MG has consulted for Abbott, Astellas, AstraZeneca, Bayer, Cardiorentis, CorThera, Cytokinetics, CytoPherx, DebioPharm, Errekappa Terapeutici, GlaxoSmithKline, Ikaria, Intersection Medical, Johnson & Johnson, Medtronic, Merck, Novartis, Ono Pharma, Otsuka, Palatin Technologies, Pericor Therapeutics, Protein Design, Sanofi-Aventis, Sigma Tau, Solvay, Sticares InterACT, Takeda, Trevena Therapeutics, Stealth Peptides, and Cardiocell. SSK declares no competing interests.

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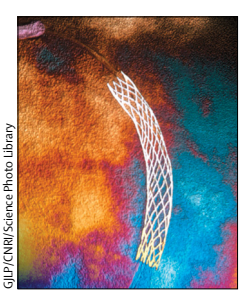
Prolonged antiplatelet therapy after drug-eluting stents



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After use of intracoronary drug-eluting stents, a regimen of two antiplatelet agents (ie, dual antiplatelet therapy [DAPT]) is necessary to prevent stent thrombosis, a complication associated with myocardial infarction and death. Conventional DAPT includes aspirin and a P2Y12 platelet receptor inhibitor such as clopidogrel, prasugrel, or ticagrelor.[1] The optimum duration of DAPT is the subject of much debate; prevention of stent thrombosis has to be balanced against the elevated risk of bleeding associated with two agents.

Because concerns were raised about the high risk of stent thrombosis associated with drug-eluting stents compared with bare-metal stents,[2,3] the default strategy has been to maintain DAPT for 12 months after drug-eluting stent implantation. However, recent observational data[4] suggested that the latest iterations of drug-eluting stents carried a lower risk of stent thrombosis over time and therefore did not need such prolonged DAPT. As a consequence, over the past few years, a series of randomised trials has been done to assess the clinical outcomes of short courses of DAPT versus long courses in patients receiving drug-eluting stents. Unfortunately, these trials were not powered to look at stent thrombosis as a primary endpoint; generally, the findings showed no difference in various combined clinical endpoints between short and long DAPT strategies, but with higher rates of bleeding in the long duration DAPT groups.[5]

As a result of these data, international guidelines have recently changed and recommend DAPT for 6 months in stable patients after implantation of a drug-eluting stent, or even less in those with an increased risk of bleeding.[6] But then the 12 or 30 months of Dual Antiplatelet Therapy after Drug-Eluting Stents (DAPT) trial was published, and knowledge about DAPT after drug-eluting stent implantation was turned on its head.[7] In this trial, patients who had already received 12 months DAPT after drug-eluting stent implantation were randomly assigned to a further 18 months of DAPT or to conventional therapy represented by aspirin alone. The trial showed significantly lower rates of both prespecified coprimary endpoints (ie, stent thrombosis, and major adverse cardiovascular and

cerebrovascular events) in the group given prolonged DAPT. Unlike its predecessors, this randomised trial was powered to look at rates of stent thrombosis and provided clear evidence for a reduction in ischaemic events by extending DAPT for 18 months beyond the accepted standard.

However, as expected, in the DAPT trial, moderate and severe bleeding was significantly higher in the long DAPT group than in the short DAPT group.[7] Furthermore, although the rate of all-cause mortality was no different between the groups, non-cardiovascular mortality in the extended DAPT cohort was double that in the aspirin plus placebo group (1·0% *vs* 0·5%; p=0·002). Although some might be tempted to attribute this latter finding to a statistical quirk or to chance, to frontline interventional cardiologists, it raised alarm bells in view of the number of patients worldwide receiving drug-eluting stent revascularisation.

In *The Lancet*, Tullio Palmerini and colleagues[8] now report a meta-analysis of all randomised trials to assess mortality associated with long-duration versus short-duration DAPT after drug-eluting stent implantation, and the findings do nothing to silence those alarm bells. In nearly 32 000 patients, all-cause mortality was significantly lower for short-duration DAPT (HR 0·82, 95% CI 0·69–0·98), which was the result of a 33% lower rate of non-cardiovascular mortality (0·67, 0·51–0·89) despite a significantly lower rate of stent thrombosis recorded in patients given long-duration DAPT. Although it is not possible to explain this result definitively, the most plausible explanation is that the significantly increased bleeding event rate observed with longer durations of DAPT is associated with mortality.

Palmerini and colleagues' analysis[8] will, and indeed should, call into question a universal shift towards a policy of 30 months of DAPT after drug-eluting stent implantation, despite the scientific rigour of the DAPT trial.[7] After all, who would swap a lower risk of stent thrombosis for an increased risk of bleeding or death? The meta-analysis and randomised trials of DAPT that the analysis incorporates raise important questions. Clinical certainty for individual patients about the optimum duration of DAPT after drug-eluting stent implantation simply cannot be achieved on the basis of current evidence because of various recurrent confounding factors. Specifically, the trials include a mixture of patients presenting with elective and acute coronary syndromes, heterogeneity of stent type, a wide range of short (ie, 3, 6, and 12 months) and long (ie, 6, 12, 24, and 30 months) DAPT regimes, and various P2Y12 inhibitors.

For now, interventional cardiologists are probably in a default situation. According to the Palmerini analysis,[8] patients treated with drug-eluting stents are at risk if cardiologists do use DAPT for longer than 1 year, but, by contrast, according to the DAPT trial, at least some of them are at risk if they do not. It is surely time to revisit a personalised approach to DAPT. The notion that this heterogeneous group of patients given drug-eluting stents can be treated with a one-size-fits-all antiplatelet strategy is looking increasingly facile.

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Mortality in patients treated with extended duration dual antiplatelet therapy after drug-eluting stent implantation: a pairwise and Bayesian network meta-analysis of randomised trials

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Summary

Background **Despite recent studies, the optimum duration of dual antiplatelet therapy (DAPT) after coronary drug-eluting stent placement remains uncertain. We performed a meta-analysis with several analytical approaches to investigate mortality and other clinical outcomes with different DAPT strategies.**

Methods **We searched Medline, Embase, Cochrane databases, and proceedings of international meetings on Nov 20, 2014, for randomised controlled trials comparing different DAPT durations after drug-eluting stent implantation. We extracted study design, inclusion and exclusion criteria, sample characteristics, and clinical outcomes. DAPT duration was categorised in each study as shorter versus longer, and as 6 months or shorter versus 1 year versus longer than 1 year. Analyses were done by both frequentist and Bayesian approaches.**

Findings **We identified ten trials published between Dec 16, 2011, and Nov 16, 2014, including 31 666 randomly assigned patients. By frequentist pairwise meta-analysis, shorter DAPT was associated with significantly lower all-cause mortality compared with longer DAPT (HR 0·82, 95% CI 0·69–0·98; p=0·02; number needed to treat [NNT]=325), with no significant heterogeneity apparent across trials. The reduced mortality with shorter compared with longer DAPT was attributable to lower non-cardiac mortality (0·67, 0·51–0·89; p=0·006; NNT=347), with similar cardiac mortality (0·93, 0·73–1·17; p=0.52). Shorter DAPT was also associated with a lower risk of major bleeding, but a higher risk of myocardial infarction and stent thrombosis. We noted similar results in a Bayesian framework with non-informative priors. By network meta-analysis, patients treated with 6-month or shorter DAPT and 1-year DAPT had higher risk of myocardial infarction and stent thrombosis but lower risk of mortality compared with patients treated with DAPT for longer than 1 year. Patients treated with DAPT for 6 months or shorter had similar rates of mortality, myocardial infarction, and stent thrombosis, but lower rates of major bleeding than did patients treated with 1-year DAPT.**

