was observed with extended vs. control DAPT duration [0.7 vs. 0.2%; 2.64 (1.31–5.30), $P = 0.006$; $I^2 = 0\%$, phet = 0.99; NNH = 227 (134–730); *Figure 3D*].

Small study effects and sensitivity analyses

The Supplementary material online, *Figure S1* shows the funnel plot distribution of the primary endpoint: the SE of the lnOR was plotted against the OR of all-cause death. Both Egger's ($P = 0.55$) and Begg's ($P = 0.50$) tests could validate the absence of bias due to small study effects. Moreover, for neither primary (*Figure 4*) nor secondary endpoints (Supplementary material online, *Figure S2A–D*) was a significant interaction of the prespecified covariates on the treatment-effect observed.

Influence analysis and adjusted indirect comparison

Influence analysis demonstrated that no single study significantly altered the summary ORs for each endpoint considered, since one-at-a-time study omission did not result in a movement of the point estimate outside the 95% CI. This suggests the absence of an imbalanced contribution from individual included studies to the risk estimates observed. Finally, the exploratory adjusted indirect comparisons confirmed the lack of advantage of extending DAPT therapy, suggesting a significantly higher risk of bleeding associated with 24-month vs. 3-month DAPT duration ($P = 0.046$) and with 24-month vs. 6-month DAPT ($P = 0.047$) (Supplementary material online, *Figure S3A–C*).

Discussion

In the present study, we report a meta-analysis of randomized trials assessing the clinical impact of extending DAPT duration after PCI. The main findings are: (i) extended DAPT duration increases the risk of bleeding; (ii) extended DAPT duration does not reduce the risk of all-cause death, MI, ST, and CVAs; (iii) no treatment-effect modification is found with respect to several covariates including DAPT duration >12 months, trial size, geographic area of enrolment, clinical indication for PCI, use of Endeavor ZES or EES and publication status; (iv) the internal validity of these observations is supported by the absence of significant heterogeneity across the trials for all outcomes assessed and the lack of evidence of influence or publication bias for the primary endpoint. These findings serve to underline the risk:benefit problems inherent to a strategy which attempts to address a local issue (i.e. late ST and delayed arterial healing) by recourse to a systemic therapy (i.e. prolonged DAPT). Moreover, it underscores the fact that the prolongation of DAPT is associated with a relatively time-independent risk of bleeding while the risk of late and very late ST likely reduces with time.

It is well recognized that in patients undergoing PCI periprocedural DAPT play an important role in reducing thrombotic events.[23] However, at what time point the declining benefit in preventing ischaemic events is outweighed by the near constant bleeding risk remains a matter of considerable controversy.[8] Although early trials performed in the bare-metal stent era documented a reduction in ischaemic events associated with the prolongation of DAPT in patients undergoing PCI, this occurred at the expense of a higher bleeding risk.[24,25] Moreover, these trials investigated a dual element strategy—namely DAPT loading plus prolonged therapy duration vs. no loading dose plus standard duration therapy—without employing a factorial design. Accordingly the ascription of any observed benefit to DAPT prolongation alone is not without concern.

First-generation DESs initially carried a recommendation for 3 months of DAPT duration in patients receiving SES and 6 months in those receiving PES.[26] Subsequently concerns emerged regarding

