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.**
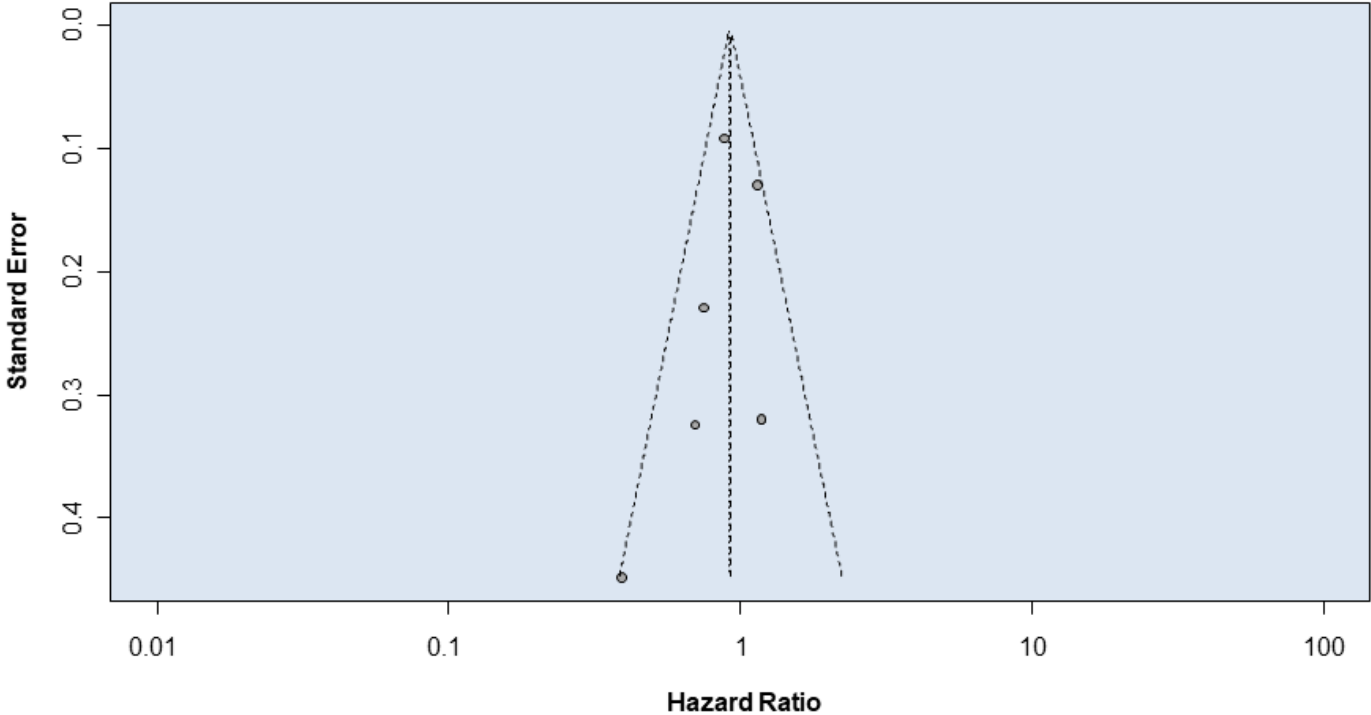
Table S4. Assessment of risk of bias.

