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ORIGINAL ARTICLE
Acute coronary syndromes

Efficacy and safety of prolonged dual antiplatelet therapy: a meta-analysis of 15 randomized trials enrolling 85 265 patients

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Aims The optimal duration of dual antiplatelet therapy (DAPT) in patients with ischaemic cardiovascular (CV) disease is still debated. Previous meta-analyses reported conflicting results about prolonged DAPT on mortality and major CV events. Aim of this study was to assess the effects of prolonged vs. no/short-term DAPT on myocardial infarction (MI), stroke, bleeding, and mortality.

Methods and results Trial inclusion criteria were: randomization to prolonged duration vs. no/short DAPT; reporting of at least one outcome among overall and CV death, MI, stroke, major non-fatal, fatal, and intracranial bleeding. Fifteen randomized studies including 85 265 patients were included. Prolonged DAPT, compared with no or short DAPT, significantly reduced MI (RR: 0.785, 95% CI: 0.729–0.845, $P < 0.001$) and stroke (RR: 0.851, 95% CI: 0.754–0.959, $P = 0.008$), but had no effect on overall (RR: 0.989, 95% CI: 0.921–1.061, $P = 0.751$) or CV (RR: 0.951, 95% CI: 0.872–1.037, $P = 0.258$) mortality. Prolonged DAPT significantly increased major non-fatal (RR: 1.690, CI: 1.322–2.159, $P < 0.001$), but not intracranial or fatal bleeding (RR: 1.236, CI: 0.899–1.698, $P = 0.192$, RR: 1.069, CI: 0.760–1.503, $P = 0.703$; respectively). The effects of DAPT were similar to those reported in the overall analysis in patients with stable CV disease, whereas in those with unstable CV disease only the significant reduction of stroke was not confirmed. Dual antiplatelet therapy prolonged beyond 1 year significantly reduced MI but not stroke, all-cause, or CV death. It significantly increased the risk of major non-fatal bleeding, with no difference in intracranial and fatal bleeding.

Conclusion Prolonged DAPT significantly reduced ischaemic CV events but not mortality. Even if a significant increase of major non-fatal bleeding was detected, no increased risks of intracranial and fatal bleeding were observed.

Keywords Dual antiplatelet therapy • acute coronary syndrome • stable coronary artery disease • randomized clinical trials • meta-analysis

Introduction

Dual antiplatelet therapy (DAPT), consisting of the combination of aspirin and a $P2Y_{12}$ inhibitor, is recommended by guidelines for up to 12 months in patients with acute coronary syndromes (ACS) or in whom coronary or peripheral stents have been implanted.[1,2] In patients with stable coronary artery disease (CAD), European guidelines recommend DAPT for at least 1 month after bare metal stent (BMS) implantation and for at least 6 months after drug-eluting stents (DES).[1] Finally, in those undergoing infra-inguinal BMS implantation DAPT is recommended for at least 1 month.[1,2] In patients with cerebrovascular disease, DAPT after carotid artery stenting is indicated, but the optimal duration of the treatment has not been not established.[1,2]

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It is well recognized that patients suffering ACS remain at increased residual cardiovascular (CV) risk beyond 1 year following an ACS compared with patients who never suffered an ischaemic CV event.[3] Thus, optimal duration of DAPT in patients suffering from an ACS remains controversial and the debate has been fuelled by the introduction of new generation $P2Y_{12}$ inhibitors such as prasugrel and ticagrelor that proved to be more efficacious in reducing ischaemic events, although at the expense of increased, yet non-fatal, major bleedings.[4,5] Similarly, optimal antiplatelet treatment and duration for stable patients with or without previous ischaemic events has been investigated with conflicting results.[6,7] Recently, the PEGASUS trial[7] reported a significant reduction of the primary composite end point of CV death, myocardial infarction (MI), and stroke in 21 162 stable patients with a previous MI, if DAPT had been initiated at a median of 1.7 years after an MI and continued for a median of 33 months.

Of note, DAPT is associated with a significant increase in major bleeding, compared with aspirin alone.[7] Thus, careful evaluation of potential prevention of ischaemic events vs. the risk of severe bleeding is required in individual patients before deciding on DAPT duration, as recently recommended by non-ST elevation ACS European guidelines.[8] Previous meta-analyses investigated the effects of DAPT on CV and all-cause mortality with conflicting results.[9–11] The only available meta-analysis that included results of the large PEGASUS trial,[7] reported a significant reduction of CV mortality, stroke, and MI in patients with previous MI, at the expense of increased major bleeding risk.[11] However, this meta-analysis was restricted to post-MI patients and only included six trials.

In light of these conflicting results, the purpose of this study was to meta-analyse all available studies on DAPT, to assess the effects of prolonged DAPT on MI, stroke, and bleedings, as well as all-cause and CV death, in patients with ischaemic cardiovascular diseases (CVD).

Materials and Methods

Search strategy

This study was designed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.[12] MEDLINE, Cochrane Database, ISI Web of Sciences, and SCOPUS were searched for articles published in English and other languages until June 2015. Studies were identified by the following headings: dual antiplatelet therapy, clopidogrel, prasugrel, ticagrelor, random, and randomized controlled trial.

Study selection

Study inclusion criteria were: randomized allocation to extended vs. no or short duration dual antiplatelet therapy; report of at least one clinical event among all-cause and CV death, MI, stroke, major non-fatal, intracranial, and fatal bleeding.

