SUPPLEMENTARY APPENDIX

Dual Antiplatelet Therapy duration after percutaneous coronary intervention in High Bleeding Risk: a meta-analysis of randomized trials

Francesco Costa et al.

SUPPLEMENTARY TABLES

Supplementary Table 1. Search strategies

Systematic review of the literature of randomized clinical trial exploring abbreviated (≤ 3 months) vs. standard (≥ 6 months) DAPT duration after PCI in patients at High Bleeding Risk.

Database		Method	Result
PubMed			
	Step 1	((((((antiplatelet therapy[Title/Abstract]) OR (dual antiplatelet therapy[Title/Abstract])) OR (aspirin[Title/Abstract])) OR (clopidogrel[Title/Abstract])) OR (prasugrel[Title/Abstract])) OR (ticagrelor[Title/Abstract])) OR (p2y12 inhibitor monotherapy[Title/Abstract]))	66,407
	Step 2	(((((percutaneous coronary intervention[Title/Abstract]) OR (pci[Title/Abstract])) OR (coronary stenting[Title/Abstract])) OR (drug-eluting stent[Title/Abstract])) OR (acute coronary syndrome[Title/Abstract])) OR (acs[Title/Abstract])	84,598
	Step 3	(((high bleeding risk[Title/Abstract]) OR (precise-dapt[Title/Abstract])) OR (HBR-ARC[Title/Abstract])) OR (high bleeding risk academic research consortium[Title/Abstract])	847
	Step 4	((((((((antiplatelet therapy[Title/Abstract]) OR (dual antiplatelet therapy[Title/Abstract])) OR (aspirin[Title/Abstract])) OR (clopidogrel[Title/Abstract])) OR (prasugrel[Title/Abstract])) OR (ticagrelor[Title/Abstract])) OR (p2y12 inhibitor monotherapy[Title/Abstract]))) AND ((((((percutaneous coronary intervention[Title/Abstract]) OR (pci[Title/Abstract])) OR (coronary stenting[Title/Abstract])) OR (drug-eluting stent[Title/Abstract])) OR (acute coronary syndrome[Title/Abstract])) OR (acs[Title/Abstract]))) AND ((((high bleeding risk[Title/Abstract]) OR (precise-dapt[Title/Abstract])) OR (HBR-ARC[Title/Abstract])) OR (high bleeding risk academic research consortium[Title/Abstract]))AND 2000/1/1:2021/09/06[Date - Publication]))	226
Embase			
	Step 1	'antiplatelet therapy':ab,ti OR 'dual antiplatelet therapy':ab,ti OR 'aspirin':ab,ti OR 'clopidogrel':ab,ti OR 'prasugrel':ab,ti OR 'ticagrelor':ab,ti OR 'p2y12 inhibitor monotherapy':ab,ti	104,292
	Step 2	'percutaneous coronary intervention':ab,ti OR 'pci':ab,ti OR 'coronary stenting':ab,ti OR 'drug-eluting stent':ab,ti OR 'acute coronary syndrome':ab,ti OR 'acs':ab,ti	148,582
	Step 3	'high bleeding risk':ab,ti OR 'precise dapt':ab,ti OR 'hbr arc':ab,ti OR 'high bleeding risk academic research consortium':ab,ti	1,418
	Step 4	('antiplatelet therapy':ab,ti OR 'dual antiplatelet therapy':ab,ti OR 'aspirin':ab,ti OR 'clopidogrel':ab,ti OR 'prasugrel':ab,ti OR 'ticagrelor':ab,ti OR 'p2y12 inhibitor monotherapy':ab,ti) AND ('percutaneous coronary intervention':ab,ti OR 'pci':ab,ti OR 'coronary stenting':ab,ti OR 'drug-eluting stent':ab,ti OR 'acute coronary syndrome':ab,ti OR 'acs':ab,ti) AND ('high bleeding risk':ab,ti OR 'precise dapt':ab,ti OR 'hbr arc':ab,ti OR 'high bleeding risk academic research consortium':ab,ti)	309
BioMed Central		'(antiplatelet therapy OR dual antiplatelet therapy OR aspirin OR clopidogrel OR prasugrel OR ticagrelor OR p2Y12 inhibitor monotherapy) AND (percutaneous coronary intervention OR PCI OR coronary stenting OR drug-eluting stent OR acute coronary syndrome OR ACS) AND (high bleeding risk OR PRECISE-DAPT OR HBR-ARC OR high bleeding risk academic research consortium)'	11
Google Scholar			
		'(antiplatelet therapy OR dual antiplatelet therapy OR aspirin OR clopidogrel OR prasugrel OR ticagrelor OR p2Y12 inhibitor monotherapy)	20,500
		(percutaneous coronary intervention OR PCI OR coronary stenting OR drug-eluting stent OR acute coronary syndrome OR ACS)	74,700
		(high bleeding risk OR PRECISE-DAPT OR HBR-ARC OR high bleeding risk academic research consortium)'	90,400
		'(antiplatelet therapy OR dual antiplatelet therapy OR aspirin OR clopidogrel OR prasugrel OR ticagrelor OR p2Y12 inhibitor monotherapy) AND (percutaneous coronary intervention OR PCI OR coronary stenting OR drug-eluting stent OR acute coronary syndrome OR ACS) AND (high bleeding risk OR PRECISE-DAPT OR HBR-ARC OR high bleeding risk academic research consortium)'	5,770