Interpretation **Although treatment with DAPT beyond 1 year after drug-eluting stent implantation reduces myocardial infarction and stent thrombosis, it is associated with increased mortality because of an increased risk of non-cardiovascular mortality not offset by a reduction in cardiac mortality.**

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Introduction

Drug-eluting stents have substantially improved the outcomes of patients with coronary artery disease undergoing percutaneous coronary intervention.[1,2] After implantation of a drug-eluting stent, patients are treated with dual antiplatelet therapy (DAPT; aspirin and a P2Y12 inhibitor) to prevent stent thrombosis, which might result in large myocardial infarction or death.[3] The optimum duration of DAPT has been a matter of debate since the introduction of drug-eluting stents. Initially recommended for 3 months after Cypher sirolimus-eluting stents and 6 months after Taxus paclitaxel-eluting stents, the duration of DAPT was subsequently extended to 1 year or longer irrespective of type of drug-eluting stent to mitigate the sustained risk of stent thrombosis reported in some observational studies.[4–6]

The need for 1-year or longer DAPT after placement of contemporary drug-eluting stents has been challenged by findings of several randomised controlled trials showing a similar risk of major adverse cardiovascular events with a significant reduction in major bleeding with 3-month or 6-month DAPT compared with 1-year or 2-year DAPT.[7–10] Furthermore, no benefit was noted by extending DAPT from 1 year to 3 years in a randomised trial in more than 5000 patients from South Korea.[11] Although these studies were individually underpowered to be definitive, collectively they were persuasive; the European Guidelines on Myocardial Revascularisation[12] recently changed the recommendation for DAPT duration from 1 year to 6 months after second generation drug-eluting stents. By contrast with previous randomised controlled trials, investigators of the recently completed DAPT trial[13] in

9965 randomly assigned patients reported that prolonging DAPT from 1 year to 2·5 years after drug-eluting stent placement reduced the long-term risk of stent thrombosis, myocardial infarction, and major adverse cardiovascular events by prevention of both stent related and non-stent related events. Prolonged DAPT substantially increased major bleeding in this trial, however, with a strong trend toward increased rates of all-cause mortality, the latter driven by greater non-cardiovascular mortality due to bleeding, trauma, and cancer. Because death was not the primary endpoint of this study and the results were borderline significant, whether the mortality increase was by chance is unclear. However, if real, an increased risk of mortality of even about 0·5% with extended DAPT (as was present in the DAPT trial) would equate to tens of thousands of deaths in the millions of patients treated with drug-eluting stents every year worldwide. Therefore, we performed an updated meta-analysis to investigate the safety and efficacy of different DAPT durations after drug-eluting stent implantation.

Methods

Study design and selection

Eligible studies for this meta-analysis were randomised controlled trials comparing different durations of DAPT in patients treated with drug-eluting stents. We searched relevant randomised clinical trials through Medline, the Cochrane database, Embase, www.tctmd.com, www.clinicaltrials.gov, www.clinicaltrialresults.org, www.cardiosource.com, and abstracts and presentations from major cardiovascular meetings, using the keywords "randomised clinical trial", "drug-eluting stent", "dual antiplatelet therapy", "clopidogrel", "aspirin", and "thienopyridine". Two investigators (TP and DDR) independently reviewed the titles, abstracts, and studies to establish whether they met the inclusion criteria, and categorised the assigned relative DAPT duration groups in each trial as shorter versus longer, and as 6 months or shorter versus 1 year versus longer than 1 year. Conflicts between reviewers were resolved by consensus. No language, publication date, or publication status

	Number of patients in each treatment group	Primary endpoint	Design and randomisation	Follow-up duration after randomisation	Results of the primary endpoint
ARCTIC-Interruption, 2014[25]	12 months (n=624); 18–24 months (n=635)	Death, myocardial infarction, stent thrombosis, cerebrovascular accident, or target vessel revascularisation	Superiority, randomisation at discontinuation of dual antiplatelet therapy	Median of 17 months	Superiority of >12-month dual antiplatelet therapy not shown
DAPT, 2014[13]	12 months (n=4941); 30 months (n=5020)	Death, myocardial infarction, stent thrombosis, cerebrovascular accident, or bleeding	Superiority, randomisation at discontinuation of dual antiplatelet therapy	18 months	Superiority of 30-month dual antiplatelet therapy shown
DES-LATE, 2013[11]	12 months (n=2514); 36 months (n=2531)	Cardiac death, myocardial infarction, or cerebrovascular accident	Superiority, randomisation at discontinuation of dual antiplatelet therapy	24 months	Superiority of 24-month dual antiplatelet therapy not shown
EXCELLENT, 2012[8]	6 months (n=722); 12 months (n=721)	Cardiac death, myocardial infarction, and ischaemia-driven target vessel revascularisation	Non-inferiority, randomisation at the time of percutaneous coronary intervention	1 year	Non-inferiority shown
ISAR-SAFE, 2014[26]	6 months (n=1997); 12 months (n=2003)	Death, myocardial infarction, stent thrombosis, cerebrovascular accident, or bleeding	Non-inferiority, randomisation at discontinuation of dual antiplatelet therapy	9 months	Non-inferiority shown
ITALIC, 2014[17]	6 months (n=953); 24 months (n=941)	Death, myocardial infarction cerebrovascular accident, target vessel revascularisation, or bleeding	Non-inferiority, randomisation at the time of percutaneous coronary intervention	1 year	Non-inferiority shown
OPTIMIZE, 2013[7]	3 months (n=1563); 12 months (n=1556)	Death, myocardial infarction, cerebrovascular accident, or major bleeding	Non-inferiority, randomisation at the time of percutaneous coronary intervention	1 year	Non-inferiority shown
PRODIGY, 2012[10]	6 months (n=751); 24 months (n=750)	Death, myocardial infarction, or cerebrovascular accident	Superiority, randomisation 1 month after percutaneous coronary intervention	24 months	Superiority of 24-month dual antiplatelet therapy not shown
RESET, 2012[9]	3 months (n=1059); 12 months (n=1058)	Cardiac death, myocardial infarction, stent thrombosis, target vessel revascularisation, or major bleeding	Non-inferiority, randomisation at the time of percutaneous coronary intervention	1 year	Non-inferiority shown
SECURITY, 2014[16]	6 months (n=682); 12 months (n=717)	Cardiac death, myocardial infarction cerebrovascular accident, stent thrombosis, bleeding	Non-inferiority, randomisation at the time of percutaneous coronary intervention	1 year	Non-inferiority shown

Table 1: **Main characteristics of the randomised trials included in the meta-analysis**

restrictions were imposed. The most updated or most inclusive data for a given study were chosen for abstraction. Internal validity of randomised controlled trials was assessed as previously described.[14,15]