Data extraction and quality assessment

Two reviewers (G.S. and P.P.F.) independently selected potentially eligible trials. Discrepancies were resolved by consensus. From each study, information about the inclusion criteria, year of publication, number of patients in treatment and control arms, duration of follow-up, age, gender, body mass index, smoking, CV risk factors, prior MI, prior stroke, and baseline medications were abstracted by one author (G.S.) and checked by another author (P.P.F.). The outcomes of the analysis were: all-cause death, CV death, MI, stroke, major non-fatal, intracranial, and fatal bleeding. Long DAPT duration was defined as any combination therapy including aspirin and a $P2Y_{12}$ inhibitor lasting $\geq$6 months whereas short duration or no DAPT was defined as aspirin alone therapy or any DAPT combination lasting $<$6 months.[9]

The methodological quality of trials was assessed by Detsky method, scoring the following items: method of randomization (1 point), adequate description of method of randomization (2 points), blindness (2 points), adequate description of outcome (1 point), and of outcome assessment (2 points), as well as inclusion/exclusion criteria (2 points), number of patients excluded and reasons (2 points), description of therapy in treatment and control groups (4 points), and appropriateness of statistical analysis (up to 5 points).[13]

Data synthesis and analysis

Relative risks (RRs) of the effect of randomized treatments were calculated using the metan routine STATA (version 12.0, StataCorps, College Station, TX, USA) to account for the probability of events occurring in the treatment group vs. the control group. The RR and 95% confidence interval (CI) for each outcome were separately calculated for each trial, with grouped data, using the intention-to-treat principle.[14] Overall, estimates of effect were calculated with a fixed-effects model or with a random-effects model when significant heterogeneity was reported.[15] The assumption of homogeneity between the treatment effects in different trials was tested with the Q and I^2 statistics. A significant heterogeneity was defined by a $P \leq 0.05$ at Q statistic; I^2 ranging from 50 to 90% might indicate substantial heterogeneity and from 75 to 100% might represent considerable heterogeneity.[16] The significance level for all outcome and heterogeneity analyses was set at $P \leq 0.05$.

Sensitivity analysis

To verify the consistency of outcome meta-analysis results, the influence of each individual study on the summary effect estimate was assessed by the one-study removed sensitivity analysis using the 'metaninf' command (STATA).[17]

Random-effects meta-regression analysis was performed with the metareg command[18,19] (STATA Statacorp, version 14.0) to test the influence of age, gender, body mass index, prior MI, prior stroke, diabetes mellitus, hypertension, hypercholesterolemia, current therapy, and length of follow-up on our results.

Subgroup analyses were performed for trials enrolling patients with stable ischaemic CVD and patients with acute CVD defined as unstable. Stable patients trials were identified as those enrolling patients with stable CVD or in which the study treatments did not start at the moment of an acute CV event (acute MI or acute stroke). Further subgroup analysis was performed for trials in which patients in the treatment group were receiving DAPT for at least 1 year.

Publication bias

To evaluate potential publication bias, funnel plots were considered and a weighted linear regression was used, with the natural log of the odds ratio as the dependent variable and the inverse of the total sample size as the independent variable. This is a modified Macaskill's test, which gives more balanced type I error rates in the tail probability areas compared with other publication bias tests.[20]

Results

Characteristics of included trials

Of 2562 papers identified in the initial search, 72 were retrieved for more detailed evaluation. Fifty-seven studies were subsequently

excluded. Therefore, 15 trials[6,7,21–33] were finally included in the analysis, which enrolled a total of 85 265 patients (28% females; mean age 63 ± 2 years) of which 46 189 were assigned to prolonged DAPT and 39 076 patients to no or short-term DAPT (Supplementary material online, *Figure S1*). The median follow-up 19 months (range: 7–42). Baseline characteristics of 15 trials included in the meta-analysis are shown in *Table 1*.

Methodological quality

Median Detsky score was 95% (range: 90–95%), indicating a good quality of the trials included. However, no trial satisfied all Detsky score items. No trial was triple-blinded, whereas 8 (53%)[6,7,22–25,28,31] were double-blinded, 6 (40%)[21,26,27,29,30,32] were open-label, and in 1 (7%)[33] blindness was not properly described. In only 1 trial of 15 (7%)[20] included in our study, the sample size was not calculated.

Outcomes analysis

Overall analysis

Myocardial infarction and stroke occurred in 3.0 and 1.2% of patients enrolled to prolonged DAPT compared with 3.6 and 1.3% of those randomized to no or short-term DAPT, respectively. Thus, prolonged DAPT significantly reduced the risk of MI by 21.5% (*P* comparison <0.001; *P* heterogeneity = 0.075, i^2= 36.8%) and of stroke by 14.9% (*P* comparison = 0.008; *P* heterogeneity = 0.811, i^2= 0.0%) compared with no or short-term DAPT (*Figure 1*).

All-cause and CV death occurred in 3.6 and 2.6% of patients randomized to prolonged DAPT compared with 3.5 and 2.7% of those allocated to no or short-term DAPT, respectively. Thus, no difference in risk of all-cause (*P* comparison = 0.751; *P* heterogeneity = 0.693, i^2= 0.0%) and CV death (*P* comparison = 0.258; *P* heterogeneity = 0.758, i^2= 0.0%) was reported between prolonged and no or short-term DAPT (*Figure 2*).

Major non-fatal bleeding occurred in 1.8% of patients allocated to prolonged DAPT compared with 1.2% of those enrolled to no or short-term DAPT, resulting in a significant 69% increase of risk in patients receiving prolonged DAPT (*P* comparison <0.001; *P* heterogeneity = 0.009, i^2= 57.7%; *Figure 3*).

Intracranial and fatal bleeding were reported in 0.3 and 0.2% of patients treated with prolonged DAPT and were the same in those receiving no or short-term DAPT, respectively, resulting in no significant difference in risk of intracranial (*P* comparison = 0.192; *P* heterogeneity = 0.654, i^2= 0.0%) and fatal (*P* comparison = 0.703; *P* heterogeneity = 0.386, i^2= 5.7%) bleeding between groups (*Figure 3*).

Definition of bleeding differed among included trials. In particular, five trials adopted GUSTO criteria,[6,23–25,30] eight trials used TIMI criteria,[7,22,26–29,31,32] one trial[21] adopted STEPPLE criteria and one trial[33] used BARC criteria. When analysis was restricted to the five trials using GUSTO criteria or to the eight trials using TIMI criteria, no differences were observed and results confirmed the overall analysis (Supplementary material online, *Table S1*).

Stable vs. unstable cardiovascular diseases

Twelve[6,7,21,22,24–26,28–30,33,34] and four trials[23,27,32,34] enrolled patients with stable (67 678 subjects) and unstable (17 587 subjects) CVD, respectively (*Figure 4*).