Cochrane Central Register		
	antiplatelet therapy OR dual antiplatelet therapy OR aspirin OR clopidogrel OR prasugrel OR ticagrelor OR p2Y12 inhibitor monotherapy in Title Abstract Keyword	20,103
	percutaneous coronary intervention OR PCI OR coronary stenting OR drug-eluting stent OR acute coronary syndrome OR ACS in Title Abstract Keyword	28,190
	high bleeding risk OR PRECISE-DAPT OR HBR-ARC OR high bleeding risk academic research consortium)	5,016
	antiplatelet therapy OR dual antiplatelet therapy OR aspirin OR clopidogrel OR prasugrel OR ticagrelor OR p2Y12 inhibitor monotherapy in Title Abstract Keyword AND percutaneous coronary intervention OR PCI OR coronary stenting OR drug-eluting stent OR acute coronary syndrome OR ACS in Title Abstract Keyword AND high bleeding risk OR PRECISE-DAPT OR HBR-ARC OR high bleeding risk academic research consortium in Title Abstract Keyword - (Word variations have been searched)	647
www.escardio.org www.acc.org www.heart.org www.pcronline.com www.tctmd.com www.crtonline.gov www.clinicaltrials.gov www.clinicaltrialsregister.eu	Keywords used were “antiplatelet therapy”, “DAPT”, “aspirin”, “clopidogrel”, “prasugrel”, “ticagrelor”,”high bleeding risk”, “PRECISE-DAPT”, “HBR-ARC”. Reports before 01 Jan 2000 were not searched.	

Systematic review of the literature of randomized clinical trial exploring abbreviated (≤ 3 months) vs. standard (≥ 6 months) DAPT duration after PCI.

Database	Method	Result
PubMed		
Step 1	((((("antiplatelet therapy"[Title/Abstract] OR "clopidogrel"[Title/Abstract]) OR "prasugrel"[Title/Abstract]) OR "ticagrelor"[Title/Abstract]) AND ((((((((((("clinical trial"[Publication Type] OR "clinical trial protocol"[Publication Type]) OR "clinical trial, phase ii"[Publication Type]) OR "clinical trial, phase iii"[Publication Type]) OR "clinical trial, phase iv"[Publication Type]) OR "comparative study"[Publication Type]) OR "controlled clinical trial"[Publication Type]) OR "journal article"[Publication Type]) OR "letter"[Publication Type]) OR "multicenter study"[Publication Type]) OR "randomized controlled trial"[Publication Type]) AND "humans"[MeSH Terms]) AND 2004/1/1:2020/12/31[Date - Publication])) AND (("percutaneous coronary intervention"[Title/Abstract] OR "drug eluting stent"[Title/Abstract]) AND ((((((((((("clinical trial"[Publication Type] OR "clinical trial protocol"[Publication Type]) OR "clinical trial, phase ii"[Publication Type]) OR "clinical trial, phase iii"[Publication Type]) OR "clinical trial, phase iv"[Publication Type]) OR "comparative study"[Publication Type]) OR "controlled clinical trial"[Publication Type]) OR "journal article"[Publication Type]) OR "letter"[Publication Type]) OR "multicenter study"[Publication Type]) OR "randomized controlled trial"[Publication Type]) AND "humans"[MeSH Terms]) AND 2004/4/11:2020/12/31[Date - Publication]))	4,303
Step 2	(((((("antiplatelet therapy"[Title/Abstract] OR "clopidogrel"[Title/Abstract]) OR "prasugrel"[Title/Abstract]) OR "ticagrelor"[Title/Abstract]) AND ((((((((((("clinical trial"[Publication Type] OR "clinical trial protocol"[Publication Type]) OR "clinical trial, phase ii"[Publication Type]) OR "clinical trial, phase iii"[Publication Type]) OR "clinical trial, phase iv"[Publication Type]) OR "comparative study"[Publication Type]) OR "controlled clinical trial"[Publication Type]) OR "journal article"[Publication Type]) OR "letter"[Publication Type]) OR "multicenter study"[Publication Type]) OR "randomized controlled trial"[Publication Type]) AND "humans"[MeSH Terms]) AND 2004/1/1:2020/12/31[Date - Publication])) AND (("percutaneous coronary intervention"[Title/Abstract] OR "drug eluting stent"[Title/Abstract]) AND ((((((((((("clinical trial"[Publication Type] OR "clinical trial protocol"[Publication Type]) OR "clinical trial, phase ii"[Publication Type]) OR "clinical trial, phase iii"[Publication Type]) OR "clinical trial, phase iv"[Publication Type]) OR "comparative study"[Publication Type]) OR "controlled clinical trial"[Publication Type]) OR "journal article"[Publication Type]) OR "letter"[Publication Type]) OR "multicenter study"[Publication Type])	286