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)	******

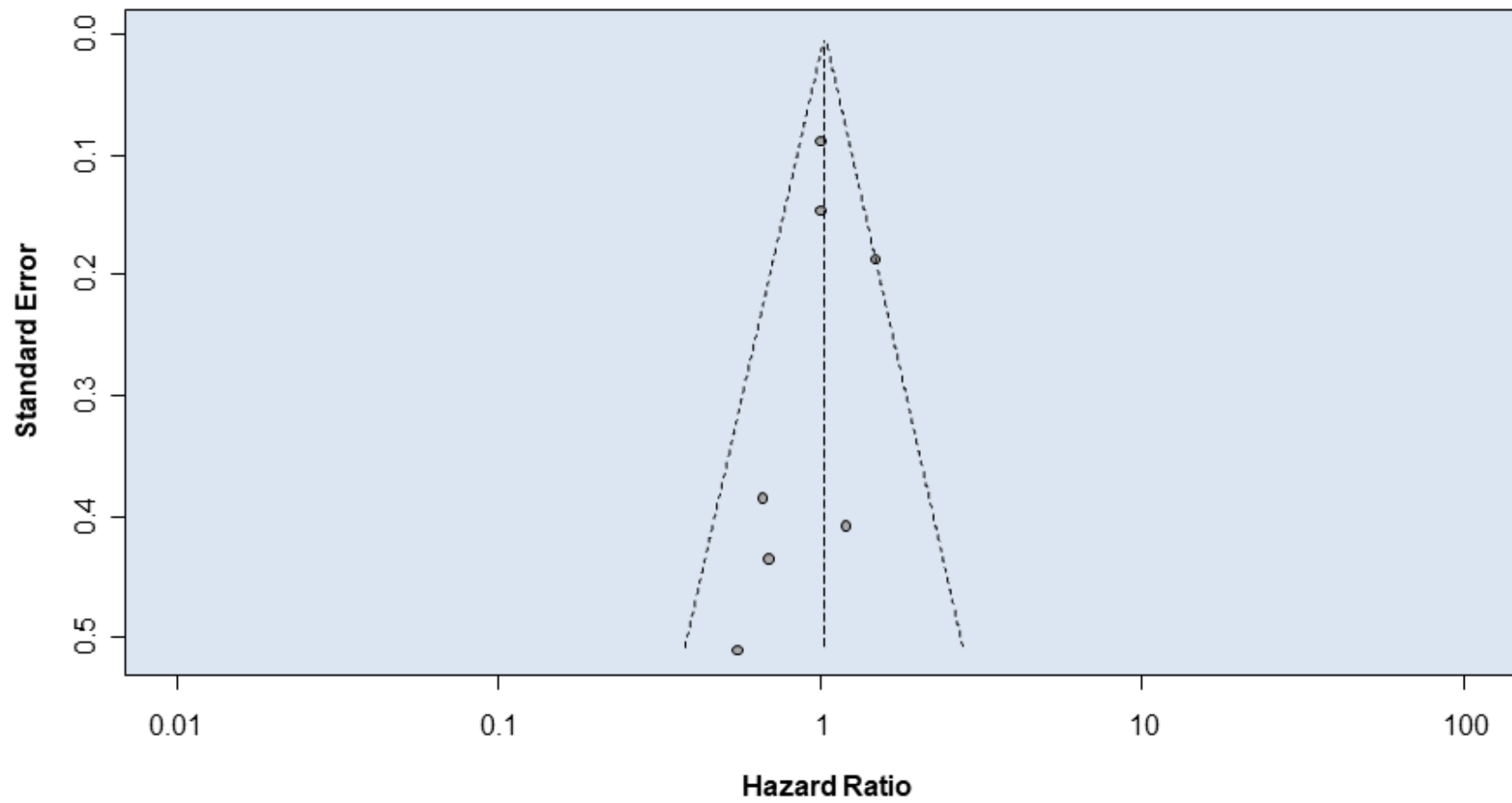|									
STOP DAPT 2	Yes (computer-generated sequence)	Yes (electronic data capture system, stochastic minimization algorithm)	No (open-label)	Yes (blinded independent CEC)	Yes (flow diagram)	No	Yes (non-inferiority-design)	Yes (industry-funded)	******
TICO	Yes (computer-generated sequence)	Yes (interactive 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.**