In patients with stable and unstable CVD, MI occurred in 2.7 and 4.2% of subjects allocated to prolonged DAPT compared with 3.1 and 5.4% of those randomized to short-term or no DAPT, respectively, resulting in a significant reduction of risk by 20.5% in patients undergoing prolonged DAPT with stable (*P* = 0.007) and by 21.7% in those with unstable (*P* < 0.001) CVD.

Stroke was reported in 1.2 and 1.4% of patients with stable CVD enrolled to prolonged and short-term or no DAPT, respectively, vs. 1.1 and 1.3% in those with unstable CVD. Thus, prolonged DAPT significantly reduced the risk of stroke by 16.8% in patients with stable (*P* = 0.007) but not in those with unstable (*P* = 0.323) CVD.

In patients with stable CVD, all-cause mortality and CV death occurred in 3.3 and 2.2% of subjects allocated to prolonged DAPT and in 3.1 and 2.1% of those randomized to short-term or no DAPT, respectively. In patients with unstable CVD, all-cause mortality and CV death were reported in 4.9 and 3.9% of patients receiving prolonged DAPT and in 5.2 and 4.2% of those enrolled to short-term or no DAPT, respectively. Compared with patients enrolled to no or short-term DAPT, prolonged DAPT did not affect all-cause and CV death in patients with either stable (*P* = 0.830 and *P* = 0.427; respectively) or unstable (*P* = 0.361 and *P* = 0.304; respectively) CVD.

In patients with stable and unstable CVD, major non-fatal bleeding was reported in 1.5 and 3.2% of subjects randomized to prolonged DAPT compared with 0.9 and 2.2% of those enrolled to short-term or no DAPT, respectively. Thus, risk of major non-fatal bleeding was significantly increased by 78.7% in patients allocated to prolonged DAPT with stable (*P* < 0.001) and by 45.5% in those with unstable (*P* < 0.001) CVD.

In patients with stable CVD, intracranial and fatal bleeding occurred in 0.4 and 0.2% of subjects enrolled to prolonged DAPT and in 0.3 and 0.1% of those receiving short-term or no DAPT, respectively. In patients with unstable CVD, fatal bleeding were reported in 0.2 and 0.3% of patients allocated to prolonged DAPT and to short-term or no DAPT, respectively. Compared with patients enrolled to no or short-term DAPT, prolonged DAPT did not affect the risk of intracranial and fatal bleeding in patients with stable (*P* = 0.465 and *P* = 0.397; respectively) CVD and, similarly, did not impact on the risk of fatal bleeding in subjects with unstable (*P* = 0.516) CVD. It was not possible to evaluate the risk of intracranial bleeding in patients with unstable CVD enrolled to prolonged DAPT vs. those undergoing short-term or no DAPT since only one study reported data on this outcome.[23]

Dual antiplatelet therapy beyond 1 year vs. shorter or no dual antiplatelet therapy

Seven trials[7,21,22–24,27,29] enrolled patients (42 906 subjects) receiving DAPT beyond 1 year. Myocardial infarction and stroke occurred in 3.0 and 0.6% of patients receiving DAPT for >1 year compared with 3.6% and 0.5 in those receiving shorter or no DAPT, respectively (*Figure 4*). Thus, DAPT beyond 1 year, when compared with shorter or no DAPT, significantly reduced by 25.7% the risk of MI (*P* = 0.022) without any significant effect on risk of stroke (*P* = 0.192).

All-cause and CV death occurred in 3.4 and 2.0% of patients randomized to DAPT beyond 1 year compared with 2.9 and 1.9% of those receiving shorter or no DAPT, respectively. Thus, no

Table 1 Baseline characteristics of trials included in the meta-analysis

Trials	Population	Design	Treatment (*n*)	Control (*n*)	Follow-up (months)
ARCTIC-interruption[21]	Patients scheduled for planned DES	Continued DAPT therapy for further 6–18 months vs. aspirin alone	635	624	17
CHARISMA[6]	Patients with multiple atherothrombotic risk factors, documented stable CAD, CBVD, or PAD	DAPT vs. aspirin alone	7802	7801	28
CREDO[22]	Patients with CAD eligible for PCI	12-month vs. 1-month DAPT	1053	1063	12
CURE[23]	Patients with ACS NSTEMI hospitalized within 24 h after the onset of symptoms	DAPT vs. aspirin alone	6259	6303	12
DAPT BMS[24]	Patients who underwent BMS implantation and tolerated DAPT to 12 months	Continued DAPT vs. aspirin alone	842	845	33
DAPT DES[25]	Patients who underwent DES implantation and tolerated DAPT to 12 months	Continued DAPT vs. aspirin alone	5020	4941	33
DES LATE[26]	Patients who underwent DES implantation at least 12 months before enrolment and receiving DAPT	Continued DAPT vs. aspirin alone	2531	2514	42
EXCELLENT[27]	Patients with at least 1 lesion in a native coronary vessel determining stenosis of ≥50% and evidence of myocardial ischaemia (included 48.5% of patients with unstable angina/NSTEMI ACS)	12-month vs. 6-month DAPT	721	722	12
ISAR-SAFE[28]	Patients receiving DAPT at 6 months after DES implantation due to symptoms or signs of coronary artery disease	Continued DAPT vs. aspirin alone	2003	1997	7
ITALIC[29]	Patients implanted with at least 1 Xience V DES and all clinical situations excluding primary PCI for acute MI and treatment of the left main artery	24-month vs. 6-month DAPT	910	912	19
OPTIMIZE[30]	Patients with symptoms of stable angina or of silent ischaemia or low-risk ACS	12-month vs. 3-momth DAPT	1556	1563	12
PEGASUS[7]	Patients with MI 1–3 years before enrolment, who were at least 50 years of age, and had one additional high-risk feature	DAPT vs. aspirin alone	14095	7067	33
PRODIGY[31]	Patients undergoing elective, urgent, or emergent coronary angioplasty with intended stent implantation	24-month vs. 6-month DAPT	987	983	24
RESET[32]	Patients with a diagnosis of angina or acute MI with >50% stenosis in a coronary artery who presented for PCI	12-month vs. 3-month DAPT	1058	1059	12
SECURITY[33]	Patients with symptoms of stable angina or unstable angina or patients with documented silent ischaemia, treated with at least 1 DES implanted in the target lesion in the past 24 h	12-month vs. 6-month DAPT	717	682	24