	OR "randomized controlled trial"[Publication Type]) AND "humans"[MeSH Terms]) AND 2004/4/11:2020/12/31[Date - Publication])))) AND DAPT duration	
Embase		
	'antiplatelet therapy':ab,ti OR 'dual antiplatelet therapy':ab,ti OR 'aspirin':ab,ti OR 'clopidogrel':ab,ti OR 'prasugrel':ab,ti OR 'ticagrelor':ab,ti OR 'duration'':ab,ti AND 'randomized clinical trial':ab,ti	4,242
BioMed Central	'(antiplatelet therapy OR dual antiplatelet therapy OR aspirin OR clopidogrel OR prasugrel OR ticagrelor) AND (percutaneous coronary intervention OR PCI OR coronary stenting OR drug-eluting stent OR acute coronary syndrome OR ACS) AND duration AND randomized clinical trial'	122
Google Scholar		
	'(antiplatelet therapy OR dual antiplatelet therapy OR aspirin OR clopidogrel OR prasugrel OR ticagrelor) AND (percutaneous coronary intervention OR PCI OR coronary stenting OR drug-eluting stent OR acute coronary syndrome OR ACS) AND duration AND randomized clinical trial'	20,600
www.escardio.org	Keywords used were "antiplatelet therapy", "DAPT", "aspirin", "clopidogrel", "prasugrel", "ticagrelor","duration","randomized clinical trial" Reports before 01 Jan 2000 were not searched.	

Supplementary Table 2. 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.	1-2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
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.	4
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.	4,5
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.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4, Appendix
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).	4,5
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.	4,5,6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4, Appendix
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	5

		any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5,6
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.	5,6
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).	5, Appendix
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5,6
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.	6, Appendix
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.	6,7, Appendix
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).	7 Appendix
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.	6-8, Appendix
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6-8, Appendix
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	5, Appendix
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	6-8, Appendix
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).	9-13
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).	12-13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9-13

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.	13

Supplementary Table 3. Time of randomization and endpoints definitions for the included studies.

Trial	Time of Randomization	Major or clinically relevant non-major bleeding definition*	Major Bleeding definition	MACE Definition 1	MACE Definition 2
GLOBAL-LEADERS/GLASSY	Index PCI	BARC 2-5	BARC 3 or 5	All-cause death, MI or stroke	Cardiovascular death, MI or stroke
MASTER-DAPT	1 month	BARC 2-5	BARC 3 or 5	All-cause death, MI or stroke	Cardiovascular death, MI or stroke
ONE-MONTH-DAPT	Index PCI	BARC 2-5	BARC 3 or 5	All-cause death, MI or stroke	Cardiovascular death, MI or stroke
OPTIMIZE	Index PCI	TIMI major or minor	TIMI major or minor	All-cause death, MI or stroke	Cardiovascular death, MI or stroke
REDUCE	Index PCI	BARC 2-5	BARC 3 or 5	All-cause death, MI or stroke	Cardiovascular death, MI or stroke
RESET	Index PCI	TIMI major or minor	TIMI major or minor	All-cause death, MI or stroke	Cardiovascular death, MI or stroke
SMART-CHOICE	Index PCI	BARC 2-5	BARC 3 or 5	All-cause death, MI or stroke	Cardiovascular death, MI or stroke
STOPDAPT-2	Index PCI	TIMI major or minor	TIMI major or minor	All-cause death, MI or stroke	Cardiovascular death, MI or stroke
STOPDAPT-2-ACS	Index PCI	TIMI major or minor	TIMI major or minor	All-cause death, MI or stroke	Cardiovascular death, MI or stroke
TICO	Index PCI	TIMI major or minor	TIMI major or minor	All-cause death, MI or stroke	Cardiovascular death, MI or stroke
TWILIGHT	3 months	BARC 2-5	BARC 3 or 5	All-cause death, MI or stroke	Cardiovascular death, MI or stroke

* According to each study definition. BARC: Bleeding Academic Research Consortium; CV: Cardiovascular; HBR: High Bleeding Risk; MACE: Major Adverse Cardiovascular Events; MI: Myocardial Infarction; ST: Stent Thrombosis, TIMI: Thrombolysis in Myocardial Infarction.

Supplementary Table 4. Inclusion and exclusion criteria across the included trials.