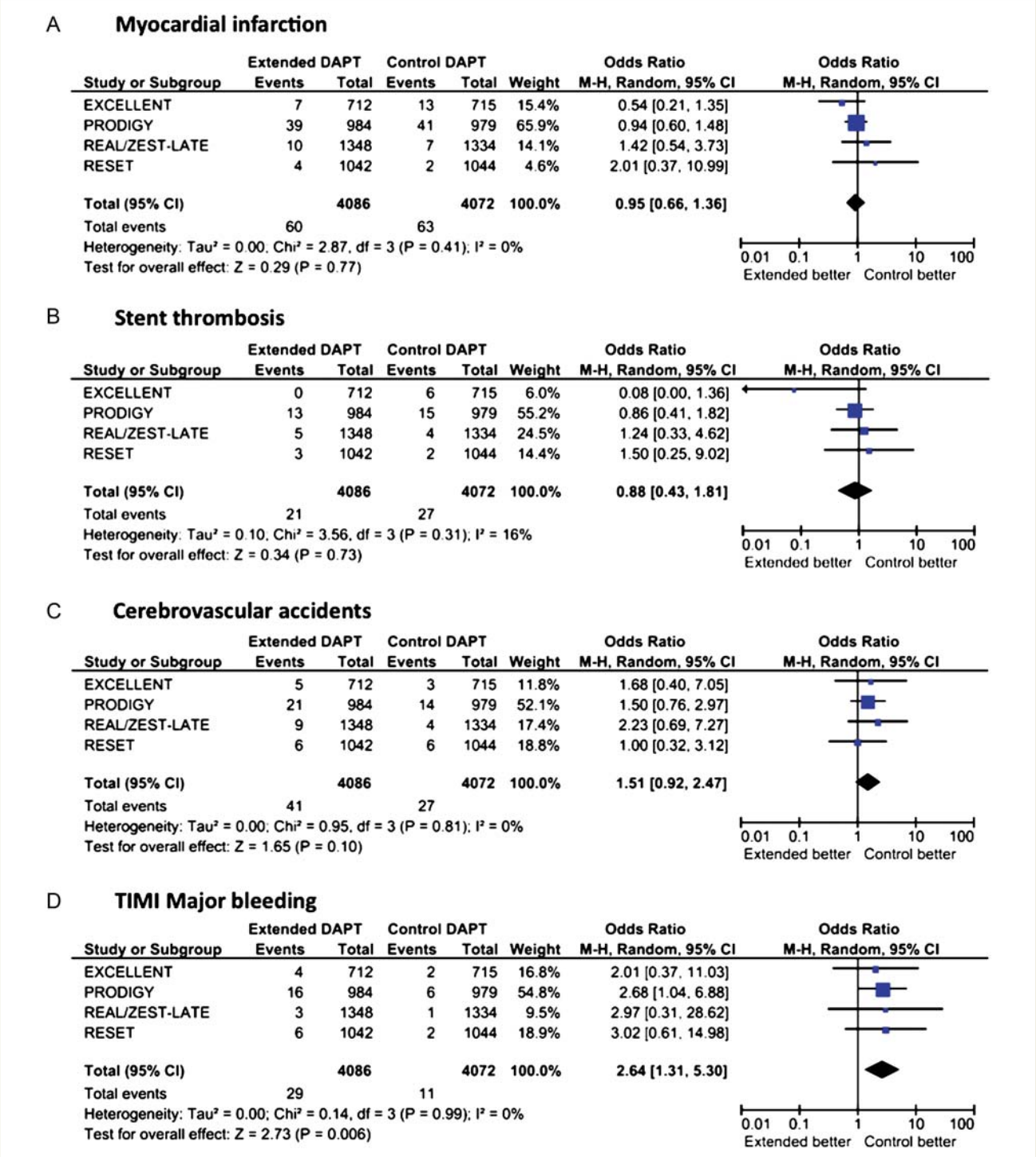

Figure 3 Outcomes of patients extending dual antiplatelet therapy after percutaneous coronary interventions. (*A*) Odds ratio with (95% confidence interval) for myocardial infarction; (*B*) stent thrombosis, (*C*) cerebrovascular accidents, and (*D*) thrombolysis in myocardial infarction major bleeding. DAPT, dual antiplatelet therapy.

an excess of cardiac events among patients prematurely discontinuing DAPT before the suggested mandatory period[27] and meta-analysis and registry data suggested a higher rate of death or MI in patients treated with DESs as opposed to bare-metal stents even in those treated with recommended duration DAPT.[28,29] Meanwhile autopsy studies confirmed the importance of delayed arterial healing as a central aetiological factor.[30] In the USA this led to the updated professional society recommendations to extend DAPT after DESs implantation out to a minimum of 1 year or 'indefinitely' in some cases, though this advice derived from consensus and

