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SYSTEMATIC REVIEW AND META-ANALYSIS

Early Aspirin Discontinuation After Coronary Stenting: A Systematic Review and Meta-Analysis

Jens Wiebe, MD; Gjin Ndrepepa, MD; Sebastian Kufner, MD; Anna L. Lahmann, MD; Erion Xhepa, MD, PhD; Constantin Kuna, MD; Felix Voll, MD; Rosanna Gosetti, MD; Karl-Ludwig Laugwitz, MD; Michael Joner, MD; Adnan Kastrati, MD; Salvatore Cassese, MD, PhD

BACKGROUND: The clinical impact of early aspirin discontinuation compared with dual antiplatelet therapy (DAPT) in patients undergoing percutaneous coronary intervention with stenting remains poorly studied. We investigated the clinical outcomes of patients assigned to either early aspirin discontinuation or DAPT after percutaneous coronary intervention with stenting.

METHODS AND RESULTS: We performed a meta-analysis of aggregate data from randomized clinical trials enrolling participants receiving a percutaneous coronary intervention with stenting and assigned to either early aspirin discontinuation or DAPT. Scientific databases were searched from inception through March 30, 2020. Trial-level hazard ratios (HRs) and 95% CIs were pooled using a random effects model with inverse variance weighting. The primary outcome was all-cause death. Secondary outcomes were myocardial infarction, stent thrombosis, stroke, and major bleeding. Overall, 36 206 participants were allocated to either early aspirin discontinuation (experimental therapy, n=18 088) or DAPT (control therapy, n=18 118) in 7 trials. Median follow-up was 12 months. All-cause death occurred in 2.5% of patients assigned to experimental and 2.9% of patients assigned control therapy (hazard ratio [HR], 0.91, 95% CI, 0.75–1.11; *P*=0.37). Overall, patients treated with experimental versus control therapy showed no significant difference in terms of myocardial infarction (HR, 1.02 [0.85–1.22], *P*=0.81), stent thrombosis (HR, 1.02 [0.87–1.20], *P*=0.83), or stroke (HR, 1.01 [0.68–1.49], *P*=0.96). However, the risk for major bleeding (HR, 0.58 [0.43–0.77], *P*<0.01) was significantly reduced by experimental as compared with control therapy.

CONCLUSIONS: In patients treated with percutaneous coronary intervention and stenting, assigned to a strategy of early aspirin discontinuation versus DAPT, the risk of death and ischemic events is not significantly different but the risk of bleeding is lower.

Key Words: aspirin ■ coronary artery disease ■ meta-analysis ■ stent

In patients treated with a percutaneous coronary intervention (PCI) for stable or unstable coronary artery disease (CAD), specialty guidelines recommend a dual antiplatelet therapy (DAPT) for prevention of thrombotic complications. DAPT regimens usually consist of aspirin and a P2Y12-inhibitor prescribed for 1 to 12 months according to clinical indication and concomitant antithrombotic therapies.[1]

The use of DAPT after coronary stenting has been standard of care since a series of clinical trials done in the 1990s showed that this was the most effective approach.[2,3] The main downside is that DAPT exposes patients to the risk of bleeding complications for the duration of therapy. In this regard, the search for alternative antithrombotic regimens, ensuring adequate platelet inhibition while having a wide therapeutic window, remains a matter of broad clinical interest. Recent randomized trials investigated the risk:benefit ratio of early aspirin discontinuation while continuing P2Y12-inhibitors as compared with DAPT

Correspondence to: Salvatore Cassese, MD, PhD, Klinik für Herz- und Kreislauferkrankungen, Deutsches Herzzentrum München, Technische Universität München, Lazarettstrasse, 36 - Munich, Germany. E-mail: cassese@dhm.mhn.de

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CLINICAL PERSPECTIVE

What Is New?

- Compared with dual antiplatelet therapy, early aspirin discontinuation after coronary stenting does not increase mortality and ischemic events but reduces bleedings.

What Are the Clinical Implications?

- The timing of aspirin discontinuation and the role of a monotherapy with more-potent antiplatelet drugs after coronary stenting warrant further investigation.

Nonstandard Abbreviations and Acronyms

DAPT	dual antiplatelet therapy
OAC	oral anticoagulation
ST	stent thrombosis

across various risk categories of patients with stable or unstable CAD treated with contemporary PCI and stenting.[4–6] Not surprisingly, by dropping aspirin from DAPT regimens the bleeding risk was reduced to some extent. However, whether this benefit is offset by an increased risk of thrombotic events remains poorly investigated. Indeed, no trial was powered to reliably detect or rule out the efficacy of P2Y12-inhibitors alone in preventing thrombotic events in this setting.

Against this background, this systematic review and meta-analysis of randomized trials investigates the clinical impact of early aspirin discontinuation versus DAPT in patients treated with coronary stenting.

METHODS

We will make the data and methods used in the analysis available to any researcher for the purposes of reproducing the results and procedures upon reasonable request.

Data Sources and Searches

Relevant electronic scientific databases (including Medline, EMBASE, the CENTRAL [Cochrane Central Register of Controlled Trials], session abstracts, and websites) were searched for scientific communications without restricting language or publication status. We extrapolated further citations by inspecting the references listed in all eligible studies. The last search was performed on March 30, 2020. Search terms included the keywords and the corresponding Medical Subject Headings for: "aspirin," "antithrombotic therapy," "(dual) antiplatelet therapy," "clopidogrel," "ticagrelor," "prasugrel," "percutaneous coronary intervention," "stent," "trial," and "randomized trial." Inclusion criteria were the following: (1) randomized design, (2) allocation to antiplatelet therapy with or without concomitant oral anticoagulation (OAC), and (3) follow-up duration ≥6 months. Trials in which the type, number, dose, or duration of OAC medications differed between treatment groups were ineligible.[7–9]

Study Selection

Two investigators (J.W. and G.N.) independently assessed publications for eligibility at title and/or abstract level. A third investigator (S.C.) helped to settle divergences. In case the studies met inclusion criteria, they entered further analysis.

Data Extraction, Quality Assessment, and Outcome Variables

Trial-level data concerning overall number of patients, mean age, proportion of females, patients with diabetes mellitus, former or current smokers, acute coronary syndromes (ACS) at admission, history of previous myocardial infarction (MI) or cerebrovascular accident were extracted from each trial. The same investigators evaluated independently the presence of any bias in each study in accordance with The Cochrane Collaboration items.[10] We did not assign composite quality scores.[11] The primary outcomes of this analysis were all-cause death and MI. Secondary outcomes were stent thrombosis (ST), stroke, and major bleeding. We considered all end points occurred up to the maximum follow-up duration in the intention-to-treat population, as per definitions reported in the original protocols.

Data Synthesis and Statistical Analysis

Hazard ratios (HRs) and 95% CIs served as summary statistics to compare the outcomes of interest associated with either early aspirin discontinuation (experimental therapy) or standard DAPT (control therapy). A random effects model with the inverse variance weighting (stratified according to concomitant OAC therapy) served to pool trial-level logHRs and corresponding SEs. We considered time-to-event data during the entire duration of follow-up in each included trial (primary analysis), and after therapies in the treatment groups actually diverged (posing a landmark at aspirin discontinuation in the experimental group). The I^2 statistic and (95% CIs) informed on the heterogeneity between the trials: I^2 values ≈25%, 50%, and 75% were considered to indicate low, moderate, or high heterogeneity, respectively.[10] In addition, we estimated the between-study variance (tau^2) according to DerSimonian-Laird

and derived the 95% prediction interval of pooled estimates.[12] In case of statistical significance in the primary analysis, the number needed to treat or to harm with (95% CI) was provided. We performed 3 sensitivity analyses.

1. The Breslow-Day χ^2 test for subgroup differences addressed the impact of concomitant OAC therapy on outcomes of interest. The same statistical method was useful to calculate the treatment-by-subgroup interaction between primary outcomes and (1) the P2Y12-inhibitor predominantly used in the experimental group (clopidogrel versus ticagrelor); (2) the time point of aspirin discontinuation (immediately versus 1 month versus 3 months after coronary stenting) as per individual protocol in each trial; (3) the predominant geographic area of enrollment (Asia versus Western countries).
2. An influence analysis assessed the changes in the direction of the summary estimates for primary outcomes computed omitting 1 study at a time.
3. A random-effect meta-regression analysis assessed the impact proportion of patients with ACS at admission on the pooled estimates for primary outcomes.

We calculated the power of our meta-analysis to detect a 30% relative risk difference for main outcomes with early aspirin discontinuation conditional on the observed precision of the pooled estimate.[13] We set the 30% threshold as benchmark because it corresponds to the average relative risk difference threshold (range 20%–58%) supporting the power of individual study designs included in this meta-analysis. The possibility of small study effects resulting from publication bias or other biases was examined for the primary outcomes by visual inspection of funnel plots of the HRs of individual trials against their SEs and by a linear regression test for funnel plot asymmetry.