Trials	Age (years)	Women (%)	DM (%)	Dyslipidaemia (%)	HYPT (%)	Smooking (%)	Prior MI (%)	Prior stroke (%)	ACE-I/ ARB (%)	BB (%)	Statin (%)	DQL (%)
ARCTIC-interruption[21]	64	20	33	68	53	24	30	5	52	60	67	90
CHARISMA[6]	64	30	42	74	74	20	35	25	18	55	77	95
CREDO[22]	62	29	26	75	69	31	34	7	34	64	56	95
CURE[23]	64	38	23	NA	59	61	32	4	37	59	25	95
DAPT BMS[24]	59	24	21	NA	64	42	20	5	NA	NA	NA	95
DAPT DES[25]	62	25	30	NA	75	24	21	3	NA	NA	NA	95
DES LATE[26]	63	31	28	NA	58	28	4	2	51	66	82	90

EXCELLENT[27]	63	35	38	76	73	27	5	7	65	60	82	90	
ISAR-SAFE[28]	67	19	24	87	91	15	25	NA	60	84	95	95	
ITALIC[29]	62	20	37	67	65	52	15	3	NA	NA	NA	90	
OPTIMIZE[30]	62	37	35	61	87	18	35	2	NA	NA	NA	90	
PEGASUS[7]	65	24	32	77	78	17	17	NA	80	83	93	95	
PRODIGY[31]	68	23	24	55	72	24	27	4	84	76	83	95	
RESET[32]	62	36	29	59	62	24	2	NA	62	68	87	90	
SECURITY[33]	65	23	31	63	73	22	21	NA	NA	NA	70	90	

DAPT, dual antiplatelet therapy; DM, diabetes mellitus; HYPT, hypertension; MI, myocardial infarction; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β-blocker; DQL, Detsky quality score; ACS, acute coronary syndrome.

difference in risk of all-cause ($P = 0.829$) and CV death ($P = 0.142$) was detected between DAPT beyond 1 year and shorter or no DAPT.

Major non-fatal bleeding occurred in 1.3% of patients receiving DAPT >1 year compared with 0.5% of those randomized to no or shorter DAPT, resulting in a significant 2.3-fold increase of risk in patients receiving DAPT >1 year ($P < 0.001$).

Intracranial and fatal bleeding were reported in 0.4 and 0.2% of patients treated with DAPT >1 year compared with 0.3 and 0.2% of those receiving no or shorter or no DAPT. Thus, the risk of intracranial ($P = 0.112$) and fatal ($P = 0.817$) bleeding did not significantly differ between groups.

Sensitivity analysis

In the overall analysis, removing one study at the time mostly confirmed all findings. Only the removal of CHARISMA[6] and PEGASUS[7] determined a non-significant reduction in risk of stroke with prolonged DAPT vs. short duration or no DAPT (RR: 0.879, 95% CI: 0.760–1.02, $P = 0.083$; RR: 0.878, 95% CI: 0.761–1.01, $P = 0.070$), but no change in results was reported for all the other outcomes. At the meta-regression analysis, no reasonable confounders were detected (Supplementary material online, *Table S2*).

Publication bias

A publication bias was identified for stroke. It is reasonable that this was due to the exclusion of trials enrolling patients with stroke randomized to prolonged DAPT vs. short duration or no DAPT (Supplementary material online, *Figure S2*).

Discussion

The current study, reporting 15 trials in which 85 265 patients were enrolled, represents the largest meta-analysis on the efficacy and safety of prolonging DAPT in patients with ischaemic CVD. The findings of this analysis indicate that prolonged DAPT significantly reduces the risk of MI and stroke in patients with ischaemic CVD, at the expense of increased major but not of fatal or intracranial bleedings.

The role of DAPT using a P_2Y_{12} inhibitor in addition to aspirin has been investigated in chronic and post-ACS patients. In patients without a recent ACS, addition of clopidogrel to aspirin did not provide a significant benefit,[6] whereas it reduced the risk of MI, with no effect on CV mortality, in those with recent ACS.[23] In both studies, DAPT increased major bleeding compared with aspirin, though with varying degrees of magnitude and statistical significance due to the different bleeding definitions used.[23,35] In patients with ACS, use of more powerful P_2Y_{12} inhibitors, compared with clopidogrel, was associated with a significant reduction in the composite risk of CV death, MI, and stroke, with a significant increase in major non-CABG-related bleeding.[4,5] More recently, addition of ticagrelor to aspirin in stable post-MI patients enrolled in the PEGASUS trial significantly reduced the composite end point of stroke, MI, and CV death, with significant increase of major bleeding.[7]

Previous meta-analyses

Previous meta-analyses assessed the efficacy of long vs. short duration DAPT in different setting of patients, reporting conflicting