Endpoints, definitions, and study populations

The primary endpoint was all-cause mortality. Secondary pre-specified endpoints included cardiac death, non-cardiac death, myocardial infarction, stroke, definite or probable stent thrombosis, major bleeding, and any bleeding. The endpoint definitions as applied in each trial were incorporated. The principal analyses were done in the intention-to-treat populations. Because in several trials, patients were randomly assigned at the time of percutaneous coronary intervention and not at the time of DAPT allocation,[7–10,16,17] we also did analyses in the cohort of patients from the assigned time of DAPT discontinuation versus continuation to the end of follow-up (post-treatment

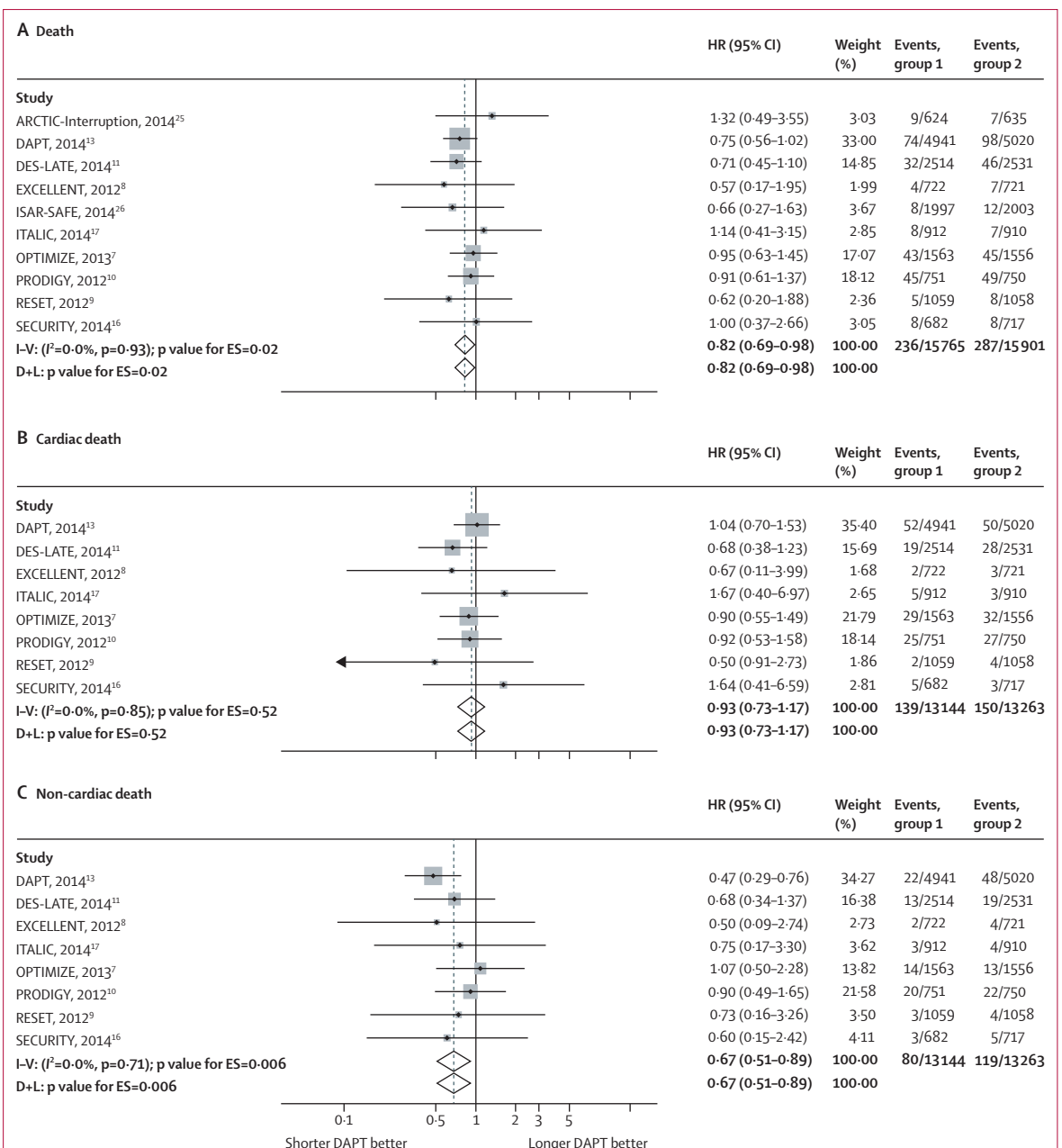

Figure 1: **Estimates of risk in the intention-to-treat population for (A) all-cause mortality, (B) cardiac mortality, and (C) non-cardiac mortality between shorter and longer DAPT**

DAPT=dual antiplatelet therapy. HR=hazard ratio. I-V=inverse variance. D+L=DerSimonan and Laird. ES=effect estimate for the randomised treatment comparison.

population), censoring events occurring earlier, deriving data from the scientific literature or directly from the principal investigators of the included trials. The present review was done according to PRISMA statements.[18]

Statistical analysis

We used both a frequentist approach and a Bayesian framework with non-informative priors for analysis of shorter versus longer DAPT. We assessed differences between groups of treatments stratified as 6 months or shorter DAPT versus 1-year DAPT versus longer than 1-year DAPT by network meta-analysis.[19] Hazard ratios (HRs) and 95% confidence intervals (CIs) were used as the summary statistic. Estimates of risk were extracted from the main publications of randomised controlled trials, obtained from principal investigators, or calculated as previously described.[20] The pooled HR was calculated with both fixed effect (inverse variance weighted) and random effect (DerSimonian and Laird) models. In the post-treatment population, in view of the variability in the length of follow-up (6–24 months), differences in event rates were expressed as estimates per patient-months of follow-up and analysed by Poisson regression analysis.[21] We assessed the extent of small study effects and publication bias by visual inspection of funnel plots and Egger's test. We assessed heterogeneity across trials with the I^2 statistic; less than 25% represented mild heterogeneity, 25–50% represented moderate heterogeneity, and higher than 50% represented severe heterogeneity. We did sensitivity analyses by assessing the effect of removing individual studies on the pooled HR, and by stratifying trials according to DAPT strategies and study design. The number needed to treat (NNT) and the number treated to harm (NNH) for each outcome were calculated as previously described for meta-analysis.[22] We deemed p values less than 0·05 as significant (and all p values were 2-sided). We used STATA (version 12) for statistical analyses. Funnel plots were derived from RevMan (version 5).

See Online for appendix

	All-cause mortality
All studies	0·82 (0·69–0·97)
ARCTIC-Interruption[25] omitted	0·80 (0·68–0·96)
DAPT[13] omitted	0·86 (0·69–1·06)
DES-LATE[11] omitted	0·84 (0·70–1·01)
EXCELLENT[8] omitted	0·83 (0·70–0·98)
ISAR SAFE[26] omitted	0·83(0·69–0·99)
ITALIC[17] omitted	0·81 (0·68–0·97)
OPTIMIZE[7] omitted	0·80 (0·66–0·96)
PRODIGY[10] omitted	0·80 (0·66–0·97)
RESET[9] omitted	0·83 (0·69–0·98)
SECURITY[16] omitted	0·82 (0·68–0·97)

Data are HR (95% CI).