Trial	Inclusion criteria	Exclusion criteria
GLOBAL LEADERS / GLASSY	• Age ≥18 years • Any clinical indication for PCI • Native coronary artery or graft (venous or arterial) stenosis ≥50% suitable for PCI and reference vessel diameter ≥2.50 mm • Written informed consent • Willingness to participate in 2-year follow-up	• Intolerance to aspirin, $P2Y_{12}$-I, bivalirudin, stainless steel or biolimus • Intake of a strong cytochrome 3A4 inhibitor • Fibrinolytic therapy ≤24 hours • Severe hepatic impairment • Major surgery ≤30 days • Planned staged CABG (hybrid revascularization) ≤12 months • Planned surgery ≤12 months • Need for anticoagulation • PCI for stent thrombosis • Active major bleeding • History of intracranial haemorrhage or intracranial aneurysm • Stroke ≤30 days • Pregnancy or breastfeeding • Inability to provide informed consent • Participation in another study
MASTER-DAPT	• Age ≥18 years • All lesions are successfully treated with Ultimaster stent in the context of routine clinical care • Free from any flow-limiting angiographic complications • All stages of PCI are complete (if any) and no further PCI is planned. • At randomization visit (one month after index PCI), the following criteria must be met: • Fulfilment of at least one HBR criterion, or on the basis of post-PCI actionable non-access site related bleeding episode • Uneventful 30-day clinical course • If not on OAC, o Patient is on a DAPT regimen of aspirin and a P2Y12 inhibitor o Patient with one type of P2Y12 inhibitor for at least 7 days • If on OAC o Patient is on the same type of OAC (e.g. Vitamin K antagonist or NOAC) for at least 7 days o Patient is on clopidogrel for at least 7 days • At least one HBR criteria is met: • Clinical indication for treatment with oral anticoagulants (OAC) for at least 12 months • Recent (<12 months) non-access site bleeding episode(s), which required medical attention (i.e. actionable bleeding). • Previous bleeding episode(s) which required hospitalization if the underlying cause has not been definitively treated (i.e. surgical removal of the bleeding source)	• Treated with stents other than Ultimaster stent within 6 months prior to index procedure • Treated for in-stent restenosis or stent thrombosis at index PCI or within 6 months before • Treated with a bioresorbable scaffold at any time prior to index procedure • Cannot provide written informed consent • Under judicial protection, tutorship or curatorship • Unable to understand and follow study-related instructions or unable to comply with study protocol • Active bleeding requiring medical attention (BARC≥2) on randomization visit • Life expectancy less than one year • Known hypersensitivity or allergy for aspirin, clopidogrel, ticagrelor, prasugrel, cobalt chromium or sirolimus • Any planned and anticipated PCI • Participation in another trial • Pregnant or breast feeding women

	• Age equal or greater than 75 years • Systemic conditions associated with an increased bleeding risk (e.g. haematological disorders, including a history of or current thrombocytopaenia defined as a platelet count <100,000/mm3 (<100 x 109/L), or any known coagulation disorder associated with increased bleeding risk. • Documented anaemia defined as repeated haemoglobin levels <11 g/dl or transfusion within 4 weeks before randomization. • Need for chronic treatment with steroids or non-steroidal anti-inflammatory drugs • Diagnosed malignancy (other than skin) considered at high bleeding risk including gastro-intestinal, genito-urethral/renal and pulmonary. • Stroke at any time or TIA in the previous 6 months • PRECISE DAPT score of 25 or greater	
ONE-MONTH-DAPT	• Patients ≥ 19 years old • Patients with ischemic heart disease who are considered for coronary revascularization with PCI • Significant coronary de novo lesion	• Acute myocardial infarction • Complex lesion morphologies such as aorta-ostial, unprotected left main, chronic total occlusion, graft, thrombosis, heavy calcified (definite calcified lesions on angiogram) or extremely tortuous lesion • Need to use of dual antiplatelet therapy more than 1 month because of other medical conditions • Cardiogenic shock or experience of cardiopulmonary resuscitation • Contraindication or hypersensitivity to Biolimus A9, stainless steel, heparin, antiplatelet agents or contrast media • History of documented prior cerebrovascular attack within 6 months • Treated with any stent within 3 months • Reference vessel diameter <2.25 mm or >4.0 mm • Pregnant women or women with potential childbearing • Inability to follow the patient over the period of 1 year after enrollment, as assessed by the investigator • Inability to understand or read the informed content
OPTIMIZE	• Age ≥18 years • Silent ischaemia, stable angina, unstable angina, or subacute myocardial infarction without elevate biomarkers • Native coronary artery stenosis >50% • Reference vessel diameter ≥2.50 mm • PCI with CoCr DP zotarolimus-eluting stent • Willingness to be compliant with the study protocol • Absence of in-hospital major complication other than periprocedure myocardial infarction • Written informed consent	• Intolerance, contraindication, or hypersensitivity to aspirin, clopidogrel, or both • STEMI • Prior PCI with DES • Prior PCI with bare-metal stent in nontarget lesion <6 months • Saphenous vein graft target lesion • Planned surgery <12 months • Unsuitable anatomy for stenting with CoCr DP zotarolimus-eluting stent • Life expectancy <3 years • Predicted impossibility to fully comply with the study protocol
REDUCE	• Age ≥18 years • Unstable angina, NSTEMI, or STEMI	• Cardiogenic shock • Recent major bleeding or contraindication to DAPT