This study was reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Table S1).[14] All analyses were performed by using the package *meta* in R (version 3.6.0; R Foundation for Statistical Computing, Vienna, Austria). No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents. Ethical approval was not required for this study.

RESULTS

Eligible Studies

The flow diagram for the trial selection process is shown in Figure 1. After application of inclusion/exclusion criteria, 7 trials (6 published as full-length manuscripts[4–6,15–17] and 1 available as a meeting presentation[18]) were included in the meta-analysis. No disagreements required solution by the third reviewer. In the selected trials, a total of 37 303 patients were randomly allocated to experimental (n=18 638) or control therapy (n=18 665) after coronary stenting. Two trials included patients with PCI with a planned OAC therapy. The WOEST (What is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting) trial included patients with any indication for OAC.[15] Conversely, the Aspirin Placebo in Patients with Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention (AUGUSTUS) trial included only patients with an indication for OAC because of atrial fibrillation.[6] The AUGUSTUS trial included a total of 1097 patients with medically treated ACS: since the current study focused on patients receiving experimental or control therapy after coronary stenting, we obtained from this latter study time-to-event data of the PCI stratum to derive summary risk estimates.[19] Thus, we analyzed the aggregate data of 7 trials in which a total of 36 206 PCI patients were allocated to experimental (n=18 088) or control therapy (n=18 118).

The main characteristics of the trials included are shown in Table S2. All trials had a multicenter design and included patients with obstructive chronic/stable or unstable CAD receiving coronary stenting.

Patients allocated to experimental therapy received aspirin 75 to 200 mg once daily for a period of time ranging between 1 and 3 months in 5 trials,[4,5,16–18] with clopidogrel 75 mg once daily or ticagrelor 90 mg twice daily as predominant P2Y12-inhibitors. In 3 trials,[6,16,17] a proportion of patients ranging between 0.7% and 39.6% received 3.75 to 10 mg prasugrel once daily according to clinical indication.

Patients assigned to control therapy received DAPT consisting of clopidogrel 75 mg once daily or ticagrelor 90 mg twice daily in combination with aspirin 75 to 200 mg once daily. Patients with an indication for OAC received either vitamin K antagonist or either apixaban or vitamin K antagonist in a random fashion in 2 trials.[6,15] Comparative Effectiveness of 1 Month of Ticagrelor Plus Aspirin Followed by Ticagrelor Monotherapy Versus a Current-day Intensive Dual Antiplatelet Therapy in All-comers Patients Undergoing Percutaneous Coronary Intervention With Bivalirudin and BioMatrix Family Drug-eluting Stent Use (GLOBAL LEADERS) trial had a peculiar design which deserves further description. The experimental therapy consisted of ticagrelor 90 mg twice daily in combination with aspirin 75 to 150 mg once daily for 1 month followed by ticagrelor monotherapy for 23 months. The control therapies

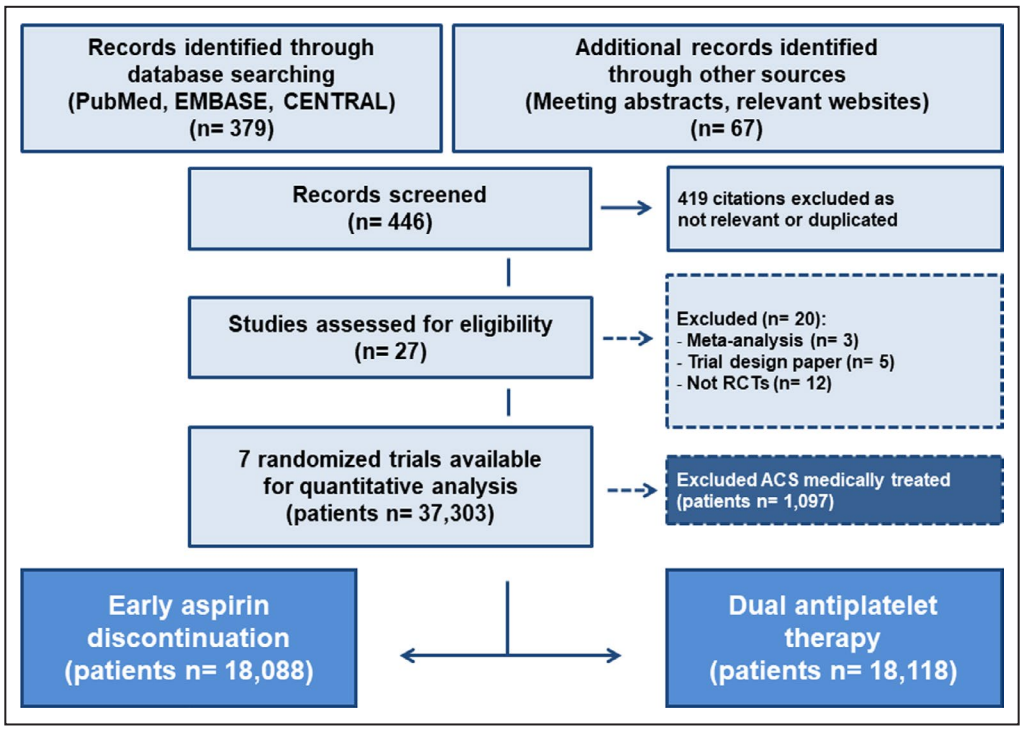


Figure 1. PRISMA flow chart for the trial selection process.
ACS indicates acute coronary syndrome; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; and RCTs, randomized controlled trials.

consisted of clopidogrel 75 mg once daily or ticagrelor 90 mg twice daily (according to clinical presentation) in combination with aspirin 75 to 150 mg once daily for 12 months followed by aspirin 75 to 150 mg once daily for an additional 12 months.[4] Finally, the Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention (TWILIGHT) trial randomized patients without bleeding or ischemic events 3 months after PCI to either continue ticagrelor as standalone therapy or DAPT (experimental and control therapy, respectively).[5]

In 3 trials the predominant diagnosis at admission was ACS or stabilized MI.[5,16,18] In the experimental group, the adherence to assigned antiplatelet regimen at the longest available follow-up ranged between 77.6% and 87.1%. All patients received ancillary therapies for acute or chronic manifestations of CAD in accordance with standard of care.

Baseline characteristics are shown in Table. Patients were more often male, had a median age of 65.1 years (interquartile range, 64.5–69.9), more than a third of them had diabetes mellitus, and nearly one-fourth of them had a history of smoking at the time of inclusion in the primary trials. Approximately 50% of patients included presented with ACS. A previous MI was reported in 25.3% of patients, and 6.4% of patients have had cerebrovascular accidents before enrollment. The weighted median follow-up available for the assessment of outcomes of interest was 12 months (mean 12.8±5.3).

Clinical Outcomes

All trials had sufficient statistical power for bleeding or composite clinical end points, which included mortality and MI in most of them. One trial reported outcome data beyond 12 months.[4] The definitions of outcomes are reported in Table S3 and the risk of bias among studies is reported in Table S4.

Primary Outcomes

Overall, all-cause deaths occurred in 981 patients (2.7%; Figure 2A).[4–6,15–19] The outcome of all-cause death occurred in 2.5% of patients assigned to experimental and 2.9% of patients assigned control therapy (HR, 0.91; 95% CI, 0.75–1.11; P=0.37). The random-effects meta-analysis had 94.7% power to detect a 30% relative risk difference of all-cause death associated with experimental therapy. The 95% prediction interval for this outcome contained the null (0.58; 1.45) and there was moderate heterogeneity. Notably, there was no impact of concomitant OAC therapy with the risk of all-cause death (P for interaction [P_{int}]=0.72). Cardiac death occurred in 128 patients (0.8%, data available for 16 740 participants). The risk of cardiac death in patients assigned to either experimental or control

Table. Main Characteristics of Patients Enrolled Among Trials Included in the Study

Trial	Patients, n	Age, y	Females, %	Diabetes Mellitus, %	Smoking, %	ACS, %	Previous MI, %	Previous CVA, %
With oral anticoagulation								
AUGUSTUS (PCI stratum)[6–19]	3498	70.6	904 (25.8)	1320 (37.7)	N/R	1714 (48.9)	N/R	466 (13.3)
WOEST[15]	573*	69.9	115 (20.4)	140 (24.9)	102 (18.1)	155 (27.5)	196 (34.8)	99 (17.6)
Without oral anticoagulation								
GLOBAL LEADERS[4]	15 968	64.5	3714 (23.2)	4038 (25.2)	4169 (26.1)	7487 (46.8)	3710 (23.2)	421 (2.6)
SMART CHOICE[16]	2993	64.5	795 (26.5)	1122 (37.4)	791 (26.4)	1741 (58.1)	783 (26.1)	201 (6.7)
STOP DAPT 2[17]	3009	68.6	672 (22.3)	1159 (38.5)	710 (23.5)	1148 (38.1)	741 (24.6)	186 (6.1)
TICO[18]	3056	61.0	628 (20.5)	835 (27.3)	1142 (37.3)	3056 (100)	113 (3.7)	126 (4.1)
TWILIGHT[5]	7199	65.1	1698 (23.5)	2620 (36.3)	1548 (21.5)	4614 (64.1)	2120 (29.4)	N/R