Table 2: **Sensitivity analysis showing the effect size for mortality after removing individual trials included in the meta-analysis**

Consistency of inferential estimates were also appraised with a Bayesian framework, computing HR and 95% credible intervals (CrI) with a hierarchical model by means of Markov chain Monte Carlo (MCMC) methods with Gibbs sampling from 1000 iterations obtained after a 5000-iteration training phase. Convergence was appraised graphically according to Gelman and Rubin.[23] Model fit was assessed with deviance information criterion. Inconsistency was assessed by contrasting direct evidence with indirect evidence from the entire network on each node (node splitting). The measure of conflict P was implemented with MCMC by counting the proportion of times direct treatment effect exceeded indirect treatment effect. We did Bayesian MCMC simulations by means of JAGS software in R by use of gemtc (R package (version 0.6) and rjags (R package version 3-13).

Results

Of 921 potentially relevant articles initially screened, 11 trials with 31882 enrolled patients met the inclusion criteria (appendix). Of these studies, we could not include the trial by Hu and colleagues[24] of 216 patients with unprotected left main coronary artery disease because it was not possible to extract estimates of risk from the reported data. Therefore, we included ten trials with 31666 patients. Table 1 shows the major characteristics of the included trials. The appendix lists major inclusion and exclusion criteria and internal validity assessment for each trial, main characteristics of patients enrolled in the included trials, and the definitions of the clinical endpoints in each trial.

Figure 1 shows estimates of risk of mortality by frequentist analysis for the intention-to-treat population. Shorter DAPT was associated with significantly lower rates of mortality compared with longer DAPT, a difference driven by a significant reduction of non-cardiac mortality with shorter DAPT, with no significant difference in cardiac mortality between the two DAPT strategies. No heterogeneity was apparent across trials for mortality (I^2=0), and no individual study unduly affected the primary effect estimate although the upper bound of the 95% CI was no longer below unity after removing the DAPT and DES LATE trials (table 2).

We noted no significant heterogeneity for all-cause, cardiac, and non-cardiac mortality between the effect size and DAPT duration (stratified by ≤6 month *vs* 1 year, 1 year *vs* >1 year, and 6 month *vs* >1 year of treatment; figure 2). We noted consistent results in the post-treatment population (figure 3). Additionally, in sensitivity analyses including only trials in which patients were randomly assigned at the time of DAPT discontinuation, shorter DAPT had significantly lower rates of mortality and non-cardiac mortality than did longer DAPT (appendix). Finally, results were similar when a Bayesian framework with non-informative priors was implemented (appendix).

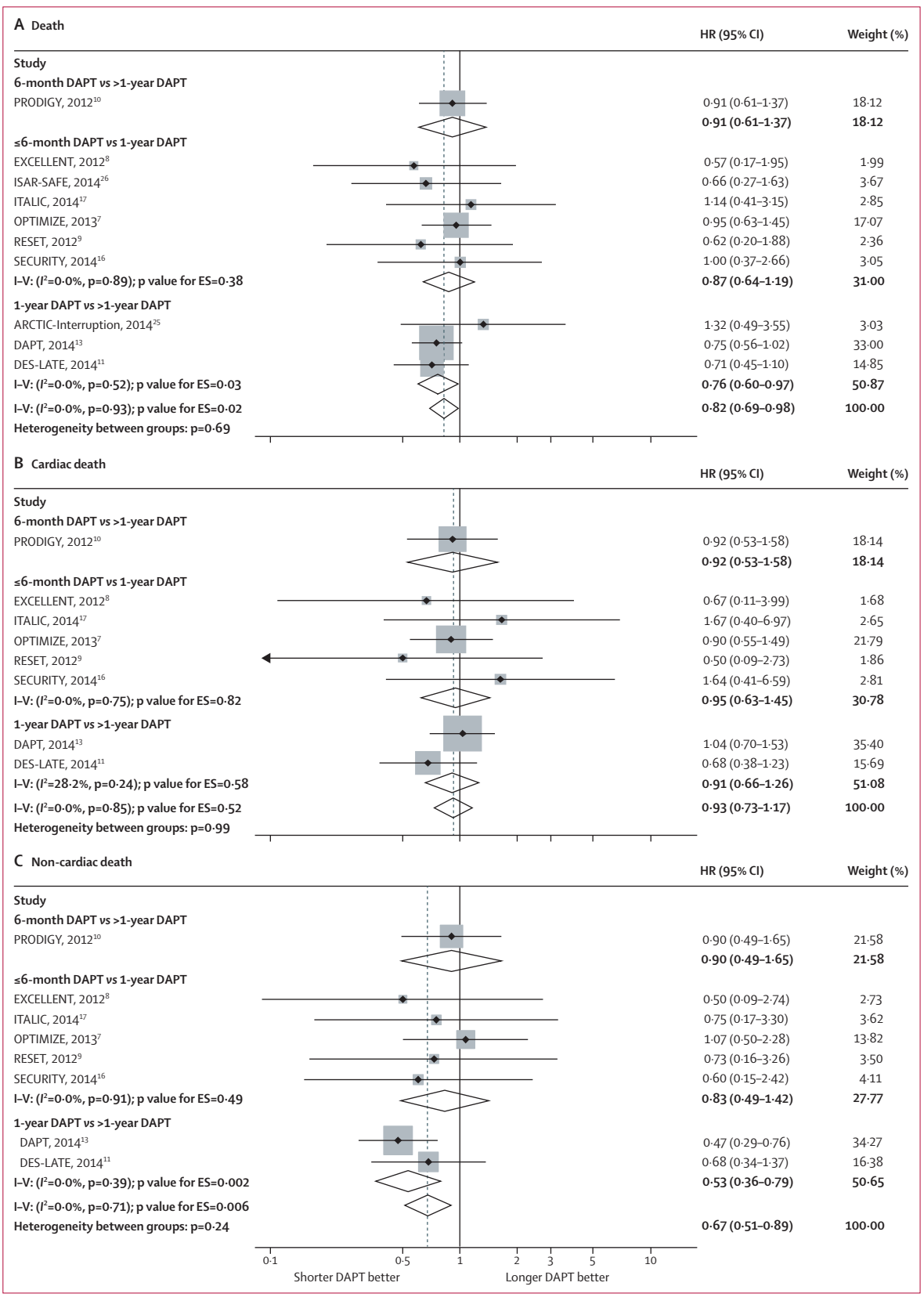

Figure 2: **Heterogeneity analysis of (A) all-cause mortality, (B) cardiac mortality, and (C) non-cardiac mortality according to DAPT duration stratified by ≤6 month versus 1 year, 1 year versus >1 year, and 6 month versus >1 year of treatment**
DAPT=dual antiplatelet therapy. HR=hazard ratio. I-V=inverse variance. D+L=DerSimonan and Laird. ES=effect estimate for the randomised treatment comparison.