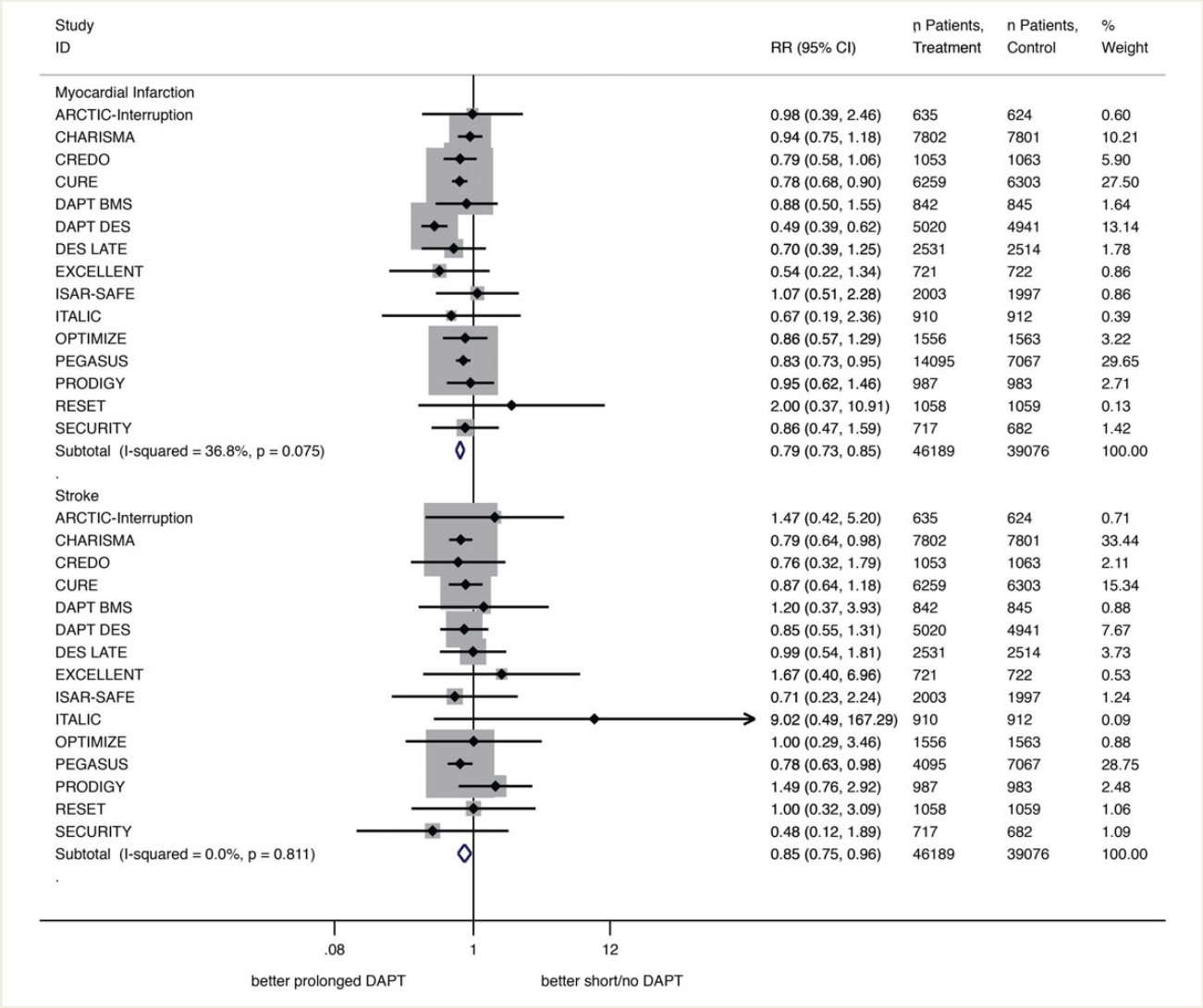

Figure 1 Risk ratios of risk of myocardial infarction and stroke. Solid squares represent risk ratios in trials and have a size proportional to the number of events. The 95% confidence intervals for individual trials are denoted by lines and those for the pooled risk ratios by empty diamonds.

results.[8–11] In a meta-analysis, collecting 69 644 patients in 14 trials, Elmariah *et al.* reported no increase in mortality in patients undergoing prolonged (≥6 months) compared with short DAPT (<6 months) or aspirin alone.[9] A major drawback of this meta-analysis was the fact that it did not include data from the recent large PEGASUS trial[7] and that the effects on MI, stroke, or bleedings were not investigated. Palmerini *et al.*, in a trial level meta-analysis collecting 31 666 patients in 10 studies, showed a reduced risk of MI and stent thrombosis but an 18% increased mortality due to an increased risk of non-CV mortality without changes in CV mortality, together with increased rates of major and overall bleeding in patients randomized to DAPT beyond 1 year vs. DAPT shorter than 6 months after DES implantation.[10] In contrast to this, Palmerini *et al.* showed similar rates of major adverse cardiac events (cardiac death, MI, or stent thrombosis) between long (≥12 months) and short (≤6 months) duration DAPT, but lower rates of bleeding in short duration DAPT arm in an individual patient meta-analysis[36] including only four trials that enrolled only patients undergoing DES implantation. On the same clinical setting, in a trial level meta-analysis including 10 studies that enrolled 32 287 patients undergoing DES implantation, Navarese *et al.* reported that long (>12 months) compared with short-term (<12 months) DAPT was associated with an increased all-cause but not CV mortality, with increased bleeding rates and no significant effects on ischaemic CV events.[37] Finally, Udell *et al.* reported in a meta-analysis of six trials enrolling 33 435 patients with previous MI, a 22% reduction of CV ischaemic events, and a 15% reduction of CV death but increased bleeding in patients undergoing long compared with short duration DAPT.[11] At variance with previous studies, our meta-analysis was not limited to studies conducted in patients undergoing DES, but collected all available data on ischaemic patients undergoing DAPT in various clinical settings, thus representing the largest meta-analysis on this topic. In particular, contrary to the analysis by Elmariah *et al.*,[9] we assessed the impact of prolonged vs. short duration DAPT not only on mortality