Overall numbers (proportions) and means are reported. ACS indicates acute coronary syndrome; CVA, cerebrovascular accident; MI, myocardial infarction; N/R, not reported; and PCI, percutaneous coronary intervention. Official titles and acronyms: AUGUSTUS, Aspirin Placebo in Patients with Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention; GLOBAL LEADERS, Comparative Effectiveness of 1 Month of Ticagrelor Plus Aspirin Followed by Ticagrelor Monotherapy Versus a Current-day Intensive Dual Antiplatelet Therapy in All-comers Patients Undergoing Percutaneous Coronary Intervention With Bivalirudin and BioMatrix Family Drug-eluting Stent Use; SMART CHOICE, Comparison Between P2Y12 Antagonist Monotherapy and Dual Antiplatelet Therapy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents; STOP DAPT 2, Short and Optimal Duration of Dual Antiplatelet Therapy-2 Study; TICO, Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus Stent for Acute Coronary Syndrome; TWILIGHT, Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention; WOEST: What is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting.

*Complete data available for 563 patients.

therapy was not significantly different (0.6% versus 0.9%; HR, 0.73 [0.52–1.04], P=0.08).

The outcome of MI occurred in 896 patients (2.5%; Figure 2B).[4–6,15–19] The risk of MI in patients assigned to either experimental or control therapy was not significantly different (2.5% versus 2.5%; HR, 1.02 [0.85–1.22], P=0.81). The random-effects meta-analysis had 97.4% power to detect a 30% risk difference of MI associated with experimental therapy. The 95% prediction interval for this outcome contained the null (0.71; 1.48). There was no impact of concomitant OAC therapy with the risk of MI (P_{int}=0.64).

Secondary Outcomes

ST occurred in 213 patients (0.6%) (Figure 3A through 3C).[4–6,15–19] In patients assigned to either experimental or control therapy, the risk of ST was not significantly different (0.6% versus 0.6%; HR, 1.02 [0.87–1.20], P=0.83).

Stroke occurred in 282 patients (0.8%). In patients assigned to either experimental or control therapy, the risk of stroke was not significantly different (0.8% versus 0.8%; HR, 1.01 [0.68–1.49], P=0.96), with moderate to high heterogeneity.

Major bleeding occurred in 812 patients (2.2%). Patients assigned to experimental therapy had a lower risk of major bleeding compared with control therapy (1.8% versus 2.7%; HR, 0.58 [0.43–0.77], P<0.01), with high heterogeneity. The number needed to treat to avoid 1 case of major bleeding with experimental therapy was 88 patients (64; 161). We found no impact of concomitant OAC therapy with the risk of ST, stroke, or major bleeding in patients assigned to either experimental or control therapy (P_{int}≥0.69).

Landmark Analysis

After aspirin discontinuation, the risk of all-cause death (HR, 0.92 [0.74–1.15], P=0.47), MI (HR, 1.01 [0.81–1.27], P=0.92), ST (HR, 1.02 [0.73–1.43], P=0.90), and stroke (HR, 1.10 [0.69–1.74], P=0.70) was not significantly different in patients assigned to either experimental or control therapy. In contrast, the risk of major bleeding was lower with the experimental compared with control therapy (HR, 0.53 [0.38–0.74], P<0.01). The concomitant OAC therapy did not impact the risk estimates for the abovementioned outcomes (P_{int}≥0.56).

Sensitivity and Influence Analyses

The test for subgroup differences did not find a significant interaction between the risk for all-cause death and MI and the use of clopidogrel or ticagrelor in the experimental arm (P=0.41 and 0.82), the discontinuation of aspirin immediately, 1 or 3 months

after coronary stenting (*P*=0.84 and 0.76), and the predominant enrollment of patients from Asia or Western countries (*P*=0.57 and 0.25). By omitting 1 study at a time, the direction of the summary HRs for the primary outcomes did not display a significant modification (Figure S1A and S1B). The linear regression test discarded a funnel plot asymmetry for all-cause death (*P*=0.54) and MI (*P*=0.48), respectively (Figure S2A and S2B). Finally, the treatment effect for all-cause death (*P*=0.71) and MI (*P*=0.40) was not dependent on the proportion of patients with ACS at admission.

DISCUSSION

This systematic review and meta-analysis of aggregate study-level data investigated the outcomes of ≈40 000 patients with CAD randomly assigned to either early aspirin discontinuation or DAPT after PCI with stent implantation. Importantly, the treatment groups in each included trial received identical antithrombotic regimens, apart from early aspirin discontinuation in the experimental group. After a median follow-up of 12 months the main findings are as follows:

1. In comparison with DAPT, the risk of all-cause death and MI with early aspirin discontinuation was not significantly different, but the risk of major bleeding was lower.
2. There are no significant differences with respect to ST and stroke associated with either early aspirin discontinuation or DAPT.

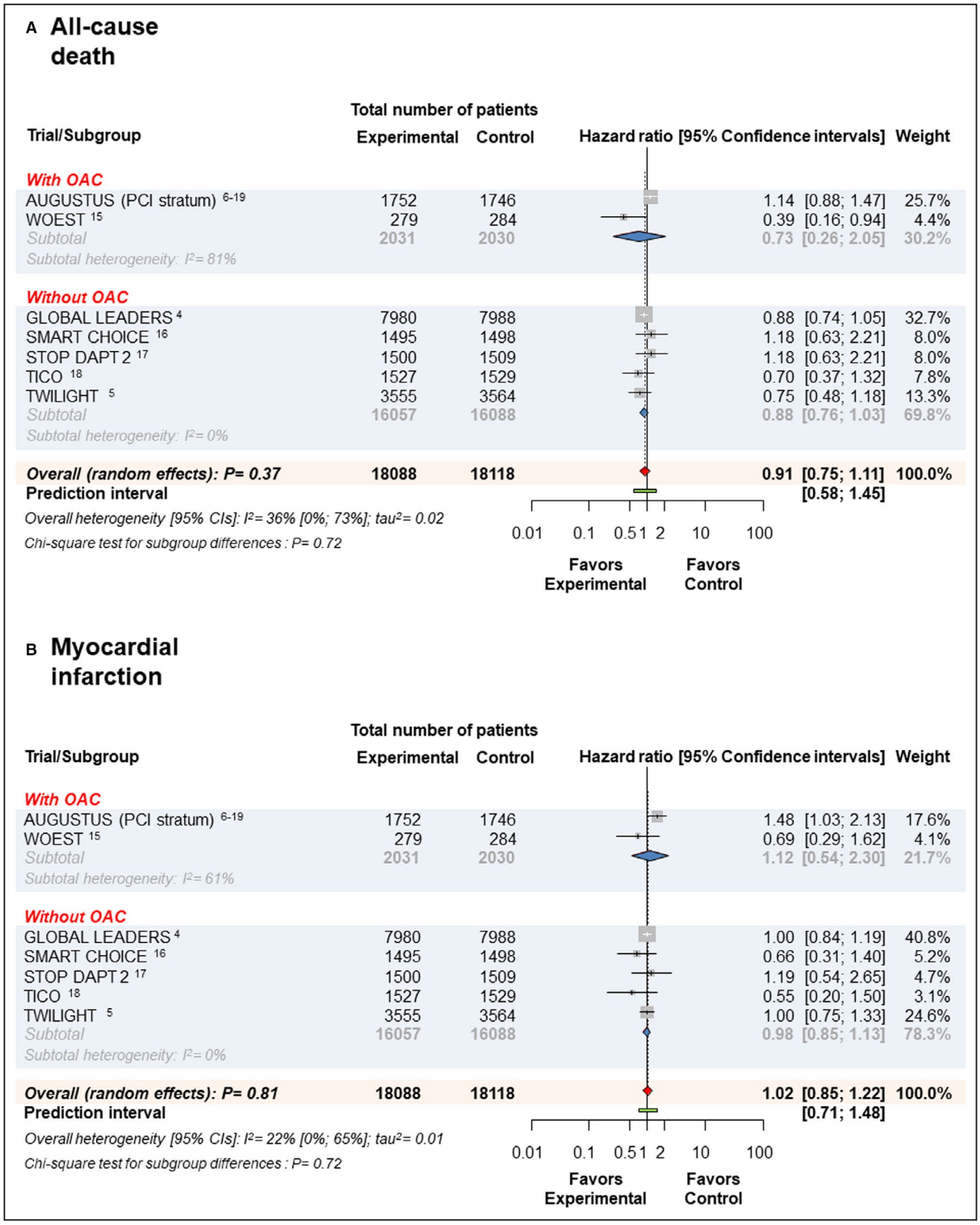
First, the results of this study are relevant in that they report a neutral treatment effect for mortality and MI and a lower risk of major bleeding with an antithrombotic regimen without aspirin. In fact, although the lower bleeding risk associated with the omission of aspirin among antithrombotic medications comes as no surprise,[20] this analysis showed no trade-off between bleeding reduction and increased thrombotic risk. This is a pervasive feature of most trials of antithrombotic therapy and accordingly, adjudication of overall patient benefit can be challenging. In this respect, all-cause death, the primary end point of the current study, might be a robust and sensitive indicator of net clinical benefit. Along the same line, the lack of significant difference in terms of ischemic risk in patients assigned to either early aspirin discontinuation or DAPT after contemporary stenting is reassuring. It is worth mentioning that the present study has sufficient statistical power to ascertain any clinically relevant benefit (or harm) in terms of mortality and MI associated with aspirin withdrawal in this setting.