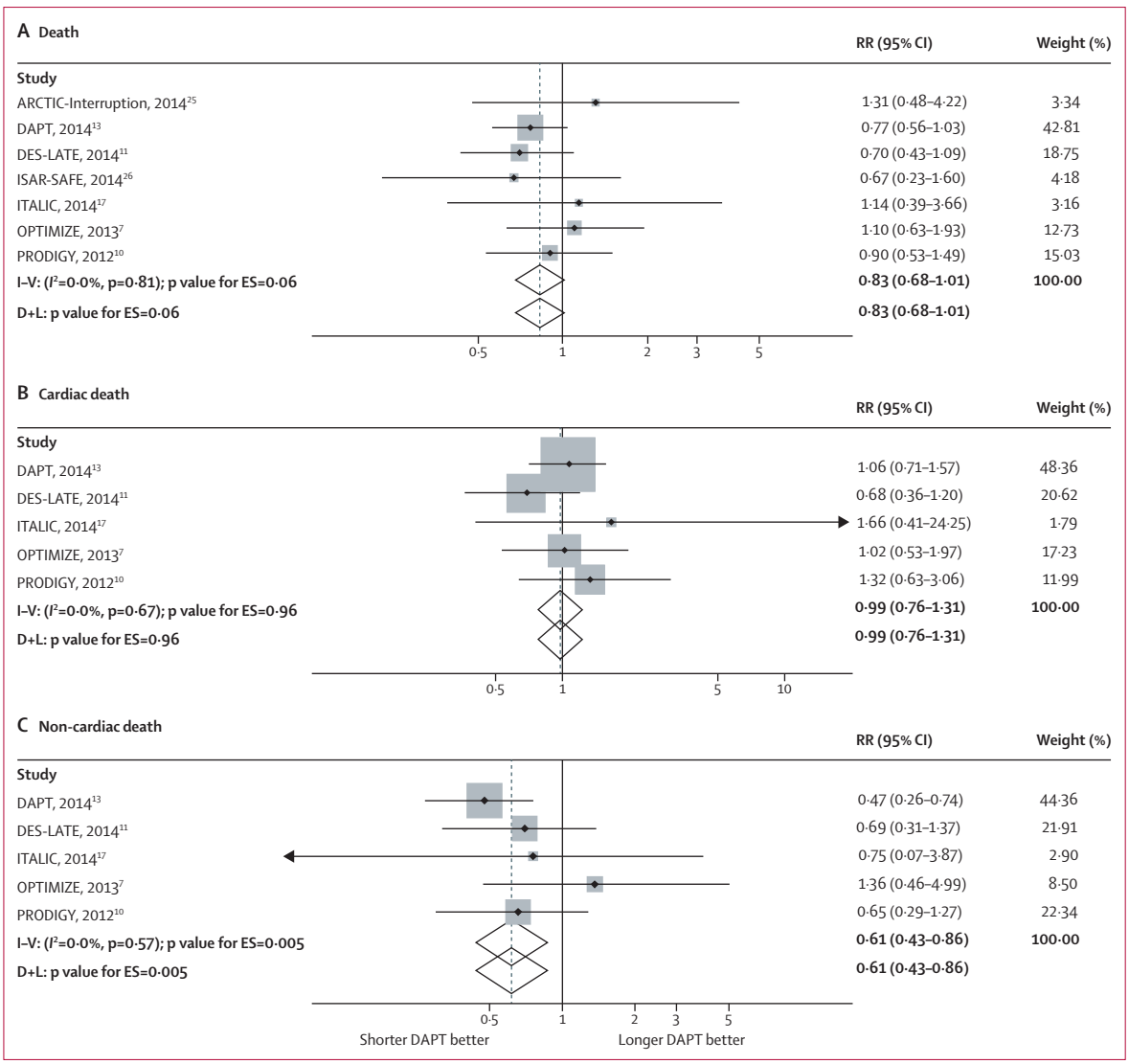

Figure 3: **Estimates of risk in the post-treatment population of patients for (A) all-cause mortality, (B) cardiac mortality, and (C) non-cardiac mortality between shorter and longer DAPT**

DAPT=dual antiplatelet therapy. I-V=inverse variance. D+L=DerSimonan and Laird. RR=rate ratio. ES=effect estimate for the randomised treatment comparison.

With frequentist analysis, shorter DAPT was associated with significantly lower rates of major bleeding and any bleeding compared with longer DAPT, with no evidence of heterogeneity across trials (I^2=0; figure 4, 5). However, with frequentist analysis, shorter DAPT was associated with significantly higher rates of myocardial infarction and definite or probable stent thrombosis compared with longer DAPT. However, moderate heterogeneity for myocardial infarction (I^2=29·3%) and for definite or probable stent thrombosis (I^2=43·7%) were apparent across trials, such that in the random effect model only a trend toward reduced rates of definite or probable stent thrombosis remained in favour of extended DAPT (p=0·06). Stroke rates did not vary with DAPT duration. Consistent results were noted with the Bayesian framework (appendix). Results were similar between the intention-to-treat analysis and the post-treatment population (appendix). Finally, we noted no apparent systematic bias as assessed by funnel plots (appendix) and Egger's test.

Table 3 shows subgroup analyses by Bayesian network meta-analysis for each outcome of interest in patients stratified according to DAPT duration. Specifically, patients treated with DAPT for 6 months or shorter or for 1 year had significantly lower rates of all-cause mortality and non-cardiac mortality than did patients treated with DAPT for longer than 1 year. Additionally, patients given therapy for 6 months or shorter or for 1 year had significantly higher rates of myocardial