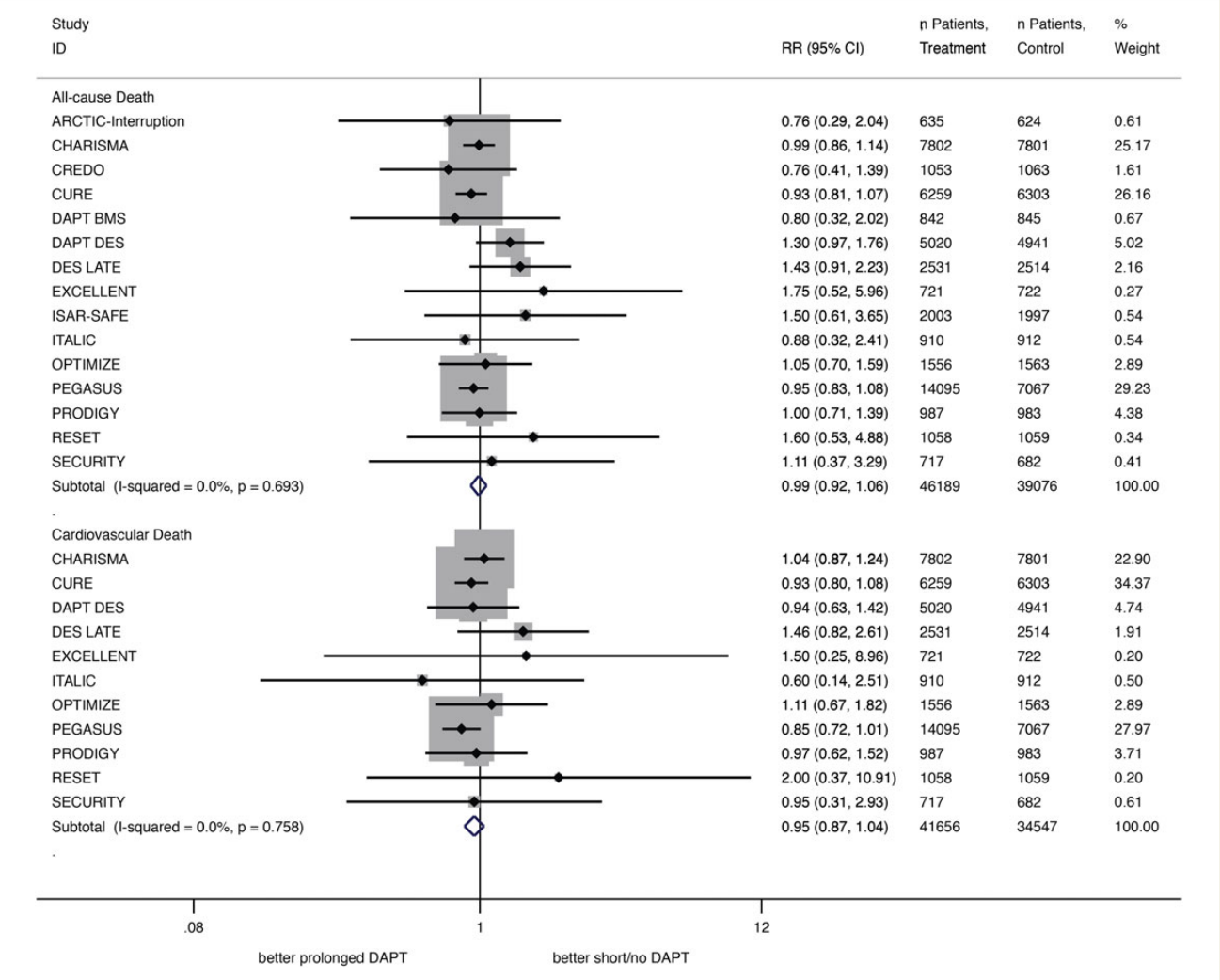

Figure 2 Risk ratios of risk of all-cause death and cardiovascular death. Solid squares represent risk ratios in trials and have a size proportional to the number of events. The 95% confidence intervals for individual trials are denoted by lines and those for the pooled risk ratios by empty diamonds.

but also on MI, stroke, major, fatal, and intracranial bleeding and, additionally, we included in the analysis also the recent PEGASUS trial.[7] At variance with the analysis by Udell *et al.*,[11] we included also patients with no previous MI, but who underwent percutaneous coronary intervention for stable angina. The large number of trials included and of patients enrolled, together with the possibility of performing a deep outcome analysis and several subgroup analyses unexplored in the previous meta-analyses, represent a strength of our meta-analysis.

Comparison of prolonged vs. short or no dual antiplatelet therapy in current study

In the entire analysis, a significant 15% reduction of stroke and 21% reduction of MI was observed in patients enrolled to long vs. short duration or no DAPT, corresponding to an absolute reduction of 0.6% in the rate of MI and of 0.1% in the rate of stroke (*Figure* 2). On the other hand, a significant 69% increase of major bleedings was noted among patients with prolonged DAPT that corresponded to a 0.6% absolute increase over the median follow-up of 19 months. Notably, fatal or intracranial bleedings were not increased in patients undergoing prolonged DAPT. No significant effects on all-cause or CV mortality were observed.

An unexpected increase of non-CV mortality was reported in the DAPT[24,25] trial that was not attributable to major bleeding leading to fatal outcome, cautioning against the potential harm of this strategy. Moreover, the more recent PEGASUS trial[7] that enrolled patients with a previous MI occurring within 3 years before randomization, a trend toward reduction of CV and non-CV mortality was observed. Thus, in accordance with a previous studies,[9] our findings reinforce the observation that prolonged DAPT is not associated with increased mortality.

A reduction in MI and stroke appears to be the clinically most important advantages of prolonged DAPT, though the size of the