Second, the magnitude of treatment effect for primary outcomes was not dependent on whether we considered time-to-event data from the entire follow-up duration or after aspirin discontinuation in the experimental group. Indeed, in the majority of trials included, patients randomized at time of PCI received the same antithrombotic regimens for a period of time ranging between 1 and 3 months.[4–6,16–18] This is an important methodological aspect, because it provides evidence that the risk for ischemic and bleeding outcomes associated with early aspirin discontinuation is not dampened from events that occurred when treatment groups receive the same antithrombotic therapies. The analysis of landmark data, the increased statistical power for clinically relevant outcomes, the selection of trials in which antithrombotic regimens across groups were identical apart from per-protocol aspirin withdrawal, and the inclusion of the latest available evidence concerning early aspirin dropping from DAPT after coronary stenting represent unique features of this study, which have some clinical relevance.

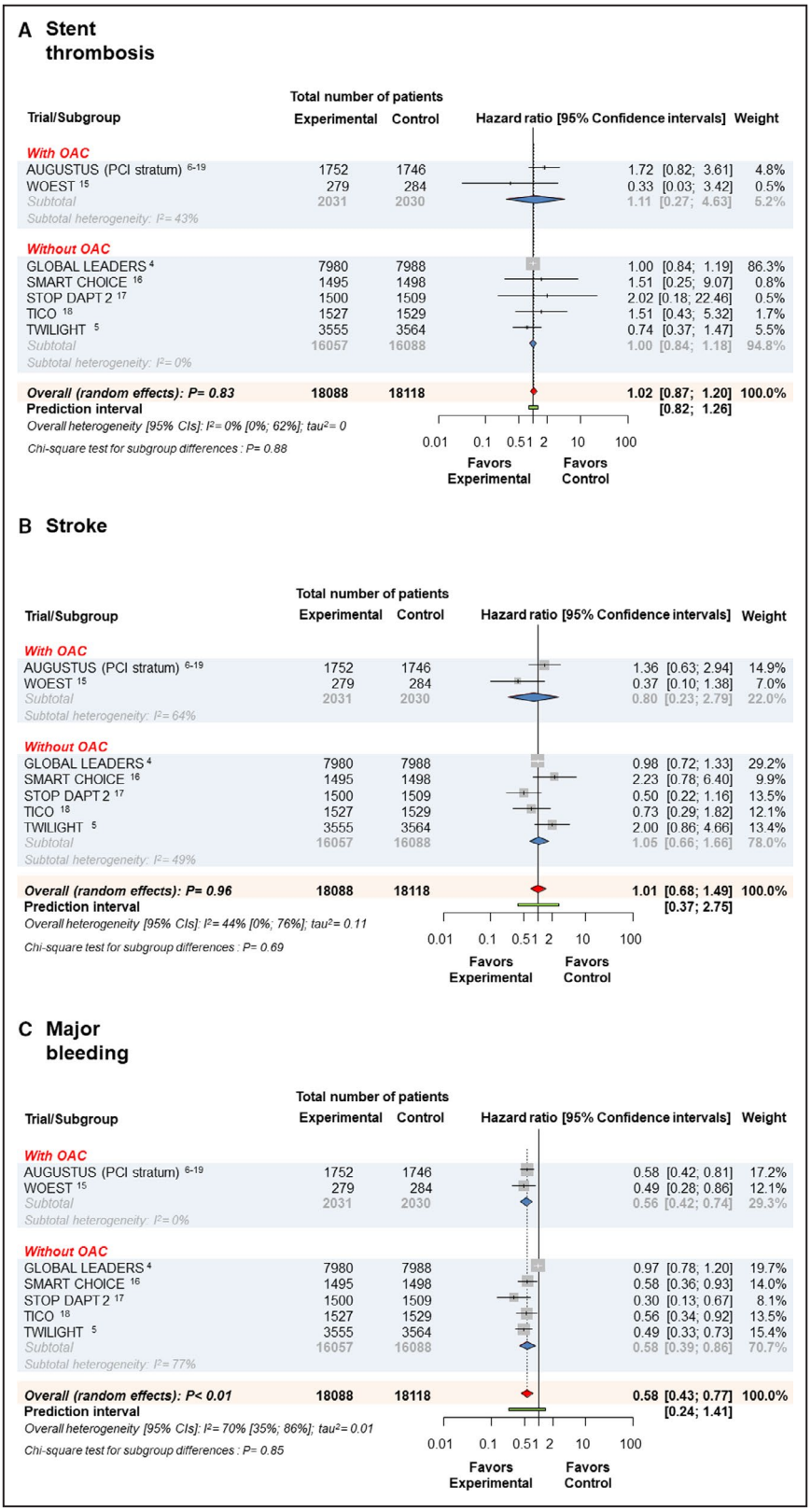
Third, the present meta-analysis is quite consistent with another study assessing the role of aspirin in primary prevention, and which demonstrated no reduction of mortality, but increased rates of major bleedings.[21] In contrast with this previous study, we did not confirm the benefit of antithrombotic regimens with aspirin in lowering nonfatal ischemic events. The findings from primary prevention studies may have implications for aspirin use in the setting

Figure 2. Summary of risk estimates for primary outcomes with early aspirin discontinuation vs dual antiplatelet therapy after coronary stenting.

Plot of hazard ratio for all-cause death (**A**) and myocardial infarction (**B**) associated with early aspirin discontinuation (experimental therapy) vs dual antiplatelet therapy (control therapy). The diamonds indicate the point estimate and the left and the right ends of the lines indicate the 95%CIs. Official titles and acronyms: AUGUSTUS: Aspirin Placebo in Patients with Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention; WOEST: What is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting; GLOBAL LEADERS: Comparative Effectiveness of 1 Month of Ticagrelor Plus Aspirin Followed by Ticagrelor Monotherapy Versus a Current-day Intensive Dual Antiplatelet Therapy in All-comers Patients Undergoing Percutaneous Coronary Intervention With Bivalirudin and BioMatrix Family Drug-eluting Stent Use; SMART CHOICE: Comparison Between P2Y12 Antagonist Monotherapy and Dual Antiplatelet Therapy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents; STOP DAPT 2: Short and Optimal Duration of Dual Antiplatelet Therapy-2 Study; TICO: Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus Stent for Acute Coronary Syndrome; TWILIGHT: Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention. OAC indicates oral anticoagulation; and PCI, percutaneous coronary intervention.



of secondary prevention, as in patients with CAD undergoing coronary stenting. Indeed, the mechanism of atherothrombotic protection of aspirin is the same, regardless of use in the setting of primary or secondary prevention. In addition, ischemic events, mostly indicated to support the benefits of aspirin in primary prevention, may be even more frequent in the setting of secondary prevention because of poorer



risk profile of patients predisposing to a higher risk of adverse events.

Finally, in the past decade the strategy of discontinuing P2Y12-inhibitors in favor of aspirin after coronary stenting has been extensively investigated.[22] However, although aspirin has been the cornerstone of antiplatelet therapy for a long time, there exists a clinical rationale for discontinuing its use in favor of P2Y12-inhibitors.