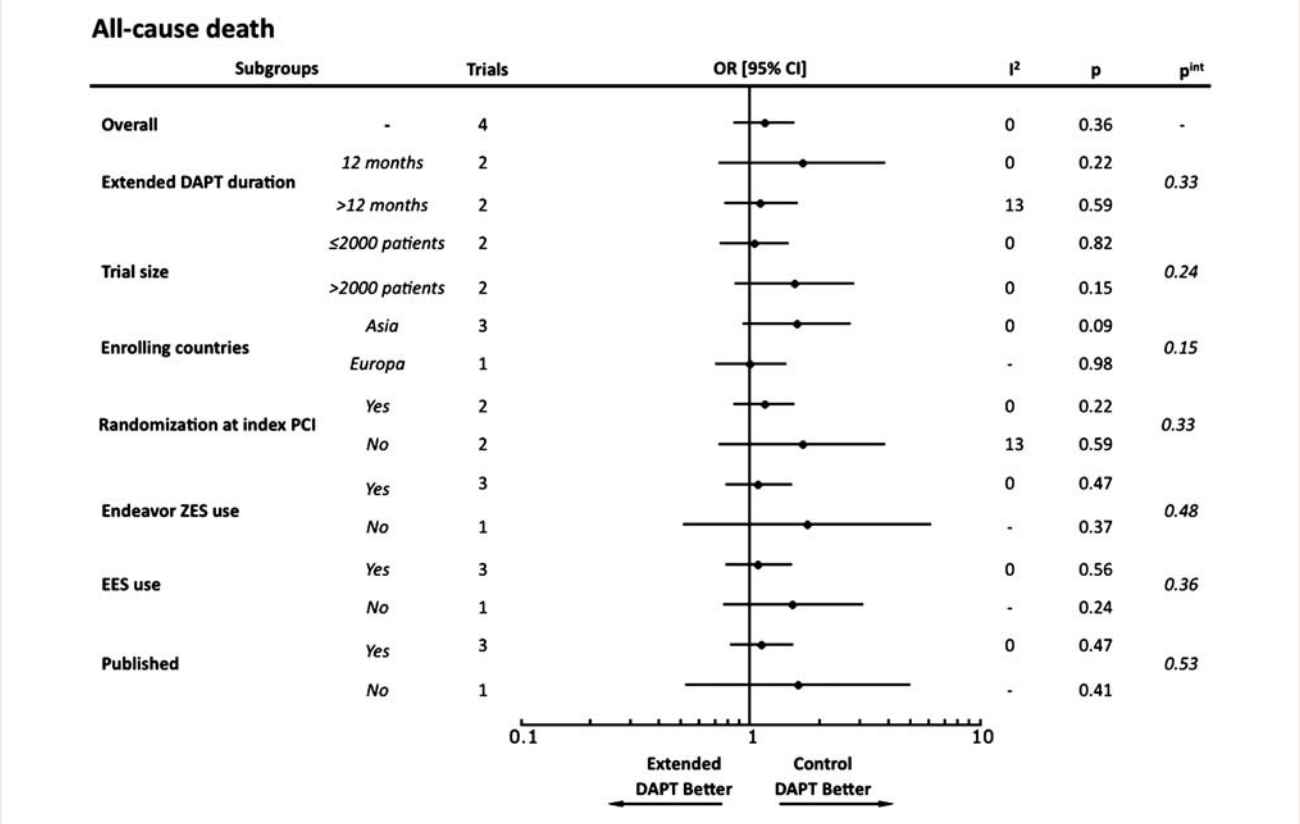

Figure 4 Sensitivity analyses of treatment-effect modification for all-cause death in the subgroups of interest. Odds ratio and (95% confidence interval) are used as summary statistics and are presented as plot: the centre indicates the point estimate and the left and the right ends of the line the (95% CI); I^2 statistic describes heterogeneity across trials included among subgroups of interest, excepting in those cases for which only one trial is included within a subgroup; P^{int}: *P*-values for interaction between treatment-effect and subgroups are derived with meta-regression analysis. DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention; ZES, zotarolimus-eluting stent; EES, everolimus-eluting stent.

was not based on solid evidence.[1,3] Moreover several subsequent retrospective analyses failed to disclose the whole spectrum of outcomes associated with extended DAPT duration (e.g. bleedings) due to the stent-oriented design of original studies; as a consequence their results largely underestimated event occurrence.[31,32]