	• Successful implantation of CoCr BP anti-CD34 antibody-coated sirolimus-eluting stent • Written informed consent • Willingness comply with the study protocol	(hypersensitivity to aspirin, clopidogrel, prasugrel, or ticagrelor; need for oral anticoagulation; history of bleeding diathesis, known coagulopathy, or refusal of blood transfusions; history of intracerebral mass, aneurysm, arteriovenous malformation, or haemorrhagic stroke; stroke or transient ischemic attack <6 months or any permanent residual neurologic impairment; gastrointestinal or genitourinary bleeding <2 months or major surgery <6 weeks; recent or known haemoglobin <10 g/dL or platelet count <100000 mm^3; planned surgical procedure necessitating $P2Y_{12}$-I interruption <12 months) • Need for cardiac surgery • Planned PCI in another lesion, within or outside the target vessel, before discharge • Implantation of DES other than CoCr BP anti-CD34 antibody-coated sirolimus-eluting stent • Prior implantation of DES <9 months • Predictable noncompliance to the study protocol • Need for permanent DAPT • Organ transplantation recipient or candidate • Life expectancy <2 years • Potential or documented pregnancy • Any significant medical or physical condition that could result in study protocol violation • Participation in another study
RESET	• Age ≥20 years • Coronary artery disease including stable angina, unstable angina, NSTEMI and STEMI • Patients with typical chest pain or evidences of myocardial ischemia (e.g., stable or unstable angina, or silent ischemia and positive functional study or reversible changes in the electrocardiogram consistent with ischaemia) • Coronary artery stenosis >50% by visual estimate considered to be amenable for coronary revascularization with stent implantation • Reference vessel diameter between 2.50 and 4.00 mm • Acute coronary syndrome, diabetes mellitus, and short lesion subgroups: length of single lesion <24 mm and total stent length <60 mm • Long lesion subgroup: single lesion >28 mm and total stent length ≤90 mm • Successful stenting defined as ≤30% residual stenosis, TIMI flow 3, and NHLBI dissection type ≤B • Written informed consent	• Contraindication to anti-platelet agents • Bleeding history ≤3 months • Known hypersensitivity or contraindication to any of the following medications: heparin, aspirin, clopidogrel, limus-related drugs • Cardiogenic shock • LVEF <40% • LM disease • Prior stenting with DES • Overlapping DES in subgroups other than long lesion • Bifurcation lesion required 2-stent strategy • In-stent restenosis • Prior stroke • Prior stent thrombosis • Prior systemic embolism • Peripheral occlusive diseases • Three-times increase above the normal reference value of liver function markers • Serum creatinine >2.0 mg/dL • Significant leukopenia, neutropenia, thrombocytopenia, anemia, or known bleeding diathesis • Life expectancy ≤3 years

		• Potential or documented pregnancy • Predictable protocol non-compliance • Participation in another study
SMART CHOICE	• Age ≥20 years • Native coronary artery stenosis ≥50% with visually estimated diameter 2.25 mm-4.25 mm • Target lesion amenable for PCI • Uncomplicated PCI with DES implantation • Written informed consent •	• Hypersensitivity or contraindication to aspirin, clopidogrel, prasugrel, ticagrelor, everolimus, and sirolimus • Hemodynamic instability or cardiogenic shock • Active pathologic bleeding • DES implantation ≤12 months • Potential or documented pregnancy • Life expectancy <2 years • Predictable protocol non-compliance • Participation in another study
STOPDAPT-2	• Age ≥20 years • PCI with CoCr DP everolimus-eluting stent • Target lesion(s) amenable for PCI • Uncomplicated PCI with DES implantation • Absence of in-hospital major complication other than periprocedure myocardial infarction • Written informed consent	• Intolerance or contraindication to clopidogrel or dual antiplatelet therapy • Need for oral anticoagulation or antiplatelet therapy other than aspirin and $P2Y_{12}$-I • Other antiplatelet drugs • History of intracranial haemorrhage • Implantation of DES other than CoCr DP everolimus-eluting • Implantation of bioresorbable vascular scaffold prior or at the time of enrolment
STOPDAPT-2-ACS	• Patients received percutaneous coronary intervention with cobalt-chromium everolimus-eluting stent under the setting of acute coronary syndrome • Patients who are capable of oral dual antiplatelet therapy consisting of aspirin and P2Y12 receptor antagonist	• Patients requiring oral anticoagulants • Patients with medical history of intracranial hemorrhage • Patients who have experienced serious complications (myocardial infarction, stroke, and major bleeding) during hospital stay after percutaneous coronary intervention • Patients with drug eluting stents other than Cobalt chromium everolimus eluting stents implanted at the time of enrolment • Patients confirmed to have no tolerability to clopidogrel before enrolment • Patients requiring continuous administration of antiplatelet drugs other than aspirin and P2Y12 receptor antagonists at the time of enrollment
TICO	• Age ≥19 years • Bioresorbable polymer sirolimus-eluting stent Implantation to treat acute coronary syndrome Written informed consent	• Age >80 years • Increased bleeding risk (prior haemorrhagic stroke; ischemic stroke, dementia, or impairment of central nervous system <1 year; traumatic brain injury or brain surgery <6 months; known intracranial tumour; documented or suspected aortic dissection; internal bleeding <6 weeks; active bleeding or bleeding diathesis; haemoglobin <8 g/dL, platelet count <100000 mm3; major surgery or traumatic injury resulting in any impairment of physical activity <3 weeks) • Need for oral anticoagulation therapy • Potential or documented pregnancy • Life expectancy <1 year