Figure 3. Summary of risk estimates for secondary outcomes with early aspirin discontinuation vs dual antiplatelet therapy after coronary stenting.
Plot of hazard ratio for stent thrombosis (**A**), stroke (**B**), and major bleeding (**C**) associated with early aspirin discontinuation (experimental therapy) vs dual antiplatelet therapy (control therapy). The diamonds indicate the point estimate and the left and the right ends of the lines indicate the 95% CIs. Official titles and acronyms: AUGUSTUS: Aspirin Placebo in Patients with Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention; WOEST: What is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting; GLOBAL LEADERS: Comparative Effectiveness of 1 Month of Ticagrelor Plus Aspirin Followed by Ticagrelor Monotherapy Versus a Current-day Intensive Dual Antiplatelet Therapy in All-comers Patients Undergoing Percutaneous Coronary Intervention With Bivalirudin and BioMatrix Family Drug-eluting Stent Use; SMART CHOICE: Comparison Between P2Y12 Antagonist Monotherapy and Dual Antiplatelet Therapy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents; STOP DAPT 2: Short and Optimal Duration of Dual Antiplatelet Therapy-2 Study; TICO: Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus Stent for Acute Coronary Syndrome; TWILIGHT: Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention. OAC indicates oral anticoagulation; and PCI, percutaneous coronary intervention.

Aspirin increases the risk of bleeding complications and the majority of studies of aspirin in patients with PCI were conceived before the advent of other established medical therapies, including new P2Y12-inhibitors.[23] For these reasons, we believe that investigations concerning the de-escalation of antithrombotic therapies by discontinuing aspirin (instead of P2Y12-inhibitors) in patients with PCI are worth pursuing. In this regard, future trials should address whether a monotherapy with the irreversible P2Y12-inhibitor prasugrel, which was prescribed in a small proportion of patients in the current analysis, is superior to a monotherapy with clopidogrel or ticagrelor after coronary stenting.

Limitations

The current study has some limitations. First, the meta-analysis was based on study-level data. Although we believe that the questions under consideration can be reliably answered by a meta-analysis of aggregate data, a meta-analysis of individual participant data remains necessary. In this context, the fact that we observed no change in the direction of treatment effect for primary outcomes dependent on several features at trial level including the need for concomitant OAC therapy, the type of P2Y12-inhibitor, the timing of aspirin discontinuation, and the proportion of patients with ACS remains speculative in nature. The analysis of individual data remains a prerequisite to disclose a variation of treatment effect according to several features at patient (clinical presentation, concomitant OAC), procedural (anatomical or interventional complexity, stent type), and pharmacological (safety and efficacy profiles of different P2Y12-inhibitors and dosages, response to antithrombotic drugs) levels. Second, all patients were on aspirin therapy at the time of PCI and discontinuation occurred at various intervals postprocedure per individual trial protocols. Although we found no statistical interaction between the timing of aspirin discontinuation and the treatment effect for the primary outcomes, we cannot recommend a specific time-point after coronary stenting at which aspirin could be dropped from DAPT. Third, the results associated with experimental versus control therapy observed in this analysis do not apply to patients with clinical and anatomical features different from those represented here. Notably, the number needed to avoid 1 case of major bleeding with the experimental therapy remains relatively high because of the inclusion of relatively low-risk patients with obstructive chronic/stable or unstable CAD. Fourth, the median follow-up duration was 12 months. An extended follow-up would be desirable and we cannot exclude the possibility that significant differences may emerge at long term. Finally, the use of funnel plots does not accurately depict publication bias for such a small sample.

CONCLUSIONS

The present study shows that in patients treated with coronary stenting and assigned to early aspirin discontinuation versus standard DAPT, the risk of mortality and ischemic events is not significantly different but the risk of bleeding is lower. This finding may challenge the current antithrombotic treatment of patients receiving coronary stenting. However, the comparative safety and efficacy of a monotherapy with more-potent antiplatelet drugs after coronary stenting remains to be addressed in randomized trials powered for clinically relevant ischemic and bleeding end points.

ARTICLE INFORMATION

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Affiliations

From the Klinik für Herz- und Kreislauferkrankungen, Deutsches Herzzentrum München, Technische Universität München, Munich, Germany (J.W., G.N., S.K., A.L.L., E.X., C.K., F.V., M.J., A.K., S.C.); 1. Medizinische Klinik, Klinikum rechts der Isar, Technische Universität München, Munich, Germany (R.G., K.-L.L.); and DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany (K.-L.L., M.J., A.K.).

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Wiebe together with Ndrepepa, Kastrati, and Cassese wrote the first draft of the manuscript. Wiebe, Ndrepepa, Kufner, Lahmann, Xhepa, Kuna, Voll, Gosetti, Laugwitz, Joner, Kastrati, and Cassese were involved in data acquisition and revised the manuscript for important intellectual contents. All authors had full access to all the data, including statistical reports and tables and approved the manuscript for final submission. Open access funding enabled and organized by Projekt DEAL.

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Disclosures

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Supplementary Material

Tables S1–S4
Figures S1–S2

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Supplemental Material

Table S1. PRISMA checklist.

Section/topic	*#*	*Checklist item*	*Reported on page #*
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	**1**
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	**2**
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	**4**
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	**5-6**
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	**Not applicable**
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	**5**
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	**5**
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	**Table S1**
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	**5-6**
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	**5**

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	**5**
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	**5-7**
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	**6**
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	**6**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	**Table S4**
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	**7**
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	**Figure S1**
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	**8-10; Table; Table S2**
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	**Table S4**
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	**10-12; Figures 1-2; Figure S2**
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	**10-12; Figures 1-2; Figure S2**
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	**Figure S3**
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression	**Figure S4**

		[see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	**12-15**
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	**14-15**
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	**12-15**
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	**16**

Search Strategy: PubMed/MEDLINE

("aspirin"[MeSH Terms] OR "aspirin"[All Fields]) AND ("antithrombotic therapy"[All Fields] OR "antiplatelet therapy"[All Fields]) AND (dual[All Fields] AND antiplatelet [All Fields] OR ("therapy"[Subheading] OR "therapy"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]) AND ("clopidogrel"[All Fields] OR "therapeutics"[All Fields]) AND ("ticagrelor"[All Fields] OR "therapeutics"[All Fields]) AND ("prasugrel"[All Fields]) AND ("percutaneous coronary intervention"[MeSH Terms] OR ("percutaneous"[All Fields] AND "coronary"[All Fields] AND "intervention"[All Fields]) OR "percutaneous coronary intervention"[All Fields]) AND ("stents"[MeSH Terms] OR "stents"[All Fields] OR "stent"[All Fields]) AND ("random allocation"[All Fields] OR "randomized"[All Fields]) AND ("clinical trials as topic"[MeSH Terms] OR ("clinical"[All Fields] AND "trials"[All Fields] AND "topic"[All Fields]) OR "clinical trials as topic"[All Fields] OR "trial"[All Fields])

Table S2. Main characteristics of included trials.

Trial	*Period of enrolment*	*Assigned therapies*	*Key inclusion criteria*	*Key exclusion criteria*	*Primary endpoint (follow-up duration)*	*Registration number*
AUGUSTUS	2015-2018	Apixaban 5 mg twice daily (or 2.5 mg twice daily if ≥2 dose-reduction criteria are present) plus P2Y12-inhibitor (clopidogrel, ticagrelor or prasugrel) plus aspirin 81 mg daily versus apixaban plus P2Y12-inhibitor (as above) plus placebo versus VKA plus P2Y12-inhibitor (as above) plus aspirin 81mg daily versus VKA plus P2Y12-inhibitor (as above) plus placebo	Age ≥18; previous, persistent, permanent, or paroxysmal atrial fibrillation; planned long-term use of OAC; ACS or PCI <14 days; planned use of P2Y12 inhibitor for ≥6 months	OAC indication; severe CKD; history of intracranial hemorrhage; recent or planned CABG; coagulopathy or ongoing bleeding	ISTH major bleeding (6 months)	NCT02415400
WOEST	2008-2011	VKA plus P2Y12-inhibitor (clopidogrel 75 mg once daily) versus VKA plus P2Y12-inhibitor (as above) plus aspirin (acetylsalicylic acid 80 mg or carboxylate	Age >18; indication for OAC for ≥1 year; indication for PCI of a significant coronary lesion (defined as ≥75% angiographically or FFR <0.80).	Age >80; history of intracranial bleeding; cardiogenic shock; gastric ulcer ≤6 months prior to PCI; severe thrombocytopenia (platelets <50 x 10^9/L); TIMI major bleeding ≤6	Any bleeding (12 months)	NCT00769938

		calcium 100 mg once daily)†		months prior to PCI		
GLOBAL LEADERS	2013-2015	P2Y12-inhibitor (ticagrelor 90 mg twice daily) plus aspirin 75-100 mg once daily for 1 month, followed by ticagrelor 90 mg twice daily monotherapy for 23 months versus aspirin 75-100 mg once daily plus P2Y12-inhibitor (clopidogrel 75 mg once daily or ticagrelor 90 mg twice daily) for 12 months, followed by aspirin 75-100 mg once daily monotherapy for 12 months	Age ≥18; any clinical indication for PCI	Intolerance to aspirin, P2Y12-inhibitors, bivalirudin, stainless steel or biolimus; intake of a strong CYP3A4 inhibitor; OAC indication; overt major bleeding	Composite of all-cause death or new Q-wave MI (23 months)	NCT01813435
SMART CHOICE	2014-2018	Aspirin plus P2Y12-inhibitor (clopidogrel, prasugrel or ticagrelor according to recommended doses and clinical indications) for 3 months followed by P2Y12-inhibitor alone (as above) versus aspirin plus P2Y12-inhibitor (as above) for ≥12 months	Age ≥20; ≥1 coronary artery stenoses of ≥50% in a native coronary artery with visually estimated diameter ≥2.25mm and ≤4.25mm amenable to stent implantation	Hypersensitivity or contraindication to aspirin, clopidogrel, prasugrel, ticagrelor, everolimus, or sirolimus; hemodynamic instability or cardiogenic shock; active bleeding; DES implantation ≤12 months before PCI; women of childbearing potential; life expectancy <2 years	MACCE ‡ (12 months)	NCT02079194