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.**
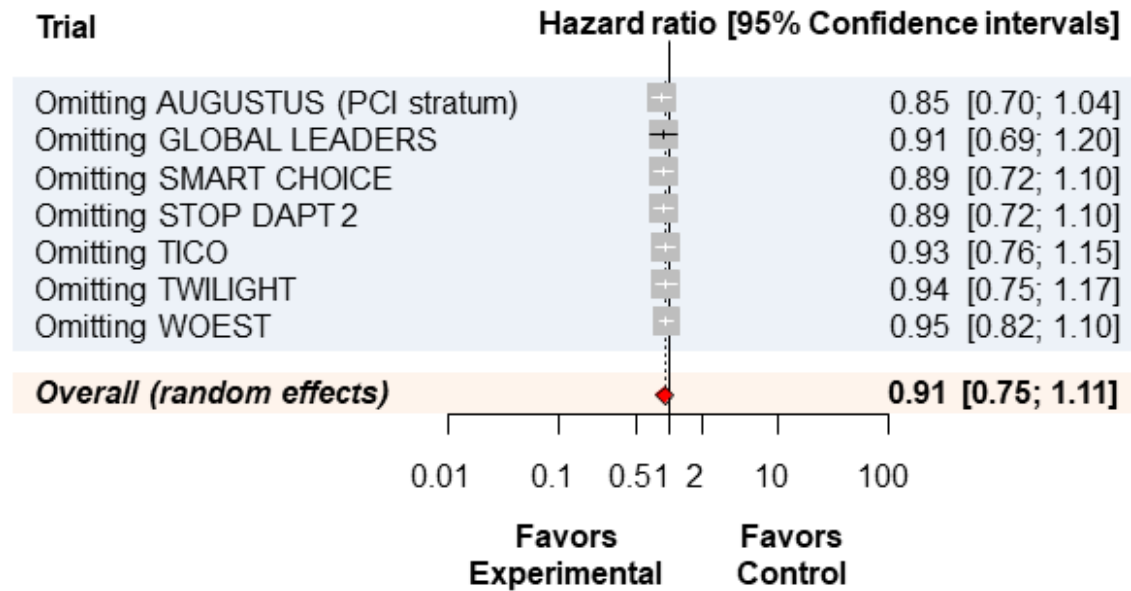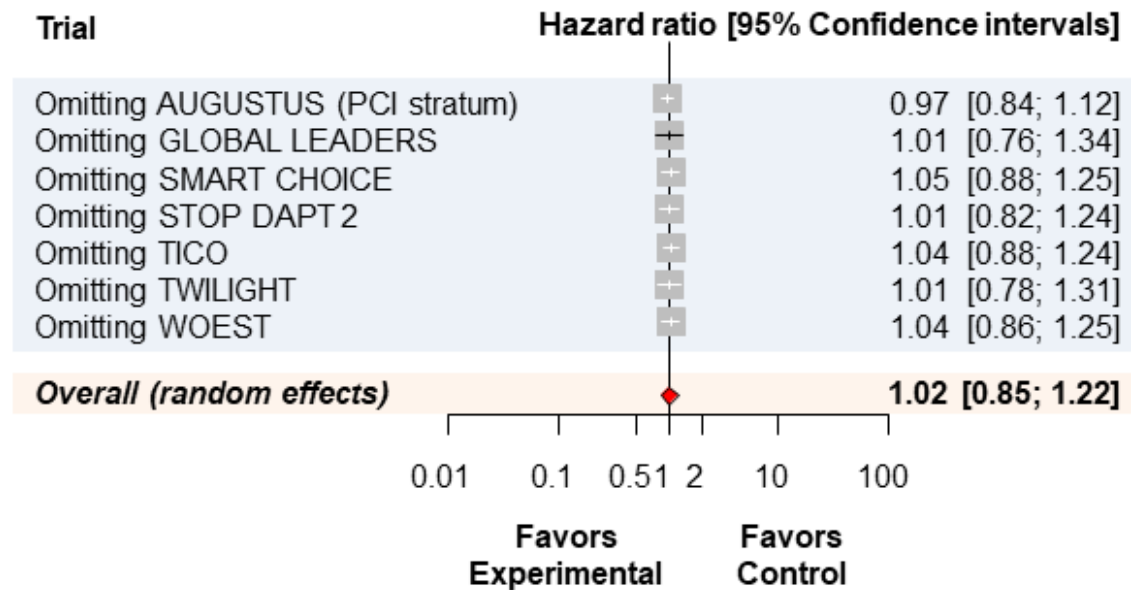

All-cause
death

Trial	Hazard ratio [95% Confidence intervals]
Omitting AUGUSTUS (PCI stratum)	0.85 [0.70; 1.04]
Omitting GLOBAL LEADERS	0.91 [0.69; 1.20]
Omitting SMART CHOICE	0.89 [0.72; 1.10]
Omitting STOP DAPT 2	0.89 [0.72; 1.10]
Omitting TICO	0.93 [0.76; 1.15]
Omitting TWILIGHT	0.94 [0.75; 1.17]
Omitting WOEST	0.95 [0.82; 1.10]
Overall (random effects)	**0.91 [0.75; 1.11]**

0.01 0.1 0.51 2 10 100

Favors
Experimental

Favors
Control

Myocardial infarction

Trial	Hazard ratio [95% Confidence intervals]
Omitting AUGUSTUS (PCI stratum)	0.97 [0.84; 1.12]
Omitting GLOBAL LEADERS	1.01 [0.76; 1.34]
Omitting SMART CHOICE	1.05 [0.88; 1.25]
Omitting STOP DAPT 2	1.01 [0.82; 1.24]
Omitting TICO	1.04 [0.88; 1.24]
Omitting TWILIGHT	1.01 [0.78; 1.31]
Omitting WOEST	1.04 [0.86; 1.25]
Overall (random effects)	**1.02 [0.85; 1.22]**

0.01   0.1   0.51 2   10   100

Favors Experimental   Favors Control

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.**