		• Strong cytochrome 3A4 inhibitors • Moderate to severe hepatic dysfunction • Increased risk of bradycardia-related symptoms
TWILIGHT	At least one of the following clinical criteria: • Age ≥65 years • Female gender • Troponin positive acute coronary syndrome • Established vascular disease (prior myocardial infarction, peripheral artery disease, prior revascularization for CAD or peripheral artery disease) • Diabetes mellitus under treatment • Chronic kidney disease defined as an estimated glomerular filtration rate <60 mL/min/1.73 m² and at least one of the following angiographic criteria: • Multivessel CAD • Left main stenosis >50% or left anterior descending stenosis >70% • Target lesion requiring total stent length >30 mm • Thrombotic target lesion • Calcified target lesion requiring atherectomy • Bifurcation lesions X,1,1 type requiring two stents	• Age <18 years • Contraindication to aspirin or ticagrelor • Planned surgery ≤90 days • Planned coronary revascularization (PCI or CABG) ≤90 days • Need for oral anticoagulation • Prior stroke • Dialysis-dependent renal failure • Active bleeding or extreme risk for major bleeding (e.g., active peptic ulcer disease, gastrointestinal disease with raised risk of bleeding, malignancies with raised risk of bleeding) • Salvage PCI for cardiogenic shock or STEMI • Liver cirrhosis • Life expectancy <1 year • Inability or unwillingness to provide informed consent • Potential or documented pregnancy • Fibrinolytic therapy ≤24 hours • Concomitant therapy with strong cytochrome P-450 3A inhibitor or inducer • Platelet count <100000 mm^3 • Need for therapy with aspirin at a dose ≥325 mg daily

CoCr=Cobalt-chromium; CABG=Coronary artery bypass grafting; CAD=Coronary artery disease; DP=Durable polymer, DES=drug eluting stent; $P2Y_{12}$-I=$P2Y_{12}$ inhibitor; PCI=Percutaneous coronary intervention; STEMI=ST-segment elevation myocardial infarction; DES=Drug-eluting stent; LM=Left main; LVEF=Left ventricular ejection fraction; NHLBI=National Heart Lung Blood Institute; NSTEMI=Non-ST-segment elevation myocardial infarction; $P2Y_{12}$-I=$P2Y_{12}$ inhibitor; PCI=Percutaneous coronary intervention; STEMI=ST-segment elevation myocardial infarction; TIMI=Thrombolysis in Myocardial Infarction.

Supplementary Table 5. Qualitative assessment of potential sources of bias across the included trials.

	RESET	OPTIMIZE	GLOBAL LEADERS	GLASSY	STOPDAPT-2	STOPDAPT-2-ACS	MASTER-DAPT	REDUCE	TWILIGHT	SMART CHOICE	ONE MONTH DAPT	TICO	*Overall*
Random sequence generation *(Selection bias)*	+	+	+	+	+	+	+	+	+	+	+	+	+
Allocation concealment *(Selection bias*)	+	+	+	+	+	+	+	+	+	+	+	+	+
Blinding of participants and personnel *(Performance bias)*	+	+	!	+	+	+	+	+	+	+	+	+	+
Incomplete outcome data *(Attrition bias)*	+	+	+	+	+	+	+	+	+	+	+	+	+
Selective reporting *(Reporting bias)*	+	+	+	+	+	+	+	+	+	+	+	+	+
Other sources of bias	+	+	+	+	+	+	+	+	+	+	+	+	+

All included trials were randomized controlled trials with a random sequence generation to assign treatment strategy. All included trials were open-label, with the exception of the TWILIGHT that was double-blind. GLOBAL LEADERS trial was the only study that not included central event adjudication by a clinical event committee. GLASSY was a pre-specified substudy of the GLOBAL LEADERS trial implementing independent central events adjudication, this included a subgroup of the GLOBAL LEADERS population comprising the same randomized design. The TWILIGHT and MASTER-DAPT trials included patients after uneventful 3 months and 1 month respectively. This trial design limits the influence of early variations in clinical events unrelated to antiplatelet therapy. Other studies reported landmark analysis after treatment divergence occurred.