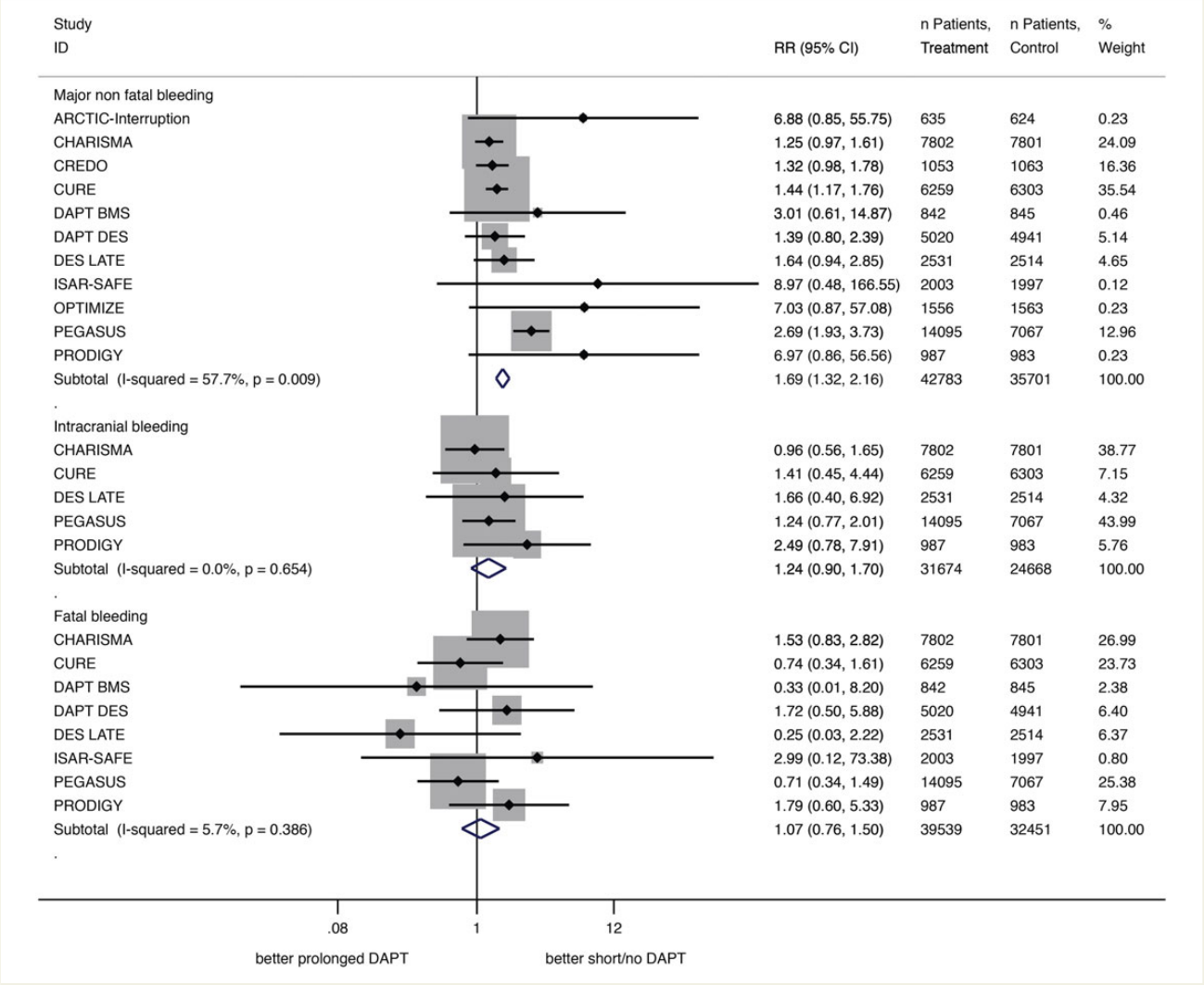

Figure 3 Risk ratios of risk of major non-fatal, intracranial and fatal bleeding. Solid squares represent risk ratios in trials and have a size proportional to the number of events. The 95% confidence intervals for individual trials are denoted by lines and those for the pooled risk ratios by empty diamonds.

absolute benefit seems rather small due to the overall low incidence of these events at follow-up in the relatively young population enrolled in the trials included in the present meta-analysis. Based on the availability data, it is not possible to determinate to what extent the reduction of MI is attributable to prevention of stent thrombosis or to prevention of non-stent-related MI. This is clinically relevant since identification of the subgroups of patients who most likely benefit most from prolonged DAPT would help to select those in whom this strategy might be most advantageous. However, it must be pointed out that in the DAPT trial both stent-related and non-stent-related MI were reduced by prolonged DAPT,[25] and that in the PEGASUS trial no interaction, and even a trend for more benefit, was observed in patients not undergoing revascularization compared with patients revascularized at the time of their index MI.[7] Thus, these observations suggest that the benefit of DAPT in preventing MI may not be restricted to prevention of stent thrombosis but rather extended to all type of MI.

Effects of prolonged dual antiplatelet therapy in subgroup analysis

To further investigate the benefit of DAPT in particular clinical settings, we performed additional analyses in clinical subgroups that were not analysed in previous studies. Since CV risk is higher in patients with unstable compared with those with stable CVD, we separately repeated the analysis in these subgroups of patients. The findings observed in the whole analysis were mostly confirmed in the separate analyses (except for the risk of stroke that was not significantly reduced in unstable patients enrolled to prolonged DAPT vs. short duration or no DAPT), indicating that the reduction of MI and stroke associated with prolonged DAPT also extend to patients with stable CVD at lower ischaemic and bleeding risk.

In a separate analysis, we further investigated the effects of prolonging DAPT beyond 1 year, i.e. the maximum period recommend by guidelines.[1,2] Notably, a significant 26% relative reduction