STOP DAPT 2	2015-2017	Aspirin, 81 to 200mg once daily, and clopidogrel 75 mg once daily, or aspirin (as above) and prasugrel, 3.75 mg/d, at the discretion of the attending physician for 1 month followed by clopidogrel monotherapy (as above) for up to 5 years versus aspirin and clopidogrel (as above) for up to 12 months§	Any patient who underwent successful PCI with CoCr everolimus-eluting stents (Xience Series, *Abbott Vascular*) without concomitant use of other types of DES or in-hospital major complications other than peri-procedural MI	OAC indication or antiplatelet therapy other than aspirin and P2Y12-inhibitor; history of intracranial bleeding; known intolerance to clopidogrel	Composite of cardiovascular and bleeding events‖ (12 months)	NCT02619760
TICO	2015-2018	Ticagrelor 90 mg twice daily plus aspirin 75-100 mg once daily for 3 months followed by ticagrelor (as above) monotherapy for up to 12 months versus aspirin plus ticagrelor (as above) for 12 months	Age ≥19 years; bioresorbable polymer sirolimus-eluting stent implantation for ACS	Age >80 years; increased risk of bleeding; major surgery or traumatic injury resulting in any impairment of physical activity <3 weeks; OAC indication; current or potential pregnancy; life expectancy <1 year; currently treatment with strong CYP3A4 inhibitors; moderate to severe hepatic dysfunction; increased risk of bradycardia-related symptoms	Net adverse cardiac events including MACCE¶ plus TIMI major bleeding (12 months)	NCT02494895
TWILIGHT	2015-2017	Ticagrelor 90 mg twice daily monotherapy plus	Patients who underwent successful PCI with at	STEMI; cardiogenic shock; OAC indication;	BARC type 2, 3, or 5 bleeding	NCT02270242

	placebo for up to 12 months or aspirin 75-100 mg once daily plus ticagrelor (as above) for 12 months#	least one locally approved DES and whom the treating clinician intended to discharge with a regimen of ticagrelor plus aspirin with ≥1 clinical feature and angiographic feature associated with a high risk of ischemic or bleeding events**	contraindication to aspirin or ticagrelor	(12 months)

ACS: acute coronary syndrome; BARC: Bleeding Academic Research Consortium; CABG: coronary artery bypass grafting; CAD: coronary artery disease; CKD: chronic kidney disease; DAPT: dual antiplatelet therapy; DES: drug-eluting stent; ISTH: International Society on Thrombosis and Haemostasis; MACCE: major adverse cardiac anad cerebrovascular events; OAC: oral anticoagulation; PCI: percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction; TIMI: Thrombolysis in Myocardial Infarction; VKA: vitamin K antagonist. * The duration of therapy was 6 months in all groups; † the duration of therapy was 1-12 months at the discretion of the treating physician in patients treated with BMS and 12 months in patients with ACS or treated with DES in both groups; ‡ a composite of all-cause death, MI, or stroke; § for patients who had received prasugrel, prasugrel was switched to clopidogrel at 1 month in both groups; || cardiovascular death, MI, definite stent thrombosis, ischemic or haemorrhagic stroke, or TIMI major or minor bleeding; ¶ a composite of all-cause death, MI, stent thrombosis, stroke, and target vessel revascularization; #after three months ticagrelor 90 mg twice daily plus aspirin 75-100 mg once daily in both groups; **clinical criteria for high risk were an age ≥65 years, female sex, troponin-positive ACS, established vascular disease, diabetes, and CKD; angiographic criteria included multivessel coronary artery disease, a total stent length of more than 30 mm, a thrombotic target lesion, a bifurcation lesion treated with two stents, an obstructive left main or proximal left anterior descending lesion, and a calcified target lesion treated with atherectomy).

Official titles and acronyms: AUGUSTUS: A Study of Apixaban in Patients With Atrial Fibrillation, Not Caused by a Heart Valve Problem, Who Are at Risk for Thrombosis (Blood Clots) Due to Having Had a Recent Coronary Event, Such as a Heart Attack or a Procedure to Open the Vessels of the Heart; WOEST: What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing, GLOBAL LEADERS: Comparative Effectiveness of 1 Month of Ticagrelor Plus Aspirin Followed by Ticagrelor Monotherapy Versus a Current-day Intensive Dual Antiplatelet Therapy in All-comers Patients Undergoing Percutaneous Coronary Intervention With Bivalirudin and BioMatrix Family Drug-eluting Stent Use; SMART CHOICE: Comparison Between P2Y12 Antagonist MonotHerapy and Dual Antiplatelet Therapy in Patients UndergOing Implantation of Coronary Drug-Eluting Stents; STOP DAPT 2: ShorT and OPtimal Duration of Dual AntiPlatelet Therapy-2 Study; TICO: Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus Stent for Acute Coronary Syndrome; TWILIGHT: Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention

Table S3. Definitions of clinical outcomes according to protocols of included trials.

Trial	*Death*	*Myocardial infarction*	*Stent thrombosis*	*Stroke*	*Major bleeding*
AUGUSTUS	All deaths including cardiovascular, non-cardiovascular, and undetermined	3rd universal MI definition	ARC criteria	An acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of haemorrhage or infarction that is not due to an identifiable nonvascular cause	ISTH major bleeding
WOEST	N/R	1st universal MI definition	ARC criteria	Focal loss of neurological function caused by an ischaemic or haemorrhagic event. A diagnosis of stroke was made by the treating neurologist. CT or MRI was used to distinguish ischaemic from haemorrhagic strokes.	BARC 3

GLOBAL LEADERS	Death from any cause; cardiovascular mortality includes unclear causes of death	3rd universal MI definition	ARC criteria	Any ischemic and haemorrhagic stroke	BARC 3 or 5
SMART CHOICE	All deaths were considered cardiac unless a definite non-cardiac cause could be established	Elevated cardiac enzyme levels (cardiac troponin or CK-MB) above the ULN with ischemic symptoms or ECG findings indicative of ischemia. Peri-procedural enzyme-level elevation <48 hours after the index PCI without concomitant ischemic symptoms or ECG findings indicative of ischemia was excluded in the assessment of end points	ARC criteria	Any non-convulsive focal or global neurologic deficit of abrupt onset lasting >24 hours or leading to death, which was caused by ischemia or haemorrhage within the brain	BARC 3 to 5

STOP DAPT 2	All deaths including cardiovascular, non-cardiovascular, and undetermined	ARC criteria	ARC criteria	Acute onset of a neurological deficit that persists >24 hours and is the result of a disturbance of the cerebral circulation due to ischemia or haemorrhage	BARC 3 or 5
TICO	All deaths including cardiovascular, non-cardiovascular, and undetermined	N/R	ARC criteria	An acute cerebrovascular event resulting in death or neurological deficit >24 hours or the presence of acute infarction demonstrated by imaging studies	Overt clinical bleeding associated with a haemoglobin drop of >5 g/dL or a haematocrit drop of >15% (absolute) according to TIMI bleeding criteria
TWILIGHT	All deaths including cardiovascular, non-cardiovascular, and undetermined	3rd universal MI definition	ARC criteria	Acute symptomatic episode of neurological dysfunction lasting >24 hours in the absence of therapeutic intervention or death, due to cerebral, spinal or retinal tissue injury as evidenced by neuroimaging or lumbar puncture	BARC 3 or 5

CK-MB: creatine kinase-myocardial band. Other abbreviations and official acronyms are reported in **Table S2.**