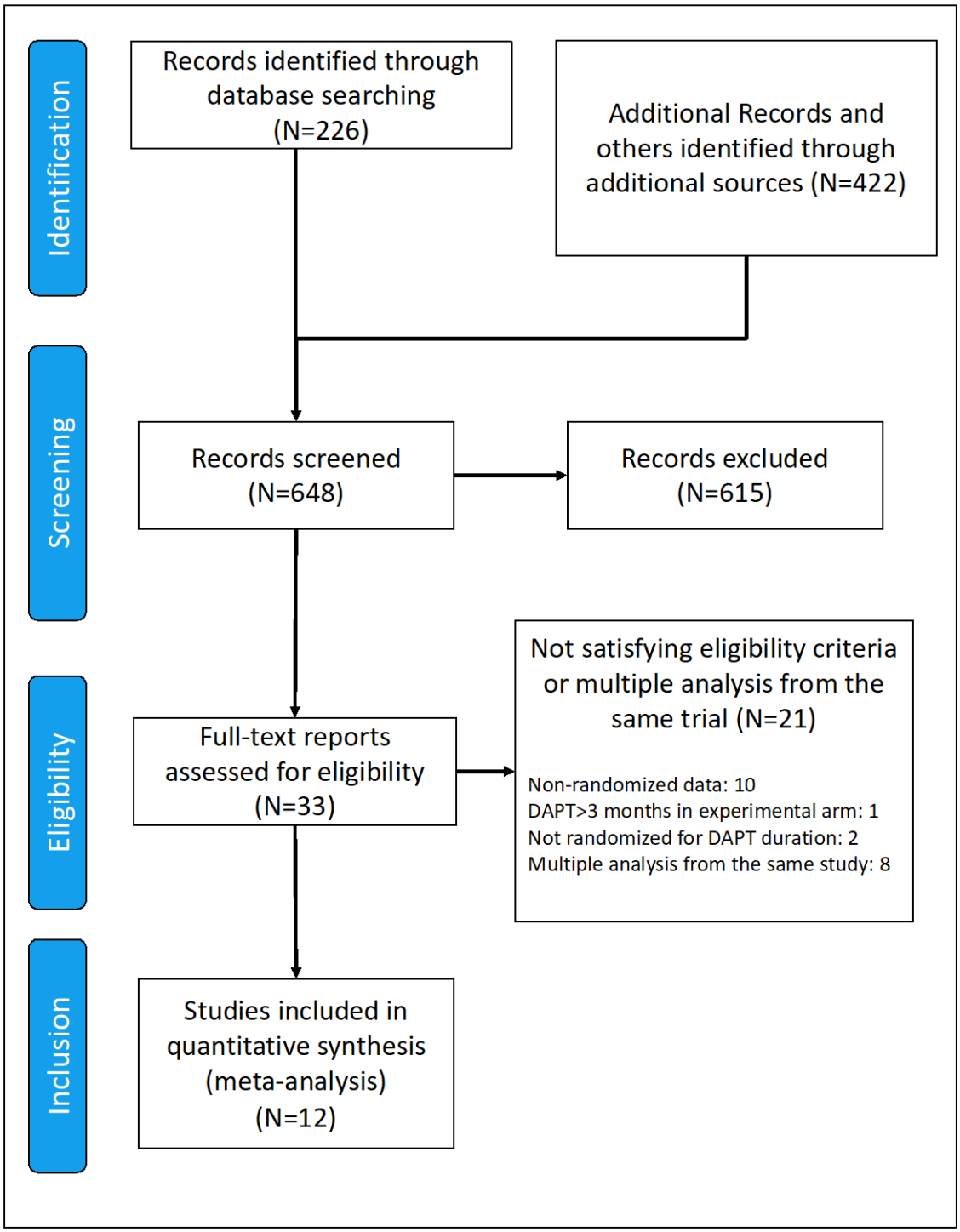
Supplementary Table 6. Leave-one-out analysis for major or clinically relevant non-major bleeding, major bleeding and major adverse cardiovascular events definitions.