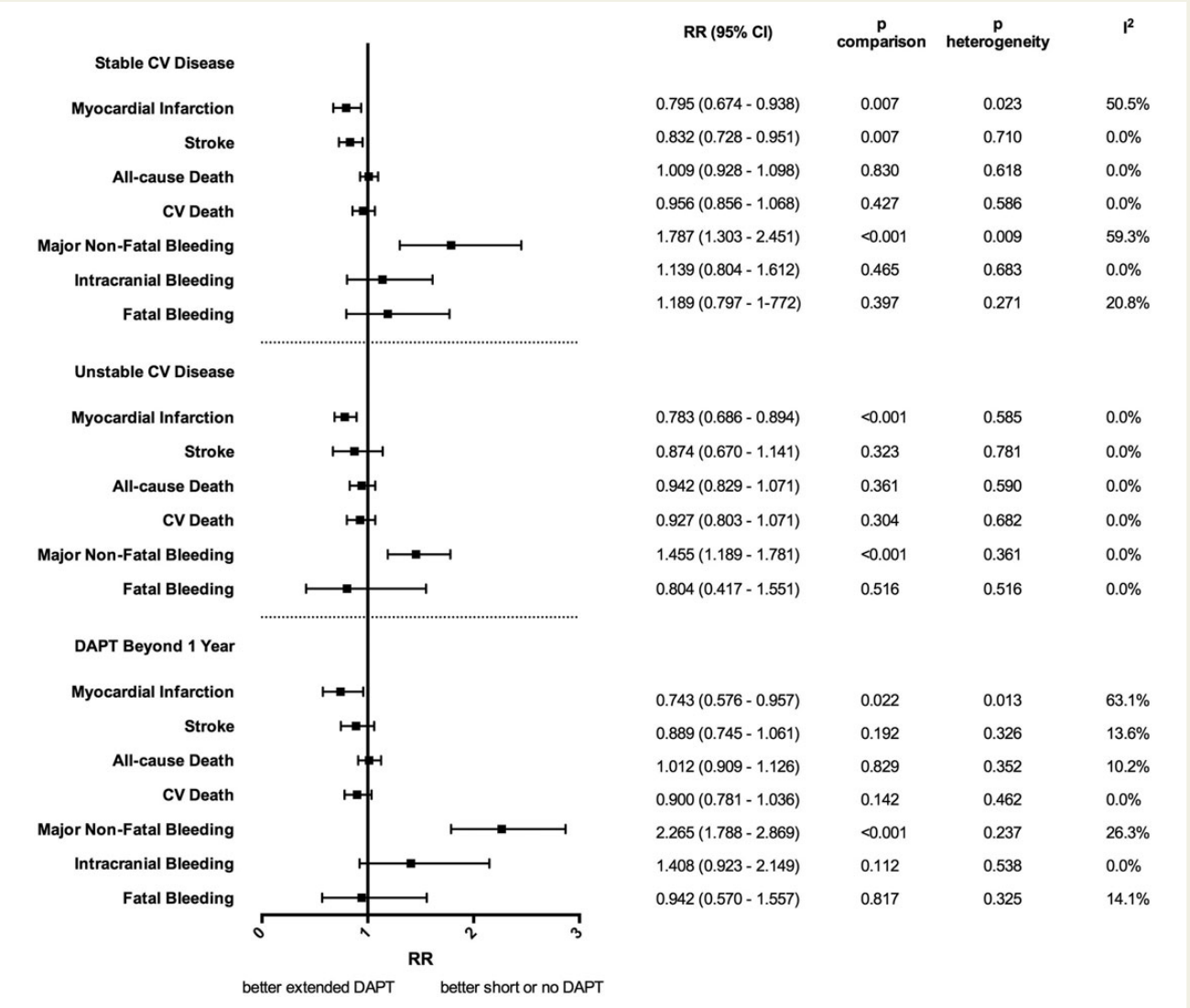

Figure 4 Subgroup analysis.

of MI, corresponding to 0.6% absolute reduction, was confirmed, without an increase of fatal or intracranial bleedings and with a 0.8% absolute increase in the rate of major non-fatal bleedings. In contrast, the observed 12% reduction in stroke rate was no longer significant. This analysis mostly consisted of trials that only enrolled patients following coronary stenting,[21,22,24–33] whereas in the PEGASUS trial[7] both revascularized and non-revascularized patients were enrolled. Thus, although in the PEGASUS trial,[7] there was no significant interaction in the observed benefit of prolonged DAPT between revascularized and non-revascularized patients, it is not possible from current data to elucidate whether a strategy of prolonging DAPT beyond guidelines recommendation maybe beneficial in patients not undergoing revascularization.

Limitations

As previous meta-analyses,[9–11,37] our meta-analysis was conducted on a trial level that represents a limitation of the study. Yet, the large number of trials included in the analyses makes quite challenging to realize a patient-level meta-analyses obtaining data from all trials. On the other hand, a patient-level meta-analysis including some, but not all studies identified in the search would introduce a bias in the analysis. The lack of patient-level data determined the impossibility of performing time-to-event analyses, thus for outcome analysis, RRs were calculated rather than hazard ratios that would have been more precise. However, meta-regression analysis excluded an impact of the different durations of follow-up in each study on outcome analysis. Another limitation of our study was the impossibility of using the same definition of bleeding for all trials. However, since we did not compare different class of drugs but different therapeutic approaches, i.e. prolonging vs. not prolonging DAPT, it is unlikely that inconsistency in the definition of bleeding might affect our findings. Additionally, the definition of bleeding events differed among trials that may represent a limitation of the analysis. However, most studies adopted either thrombolysis in myocardial infarction (TIMI) (53%) or global utilization of streptokinase and t-PA for occluded coronary arteries (GUSTO)(33%) criteria,

allowing to separately assess them. The observed consistency of findings in trials adopting GUSTO or TIMI bleeding criteria makes unlikely a potential confounding interference of bleeding definition on our bleeding results. Furthermore, it was not feasible to separately evaluate clinically relevant subgroups of patients, including patients with diabetes, renal dysfunction, the elderly, or patients at very high CV risk. In fact, the benefit of prolonging DAPT is likely to be more evident in selected groups of patients at high risk of ischaemic events in whom the excess of non-fatal bleedings would be more outweighted by prevention of MI and stroke and of their potential disabling sequelae.[38] Thus, our findings should prompt further assessment, ideally in a patient-level analysis, of the risk-to-benefit ratio of prolonging DAPT in selected categories of patients. Finally, it was not possible to separately assess the efficacy and safety of the individual P_2Y_{12} antiplatelet agents that show different efficacy and safety profiles, in addition to aspirin when used in prolonged DAPT. The protocol of our meta-analysis has not been registered ahead of the study and this has to be acknowledged according to PRISMA guidelines.[12]

Conclusions

The findings of this meta-analysis indicate that prolonged DAPT significantly reduces the rates of MI and stroke in patients with ischaemic CVD, with an increased risk of major bleedings but no increase of fatal or intracranial bleedings. The absolute increase in the rate of major bleeding and the absolute reduction in the rates of MI and stroke associated with prolonged DAPT are of similar size, making it mandatory an individual risk stratification, particularly in patients older than the mean age of the populations included in most clinical trials.[39] Further research is needed to identify subgroups of patients who are likely to benefit most from DAPT.

Supplementary material

Supplementary material is available at *European Heart Journal–Cardiovascular Pharmacotherapy* online.

Conflict of interest: none declared.

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