Data from specifically designed randomized trials aiming to address the most appropriate duration of DAPT after drug-eluting stenting have recently been published or presented and their results are synthesized within the framework of the present analysis. However, two pivotal factors have prevented the investigators in these studies from drawing firm conclusions. Firstly, the identification of differences in rarely occurring adverse events—such as ST—requires the analysis of large patient numbers.[10] Indeed, the power of the studies thus far published has been limited in this regard. This aspect was reflected by the lack of common findings within the studies included: in the Efficacy of Xience/Promus vs. Cypher to Reduce Late Loss After Stenting (EXCELLENT) study thrombotic stent occlusion occurred more frequently in the control DAPT group;[6] the Prolonging Dual antiplatelet treatment after Grading stent-induced Intimal hyperplasia (PRODIGY) study found a significant increase in the risk of bleeding in the extended DAPT group;[5] the Correlation of Clopidogrel Therapy Discontinuation in Real-World Patients Treated with Drug-Eluting Stent Implantation/ Evaluation of the Long-Term Safety after Zotarolimus-Eluting Stent, Sirolimus-Eluting Stent, or Paclitaxel-Eluting Stent Implantation for Coronary Lesions—Late Coronary Arterial Thrombotic Events (REAL/ZEST-LATE) trial[4] found a trend to increased risk of MI/stroke and death (cardiac and non-cardiac) in the extended DAPT group; in the Real Safety and Efficacy of a 3-month DAPT Following the Zotarolimus-eluting Stents Implantation (RESET) trial there was no significant difference with regard to adverse events between treatment arms.[22] Secondly, it is imperative that studies investigating the role of the prolongation of DAPT have broad inclusion criteria—both in terms of patients enrolled as well as and stent types used—in order to provide a reliable picture of current practice. Indeed, the atherosclerotic milieu varies among stable and unstable CAD patients,[33] and different stent platforms may be associated with different risks of adverse events.[34,35]

The current report represents the first meta-analysis of randomized trials specifically designed to assess the clinical impact of extending DAPT after coronary stenting in contemporary practice.

We found that extending DAPT duration after PCI does not reduce the risk of all-cause death, MI, ST, or CVAs. Notably, however, longer DAPT duration significantly increases the risk of TIMI major bleeding [absolute risk increase 0.44% (0.14–0.74)] an endpoint that has a considerable prognostic impact in patients undergoing PCI.[36] In this regard, time-independent bleeding hazard may be thought to play a central role in the impact associated with an extension of DAPT duration, acting as a major determinant of the benefit:risk balance. In a recent meta-analysis,[37] Zhang *et al.* found that in patients undergoing DES implantation the risk of death/non-fatal MI increases with a DAPT duration <6 months and it is not reduced with a DAPT duration >12 months. At least two major differences between this meta-analysis and the present study should be acknowledged: as first, Zhang *et al.* predominantly pooled observational studies and *post hoc* analyses of stent registries instead of specifically designed randomized trials, as we did in the present study. Secondly, we thoroughly addressed the usefulness of extending DAPT in terms of balance between reduction in ischaemic events and increase in bleeding risk. In this respect, the meta-analysis of Zhang *et al.* can provide informations only regarding the efficacy of different DAPT durations in terms of death/non-fatal MI risk, while inherent safety issue (risk of bleeding), the main finding of the current study, was not investigated. In the present study, we included a total of 8231 patients by pooling the results of four randomized trials enrolling patients with a broad spectrum of clinical presentations. This represents the largest number of patients analysed in such type of studies and is likely to remain the best evidence base for guiding DAPT duration after contemporary stenting in advance of data from the ongoing Intracoronary Stenting and Antithrombotic Regimen—Safety And EFficacy of Six Months Dual Antiplatelet Therapy After Drug-Eluting Stenting (ISAR-SAFE—NCT00661206)[11] and Dual Antiplatelet Therapy (DAPT—NCT00977938)[12] randomized controlled trials. These two double-blind trials plan to randomize patients undergoing PCI to a strategy of 6 vs. 12 months DAPT ($n = 6000$)[11] or to a strategy of 12 vs. 30 months DAPT ($n = 20\,645$),[12] after a complete DAPT course of 6 [11] or 12 months,[12] respectively. In addition, further randomized trials investigating the role of new biodegradable-polymer DES in association with (Global LEADERS)[38] or without new potent antiplatelet drugs (A Randomized Clinical Evaluation of the BioFreedom™ Stent—LEADERS Free)[39] have been recently announced. The results of these studies will be eagerly expected over the coming years.