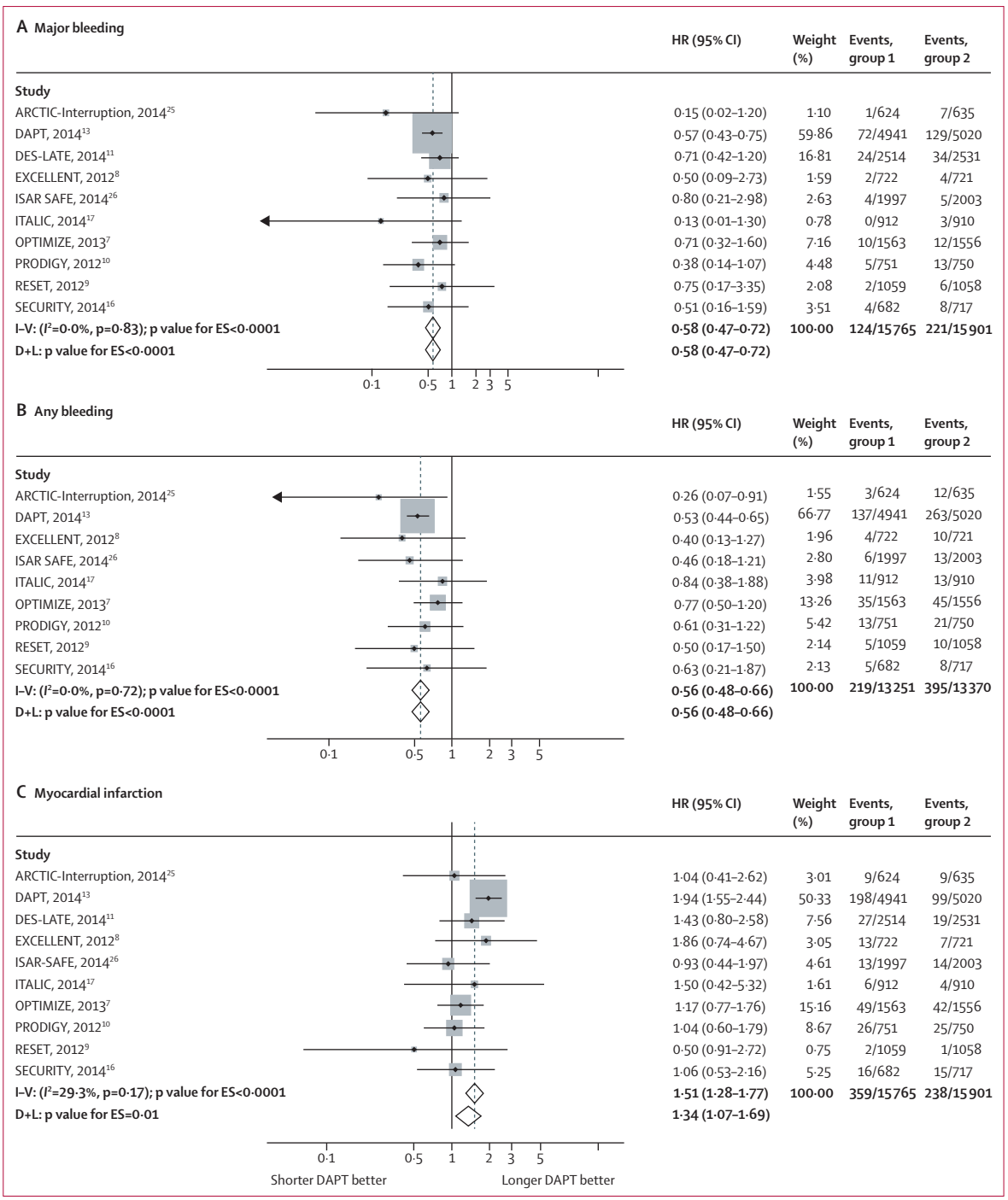

Figure 4: **Estimates of risk in the intention-to-treat population for (A) major bleeding, (B) any bleeding, and (C) myocardial infarction**
DAPT=dual antiplatelet therapy. HR=hazard ratio. I-V=inverse variance. D+L=DerSimonan and Laird. ES=effect estimate for the randomised treatment comparison.

infarction and definite or probable stent thrombosis, but lower rates of major bleeding, than patients treated with DAPT for longer than 1 year. Finally, patients treated with DAPT for 6 months or shorter had similar mortality, myocardial infarction, and definite or probable stent thrombosis, but lower rates of major bleeding than did patients treated with DAPT for 1 year (table 3). No inconsistency between direct and indirect estimates in node splitting was apparent for any outcome.

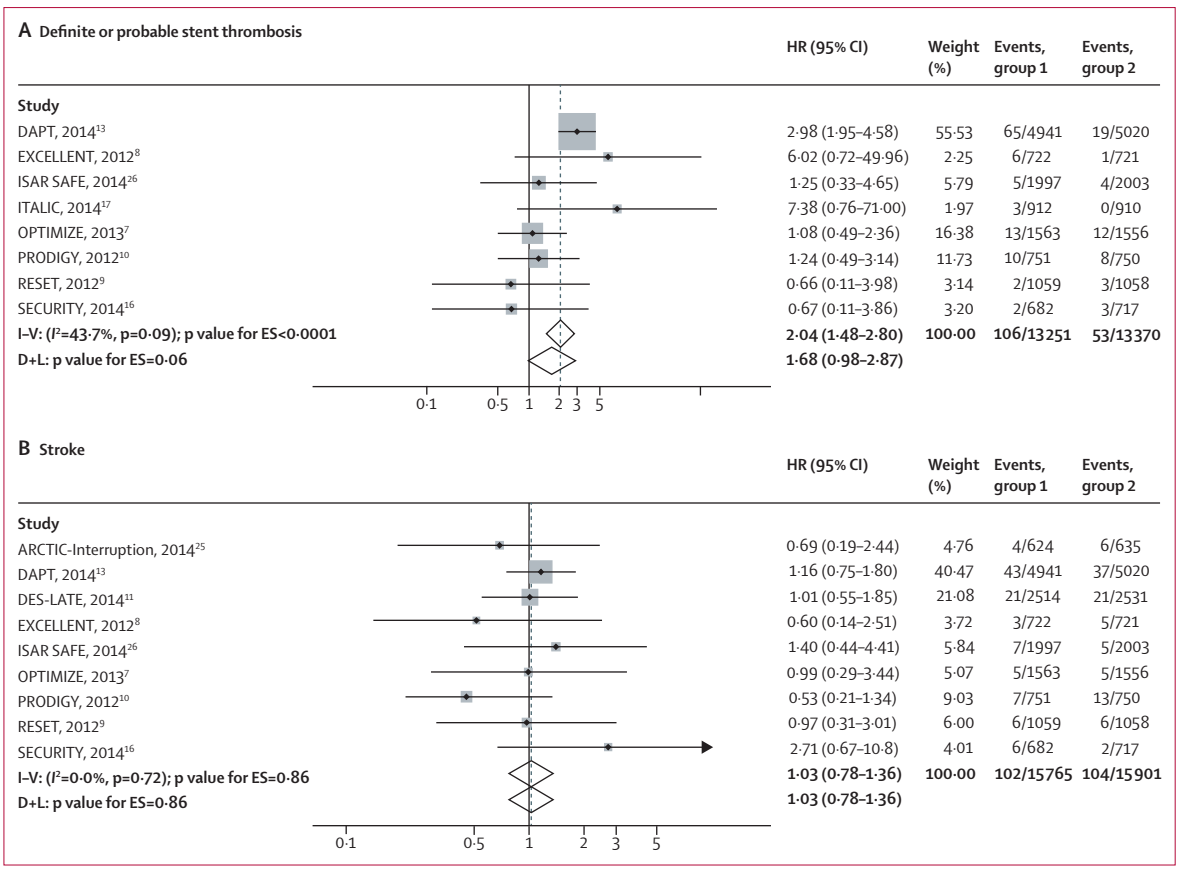

Figure 5: **Estimates of risk in the intention-to-treat population for (A) definite or probable stent thrombosis and (B) stroke between short and long DAPT**
DAPT=dual antiplatelet therapy. HR=hazard ratio. I-V=inverse variance. D+L=DerSimonan and Laird. ES=effect estimate for the randomised treatment comparison.

	≤6-month *vs* 1-year DAPT	≤6-month *vs* >1-year DAPT	1-year *vs* >1-year DAPT
All-cause death	0·95 (0·76–1·20)	0·78 (0·59–1·00)	0·82 (0·65–1·00)
Cardiac death	0·96 (0·68–1·40)	0·90 (0·62–1·30)	0·93 (0·69–1·20)
Non-cardiac death	1·00 (0·69–1·60)	0·65 (0·41–1·00)	0·61 (0·42–0·87)
Myocardial infarction	1·00 (0·75–1·30)	1·70 (1·30–2·40)	1·70 (1·40–2·10)
Definite or probable stent thrombosis	1·10 (0·66–1·70)	2·70 (1·50–5·00)	2·50 (1·70–4·00)
Major bleeding	0·59 (0·36–0·95)	0·34 (0·20–0·55)	0·58 (0·45–0·74)

Data are HR (95% CrI). DAPT=dual antiplatelet therapy. HR=hazard ratio. CrI=credible intervals.