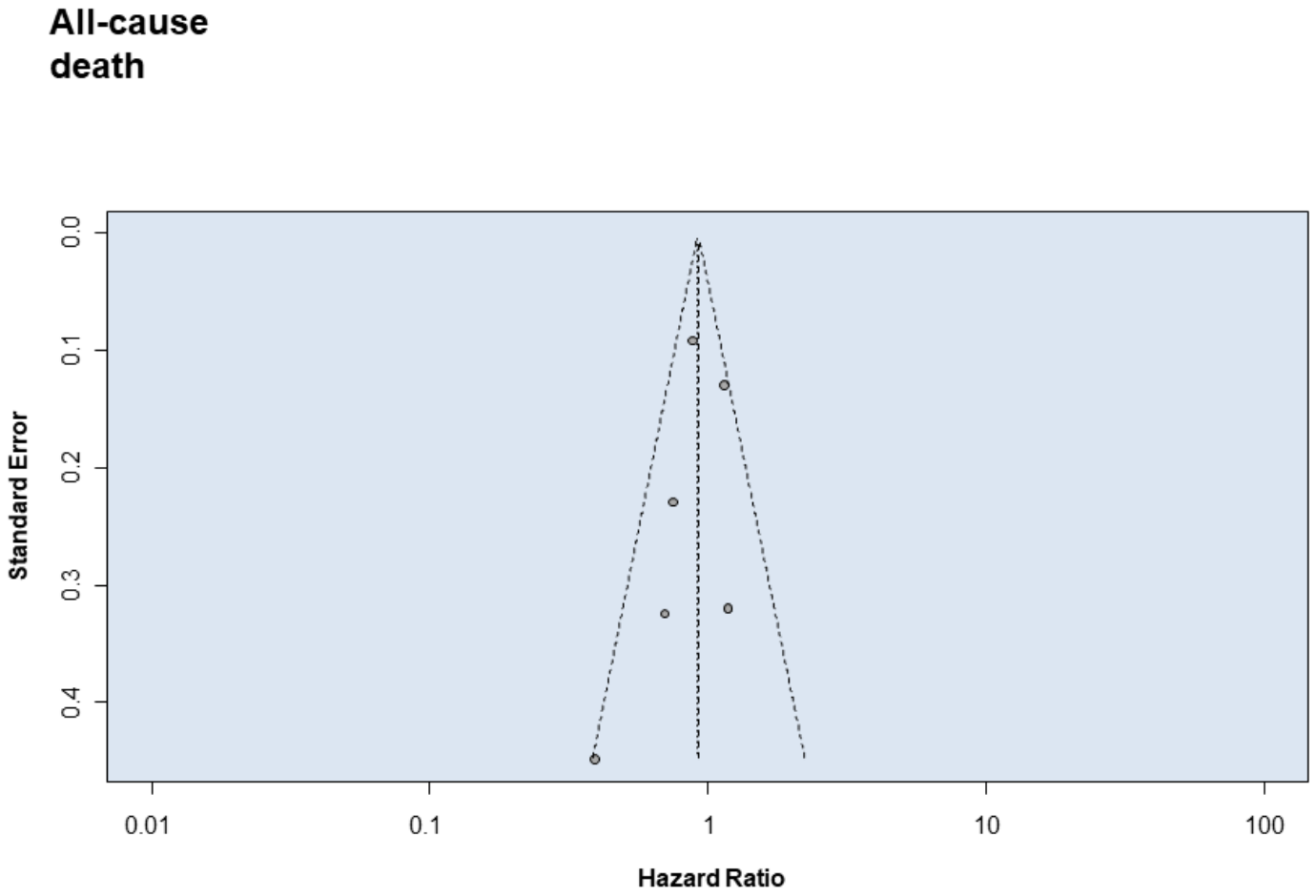
Table S4. Assessment of risk of bias.

Trial	*Random sequence generation*	*Allocation concealment*	*Blinding of participants*	*Blinding of outcome assessment*	*Description of incomplete outcome data*	*Selective outcome reporting**	*Sample size calculation*	*Funding source*	*Overall assessment*
AUGUSTUS	Unclear	Yes (interactive voice response system, stratification)	Yes (open-label)	Yes (blinded independent CEC)	Yes (flow diagram)	No	Yes (non-inferiority-design)‡	Yes (industry-funded; industry-initiated)	******
WOEST	Yes (computer-generated sequence)	Yes (sequentially numbered sealed envelopes)	No (open-label)	Yes (blinded CEC)	Yes (flow diagram)	Yes†	Yes (superiority-design)	Yes (investigator-initiated)	*****
GLOBAL LEADERS	Yes (computer-generated sequence)	Yes (locked web-based system, stratification, randomly varied block sizes)	No (open-label)	Yes (blinded independent CEC for primary outcome)	Yes (flow diagram)	No	Yes (non-inferiority-design)	Yes (industry-funded; industry-initiated)	******
SMART CHOICE	Yes (computer-generated sequence)	Yes (interactive web-based system, stratification, blocks of 4)	No (open-label)	Yes (blinded independent CEC)	Yes (flow diagram)	No	Yes (non-inferiority-design)	Yes (investigator-initiated; scientific society and industry funded)	******

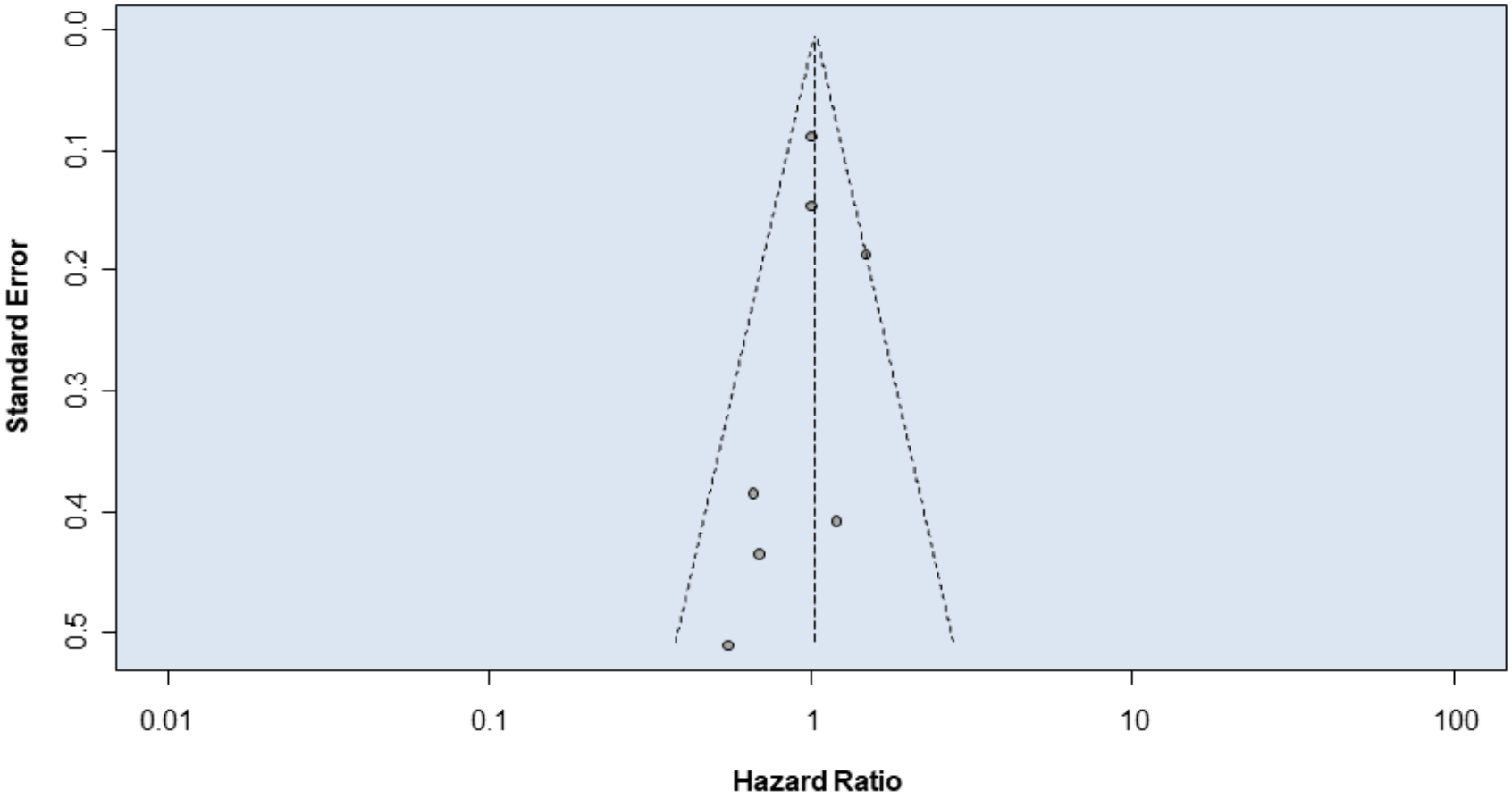
STOP DAPT 2	Yes (computer-generated sequence)	Yes (electronic data capture system, stochastic minimization algorithm)	No (open-label)	Yes (blinded independent CEC)	Yes (flow diagram)	No	Yes (non-inferiority-design)	Yes (industry-funded)	******
TICO	Yes (computer-generated sequence)	Yes (interactive web-based system, permuted-mixed block of 4 or 6, stratification)	No (open-label)	Yes (blinded CEC)	Yes (flow diagram)	No	Yes (superiority-design)	Yes (investigator-initiated; industry funded)	******
TWILIGHT	Yes (computer-generated sequence)	Yes (secure web-based system; block sizes of 4, 6, and 8, stratification)	No (open-label)	Yes (blinded CEC)	Yes (flow diagram)	No	Yes (superiority- and non-inferiority design)§	Yes (industry-funded)	******