In this meta-analysis, treatment effect modifications among different subgroups of interest were tested: there was no interaction of DAPT duration >12 months, of studies enrolling >2000 patients, of when the randomization took place, or of the publication status of the studies. Similarly, we investigated whether the inclusion of trials performed in Asia (which typically show lower adverse events rates when compared with trials performed in other geographic areas[40]), the use of the Endeavor ZES (which was associated with the shortest DAPT duration[22]), or the use of EES (which may have lower rates of cardiac events when compared with different DES platforms[35,40]) might have an impact on events occurrence. The lack of evidence for interaction is reassuring and reinforces the validity of present findings.

Study limitations

There are a number of limitations to the current analysis, which should be acknowledged. First of all, this is a meta-analysis performed on study-level data. Although some investigators may prefer patient-level analyses, we believe that the questions under consideration can be reliably answered by a meta-analysis of aggregate data. Secondly, the total number of events remained relatively low despite pooling the data from 8231 patients: this limits the strength of conclusions regarding differences in rare events such death and ST. Moreover, due to the design of most of the included trials, especially of those in which enrolment was limited to patients who remained event-free some months after the index PCI, higher-risk patients were more likely to be excluded. Thus, the present results might not be generalizable to such higher-risk patients. Thirdly, in only one of four studies patients were randomized to continue or stop DAPT 12 months after PCI.[4] In the other three studies,[5,6,22] patients were randomized at time of PCI[6,22] or 1 month after the procedure.[5] Thus, they received the same therapy for at least 3[22] to 6 months[5,6] and a relevant part of the adverse events occurred during this period. However, landmark analyses available in two of the latter three studies[5,6] showed no effect of extending DAPT therapy even when only events occurring after the control group stopped DAPT were assessed. This is in line with the results of the study mentioned above in which event assessment started at 12 months after PCI when the control group stopped DAPT.[4] Fourthly, the duration of follow-up was limited to a median of 16.8 months. More extended follow-up would have been highly desirable and we cannot exclude that significant differences may emerge at long term, even though the available 24-month follow-up[4,5] did not reveal directional changes in events. Fifthly, patients treated with a number of different DES types were included and although this reflects real-world practice, it remains possible that the requisite duration for DAPT varies for each individual DES platform. In this regard, although we did not find an interaction between the use of EES and the risk of ST, the confirmation of the lower thrombogenicity of this platform as compared with other DES[40,41] was beyond the scope of this study. Similarly, a total of 462 patients from one trial (5% of overall included patients) were treated with bare-metal stents, a fact that is less likely to influence overall results.[5] Sixthly, recent pharmacological innovations might have improved revascularization safety and efficacy: in this regard, the proficiency of a clopidogrel-based DAPT compared with one based on newer potent antiplatelet drugs needs to be assessed in specifically designed studies. Finally, the lack of a common comparator among the trials included clearly precludes recommendation concerning the ideal DAPT duration in patients undergoing PCI. The present analysis aims to define the benefit and harm associated with extended DAPT duration after PCI, rather than to address the minimum DAPT period after stenting. The aggregate results of direct comparisons suggest that the extension of DAPT is related to no measurable benefit beyond 6 months and possible harm beyond 12 months. However, we strongly believe that increasing knowledge of clinical, mechanical, and pathophysiological factors associated with ST after PCI may lead to a paradigm-shift, with tailoring of treatment duration according to the need of the individual patient.[13]

Conclusions

The results of the present meta-analysis demonstrate that a universal strategy of extending the duration of DAPT in patients undergoing PCI with DES implantation does not reduce death, MI, ST, or CVAs but does result in an increased risk of bleeding. To improve clinical outcomes patient-specific benefit: risk assessment and tailored DAPT is likely to represent the most successful approach.

Supplementary material

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

Conflict of interest: A.K. reports receiving consulting or lecture fees from Abbott, AstraZeneca, Biotronik, Bristol-Myers Squibb, Cordis, Daiichi Sankyo/Eli Lilly, Medtronic, and The Medicines Company. The other authors declare no potential conflict of interest.

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