Table 3: **Clinical outcomes stratified by different durations of dual antiplatelet therapy established by network meta-analysis**

Discussion

In our meta-analysis including ten randomised controlled trials and 31666 patients, we analysed the relative safety and efficacy of different DAPT durations after drug-eluting stent implantation. To increase confidence in our findings, we used many analytical approaches including frequentist and Bayesian frameworks, in intention-to-treat and post-treatment populations. We noted that shorter DAPT was associated with significantly lower rates of all-cause mortality compared with longer DAPT due to an increased risk of non-cardiovascular mortality with extended duration DAPT not offset by a reduction in cardiac mortality; no heterogeneity was reported across trials or between pooled trials stratified by DAPT duration. Second, compared with longer DAPT, shorter DAPT was associated with significantly lower rates of major bleeding and any bleeding, but with increased rates of myocardial infarction and definite or probable stent thrombosis, with moderate heterogeneity across trials for myocardial infarction and stent thrombosis. Third, by network meta-analysis, patients treated with DAPT for 6 months or shorter or for 1 year had significantly lower all-cause mortality and non-cardiac mortality than did patients treated with DAPT for longer than 1 year; we noted no significant difference in mortality between patients treated with DAPT for 6 months or shorter and those treated with DAPT for 1 year. Finally, our results were consistent in the intention-to-treat and post-treatment populations, and were consistent in all sensitivity analyses, and in the Bayesian framework.

Establishing the optimum duration of DAPT after drug-eluting stent implantation is crucial for balancing the risks of ischaemic and bleeding complications. Although findings of previous studies[8–10,16,17,26] showed similar rates of major adverse cardiovascular events between patients treated with DAPT for 3 or 6 months

versus those treated with DAPT for 1 year or longer, and between those treated with DAPT for 1 or 3 years,[11] researchers of the DAPT trial recently reported lower rates of stent thrombosis, myocardial infarction, and major adverse cardiovascular events in patients treated with DAPT for 2·5 years compared with those treated with 1-year DAPT, but at a cost of increased major bleeding.[13] Moreover, an unexpected finding of the DAPT trial was an increased risk of mortality in patients treated with prolonged DAPT, which was attributed to increased non-cardiovascular mortality due to cancer, bleeding, and trauma-related deaths. However, an imbalance in the baseline number of patients with a history of cancer might have partly contributed to this risk. As a result, the optimum duration of DAPT after coronary drug-eluting stent placement remains uncertain.

To address this complex issue, we analysed the safety and efficacy of different DAPT strategies in an updated meta-analysis with various analytical approaches. Meta-analysis is a well-established research method for summarising the results of different research studies while maintaining the randomisation design.[27] Thus, meta-analysis achieves greater statistical power for low-frequency endpoints such as mortality than individual studies, providing important information for clinical decision making. In our meta-analysis, the large patient cohort provides sufficient statistical power to show or exclude differences in mortality between different DAPT strategies, and to allow for sensitivity analyses to exclude single study effects. In this regard, 351 (67%) of the 523 total deaths in the present meta-analysis were recorded in trials other than DAPT. The major findings of this meta-analysis are that compared with DAPT for 6 months or shorter or DAPT for 1 year, prolonging treatment beyond 1 year was associated with increased major bleeding and mortality because of a significant increase in non-cardiac mortality, despite a reduction in the risk of myocardial infarction and stent thrombosis. By contrast, we noted no significant differences in the risks of mortality (all-cause, cardiac, or non-cardiac), myocardial infarction, or definite or probable stent thrombosis between 6-month or shorter DAPT versus 1-year DAPT, although the latter was associated with a significantly higher risk of major bleeding. Importantly, we observed no heterogeneity across trials for the primary mortality endpoint (I^2=0), including in the analysis in which randomised clinical trials were stratified by DAPT duration, and the effect of greater mortality with longer DAPT was still present after removal of the DAPT trial results.

Importantly, the overall frequentist results were confirmed in both the intention-to-treat and post-treatment populations (in fixed-effect and random-effect models), in subgroup analysis stratified by groups of DAPT duration (network meta-analysis), and in the Bayesian framework. Therefore, these findings have robust statistical consistency and are relevant for daily clinical practice when deciding the best DAPT duration after drug-eluting stent placement. The results of our meta-analysis support a short-term (3 or 6 months) DAPT strategy in patients at low risk of recurrent coronary events (eg, stable coronary artery disease), in those at low risk of stent thrombosis (especially after treatment with contemporary drug-eluting stents),[28] and in those at high risk of bleeding. However, an extended DAPT strategy (>1 year) might still be appropriate in some patients in whom prevention of stent and non-stent-related coronary events are likely to offset the adverse events associated with extended DAPT, thereby resulting in reduced or a neutral effect on mortality.

Of note, all-cause mortality was increased with longer DAPT despite the fact that stent thrombosis and myocardial infarction were reduced with this strategy. However, this reduction did not result in a decrease in cardiac mortality with longer DAPT. Results of a large cohort study[29] recently showed that fewer cardiac deaths were due to myocardial infarction in the years 2003–08 than in the preceding decade. Earlier recognition of myocardial infarction together with improved pharmacological and interventional treatments have significantly improved survival after myocardial infarction. Additionally, the broad definition of myocardial infarction (any increase in cardiac biomarkers above the upper normal limit) used in the component trials of the meta-analysis could have led to inclusion of small myocardial infarctions with less prognostic relevance, diluting the effect of large myocardial infarctions on mortality. Finally, data from some reports have suggested that the risk of mortality is greatest in patients with early stent thrombosis, intermediate for late stent thrombosis, and lowest for very late stent thrombosis.[30] Investigators of a recent large-scale multicentre collaborative study[31] reported 3·8% mortality after very late stent thrombosis, significantly lower than the 30% reported after early stent thrombosis.[3]

Thus, the increase in non-cardiac mortality with prolonged DAPT, not offset by any benefit in reduced cardiac mortality, resulted in overall greater all-cause mortality. The mechanistic underpinnings of the greater risk of non-cardiac mortality with extended DAPT remain unclear. Findings of recent studies[32,33] have shown that major bleeding is strongly associated with mortality after percutaneous coronary intervention, and that by reducing the risk of bleeding, total mortality can be reduced.[34] The lower rates of major bleeding with shorter DAPT compared with longer DAPT in the present meta-analysis might thus partly explain the reduction in non-cardiac mortality. Additionally, a greater propensity to bleed on DAPT might increase mortality in patients who have trauma, or in whom cancer develops. These mechanisms are consistent with the findings from the DAPT trial, in which prolonged DAPT resulted in greater bleeding-related, trauma-related, and cancer-related deaths.

However, because individual patient data were not available from all the trials in the meta-analysis, we could not establish a causal association between bleeding and mortality. Therefore, further studies are needed to establish the mechanisms of greater non-cardiac death with prolonged DAPT.