CEC: Clinical event committee. *There was no selective reporting for any of the endpoints used in the current meta-analysis; † the primary endpoint reported was 'any bleeding', whereas that pre-specified on clinicaltrials.org was 'the combined endpoint of minor, moderate, or major bleeding (TIMI & GUSTO criteria); the secondary endpoint reported (composite of death, myocardial infarction, target-vessel revascularisation, and stent thrombosis) differed from that pre-specified in clinicaltrials.org (composite of death, myocardial infarction, target-vessel revascularisation, and systemic embolization). Moreover, rates of systemic embolization were not reported; ‡ 2x2 factorial design with a non-inferiority design (sample sized based on this hypothesis) with a prespecified superiority analysis with respect to one hypothesis and a superiority design with respect to the second hypothesis; §superiority for the primary endpoint of BARC type 2, 3, or 5 bleeding at 12 months and non-inferiority for the key secondary endpoint of composite of death from any cause, non-fatal myocardial infarction, or non-fatal stroke at 12 months. Other abbreviations and official acronyms are reported in **Table S2.**

Figure S1. Funnel plot for primary outcomes with early aspirin discontinuation versus dual antiplatelet therapy after coronary stenting.

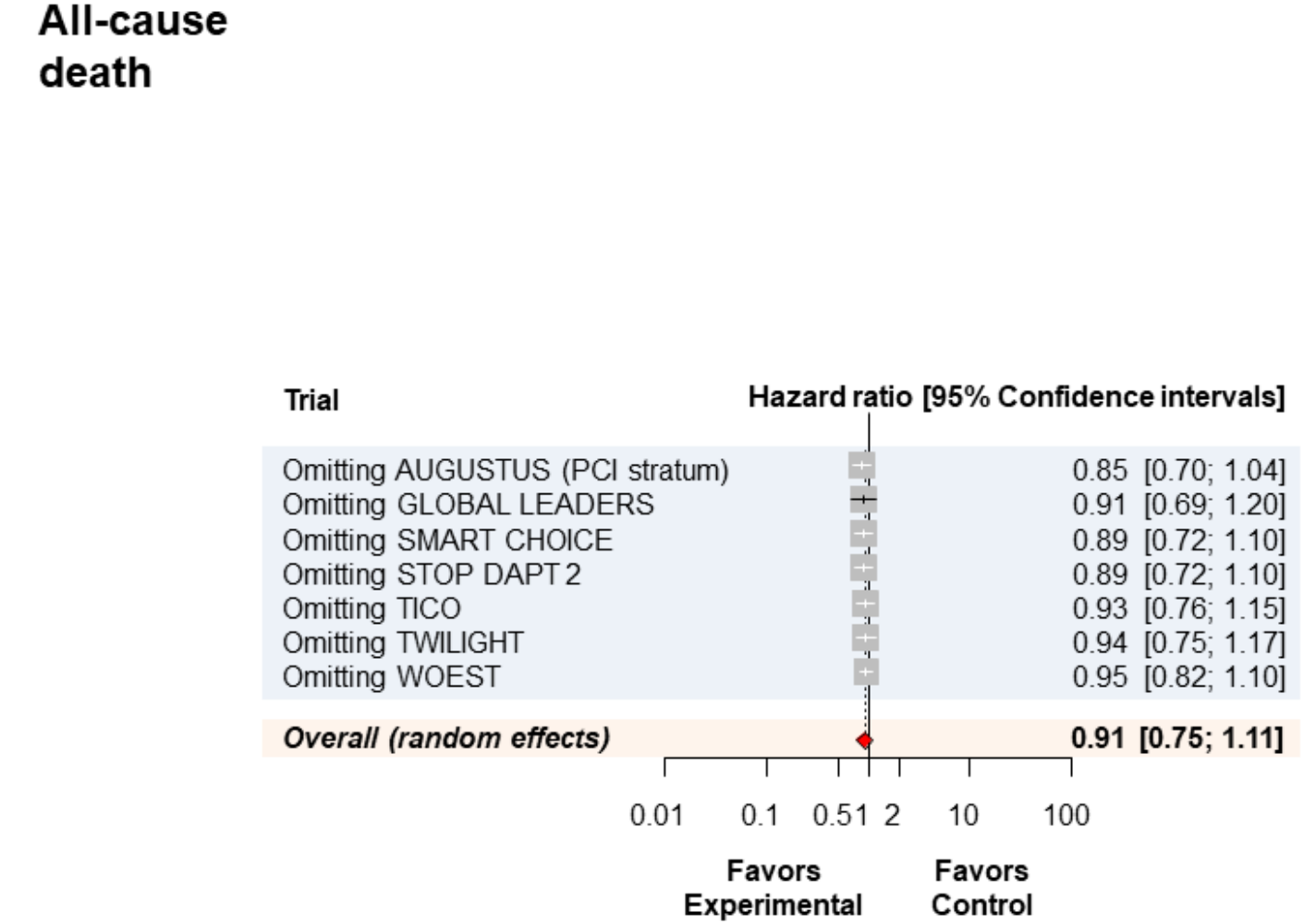


Myocardial infarction

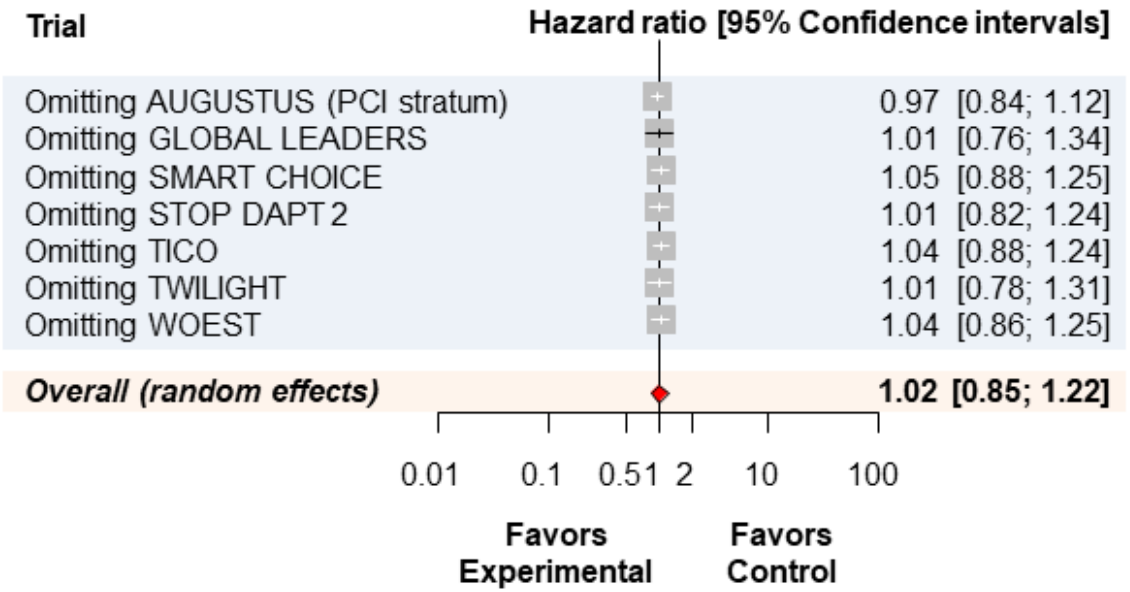


The publication bias for all-cause death (**A**) and myocardial infarction (**B**) is evaluated by visual inspection and by a linear regression test of funnel plot asymmetry

Figure S2. Influence analyses for primary outcomes with early aspirin discontinuation versus dual antiplatelet therapy after coronary stenting.



Myocardial infarction



Random-effects estimates for all-cause death (**A**) and myocardial infarction (**B**) associated with early aspirin discontinuation (experimental therapy) versus dual antiplatelet therapy (control therapy) and computed omitting one study at time. The diamonds indicates the point estimate and the left and the right ends of the lines the [95% Confidence intervals]. Trial acronyms are reported in **Table S2.**