Concomitantly with the publication of the DAPT trial, Elmariah and colleagues[35] reported a meta-analysis with 14 RCTs and 69 644 randomly assigned patients showing no significant increase in mortality with extended DAPT compared with shorter DAPT (HR 1·05, 95% CrI 0·96–1·19). Our meta-analysis differs in several ways from that study. First, the meta-analysis by Elmariah and colleagues included a heterogeneous population of patients across the range of atherosclerotic disease, including studies of patients with peripheral artery disease, atrial fibrillation, and coronary artery disease managed medically, and those undergoing percutaneous coronary intervention. As a consequence, moderate heterogeneity (I^2=27%) was apparent for the effect size across component trials, suggesting the presence of effect modifiers across the population included. The risk–benefit ratio of prolonged DAPT, and its relative effects on cardiac versus non-cardiac mortality, might be disease specific. The effects of prolonged DAPT on the incidence and outcomes of adverse events (both cardiac and non-cardiac) might also be strongly affected by the underlying comorbidities typical to each disease state. Therefore, we restricted the present study to a uniform population of patients with coronary artery disease undergoing drug-eluting stent implantation, as done in the DAPT trial. In this cohort of patients, no heterogeneity was apparent for the significant reduction in mortality associated with shorter DAPT compared with longer DAPT (I^2=0%). Moreover, most of the stents used in the studies represented in the present meta-analysis were first generation drug-eluting stents. Contemporary second generation drug-eluting stents have been associated with substantially lower stent thrombosis rates,[28] which might further move the benefit–risk ratio toward shorter duration of DAPT. Such an effect was evident in the DAPT trial, in which second generation everolimus-eluting stents compared with other drug-eluting stents were associated with a smaller absolute reduction in stent thrombosis and no reduction in major adverse cardiovascular events with longer compared with shorter DAPT.[13] Second, we included two recent trials in our meta-analysis, ITALIC and ISAR SAFE,[17,26] which provided roughly a further 6000 randomly assigned patients which were not included in the study by Elmariah and colleagues. Finally, the meta-analysis by Elmariah and coworkers focused only on mortality, whereas we analysed other outcomes, including myocardial infarction, stroke, stent thrombosis, and bleeding to provide a comprehensive picture of the risks versus benefits of extending DAPT after drug-eluting stents.

As with any meta-analysis, our report shares the limitations of the original studies. Definitions of some clinical endpoints differed slightly across trials, potentially reducing precision. Trials with different designs and DAPT strategies were pooled such that 1-year DAPT was regarded (relative to the comparator group) as longer treatment in some studies and as shorter treatment in others. Despite this limitation, no heterogeneity in effect size was apparent for the risks of all-cause mortality, cardiac mortality, and non-cardiac mortality across these trials. Additionally, further analyses were done stratifying patients according to actual DAPT duration, and these provided concordant results. In a sensitivity analysis, the association between longer DAPT and increased mortality was consistent after removing individual studies, although the upper bound of the 95% CI was no longer lower than unity after removing the DAPT and DES LATE trials. However, the overall point estimates after removing these two studies (HR 0·86 and 0·84, respectively) were similar to the overall treatment effect of 0·82, suggesting the loss of significance is due to type 2 error (smaller remaining sample size). Different types of drug-eluting stents were included so it is not possible to establish whether there is an interaction between the type of drug-eluting stent and the duration of DAPT (as suggested in the DAPT trial for major adverse cardiovascular events).[13]

Most patients included in the meta-analysis were treated with clopidogrel as adjunctive treatment to aspirin. We did not establish whether the results would have varied with prasugrel and ticagrelor. The raw data from the component trials were not available, and thus we were unable to establish which subsets of patients, if any, might benefit (or at least have a neutral effect) from prolonged DAPT. One trial[24] eligible for the meta-analysis could not be included because it was not possible to define estimates of risk from the reported data. However, this study enrolled only 216 patients and therefore it is unlikely that including it would have affected the results of the meta-analysis. The post-treatment population of patients might not be representative of the initially randomly assigned population. Notwithstanding this limitation, the results in this cohort were consistent with those in the intention-to-treat population, providing uniformity in support of the main findings of the study. Finally, most studies included in the meta-analysis were not masked, although this should have little or no effect on the endpoint of all-cause mortality.

In conclusion, in our meta-analysis including 31 666 patients from ten randomised trials treated with drug-eluting stents, extended duration DAPT was associated with a 22% increased rate of all-cause mortality, due to a 49% increased rate in non-cardiac mortality, with no significant difference in cardiac mortality. The interpretation of these data should be nuanced, and does not imply that long-term DAPT

should not be considered for selected patients in whom preventing the risks of very late stent thrombosis and myocardial infarction are likely to outweigh the risks of major bleeding and the other disadvantages of chronic antiplatelet therapy. Therefore, we recommend an individualised approach wherein the specific benefit-risk profile of each patient is carefully considered, rather than adopting a one-size-fits-all policy. Further studies are required to model the demographic, laboratory-based and genetic variables that affect the benefit versus risk balance of prolonged DAPT that might remove the guesswork from this equation.

Contributors

TP, GWS, GB-Z, and UB contributed to study concept and design; TP, DDR, GB-Z, UB, and CO contributed to acquisition of data; LB-R, UB, and GB-Z did the statistical analysis; TP and GWS drafted the report; and UB, LB-R, DDR, GB-Z, FF, AA, M-KH, B-KK, YJ, H-SK, KWP, PG, DLB, CO, SDS, CR, and MP contributed to critical revision of the manuscript for important intellectual content.

Declaration of interests

None of the funders of any of the individual trials had any role in the study design, data collection, data interpretation or drafting or review of the manuscript. TP has received speaker fee from Abbott Vascular and research grant from Eli Lilly. GB-Z has consulted for Bayer Pharma, and Novartis, has lectured for Abbott Vascular, AstraZeneca, DirectFlow Medical, and St Jude Medical, and has received career grant support from Medtronic. PG has received speaker fees from Abbott and Cardiovascular System Inc. FF has received speaker fees from Biosensors and Eli Lilly, and has been consultant for Medtronic and Scitech. DLB discloses the following relationships: advisory board of Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences; Board of Directors of Boston VA Research Institute, Society of Cardiovascular Patient Care; Chair of American Heart Association Get With The Guidelines Steering Committee; Data Monitoring Committees of Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, and Population Health Research Institute; Honoraria from American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (Editor in Chief, *Journal of Invasive Cardiology*), *Journal of the American College of Cardiology* (Associate Editor; Section Editor, *Pharmacology*), Population Health Research Institute (clinical trial steering committee), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), WebMD (CME steering committees); and Clinical Cardiology (Deputy Editor); research funding from Amarin, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Forest Laboratories, Ischemix, Medtronic, Pfizer, Roche, Sanofi-Aventis, and The Medicines Company; and unfunded research from FlowCo, PLx Pharma, Takeda. GWS has served as a consultant for Osprey, Reva, Boston Scientific, AstraZeneca, Eli Lilly, Daiichi Sankyo partnership, Gilead, InspireMD, TherOx, Atrium, Volcano, InfraReDx, Miracor, Velomedix, CSI, AGA, and Thoratec, and has equity in the Biostar family of funds, the MedFocus family of funds, Caliber, Guided Delivery Systems, Micardia, Embrella, and VNT. The other authors declare no competing interests.

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