	MCRB			***Major bleeding***			***MACE 1***			***MACE 2***		
excluded study	*RR*	*95% CI*	*p*	*RR*	*95% CI*	*p*	*RR*	*95% CI*	*p*	*RR*	*95% CI*	*p*
none	0.7573	[0.6086; 0.9423]	0.0177	0.7999	[0.6430; 0.9950]	0.0458	0.9672	[0.7401; 1.2640]	0.7871	0.9190	[0.7682; 1.0994]	0.3183
RESET	0.7539	[0.5945; 0.9561]	0.0248	0.8023	[0.6337; 1.0158]	0.0639	0.9794	[0.7318; 1.3108]	0.8752	0.9257	[0.7672; 1.1170]	0.3769
OPTIMIZE	0.7619	[0.5982; 0.9705]	0.0316	0.8170	[0.6431; 1.0380]	0.0885	0.9407	[0.7013; 1.2617]	0.6487	0.9010	[0.7463; 1.0878]	0.2422
SMART-CHOICE	0.7620	[0.5993; 0.9689]	0.0307	0.7790	[0.6224; 0.9750]	0.0329	0.9467	[0.7017; 1.2773]	0.6889	0.9227	[0.7573; 1.1243]	0.3811
REDUCE	0.7510	[0.5931; 0.9510]	0.0227	0.7987	[0.6314; 1.0103]	0.0588	0.9584	[0.7148; 1.2851]	0.7507	0.9195	[0.7578; 1.1157]	0.3519
GLOBAL-LEADERS	0.6613	[0.5562; 0.7862]	0.0004	0.7043	[0.5748; 0.8628]	0.0036	0.9658	[0.6955; 1.3411]	0.8159	0.9126	[0.7207; 1.1556]	0.4038
STOPDAPT-2	0.7793	[0.6307; 0.9630]	0.0258	0.8235	[0.6725; 1.0084]	0.0582	0.9653	[0.7102; 1.3119]	0.8003	0.9205	[0.7551; 1.1222]	0.3689
STOPDAPT-2-ACS	0.7585	[0.5987; 0.9610]	0.0268	0.8075	[0.6389; 1.0206]	0.0689	0.9218	[0.7708; 1.1024]	0.3303	0.8914	[0.7583; 1.0478]	0.1422
MASTER-DAPT	0.8047	[0.6308; 1.0265]	0.0742	0.8111	[0.6282; 1.0474]	0.0970	0.9787	[0.7087; 1.3515]	0.8833	0.9020	[0.7286; 1.1167]	0.3029
TWILIGHT	0.7832	[0.6119; 1.0025]	0.0519	0.8329	[0.6624; 1.0473]	0.1044	0.9723	[0.7110; 1.3296]	0.8436	0.9239	[0.7533; 1.1331]	0.4031
ONE-MONTH DAPT	0.7300	[0.5909; 0.9019]	0.0083	0.7900	[0.6263; 0.9964]	0.0472	1.0121	[0.7944; 1.2894]	0.9130	0.9477	[0.8018; 1.1202]	0.4859
TICO	0.7595	[0.5922; 0.9740]	0.0338	0.8229	[0.6407; 1.0568]	0.1118	1.0072	[0.7873; 1.2885]	0.9491	0.9379	[0.7943; 1.1073]	0.4050

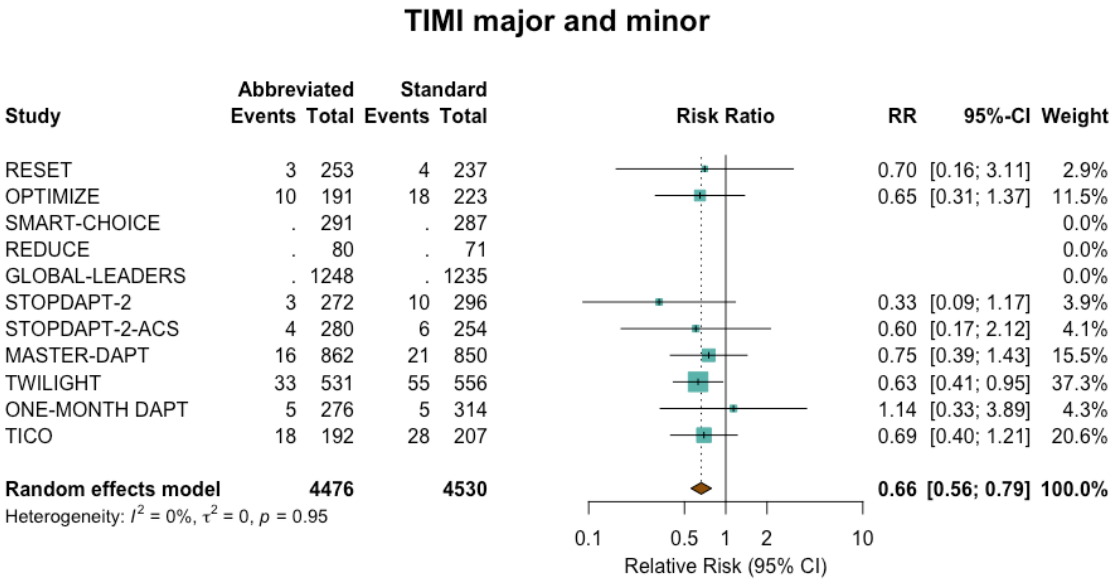
MACE: Major Adverse Cardiovascular Events; MCRB: Major or Clinically Relevant non-major Bleeding.

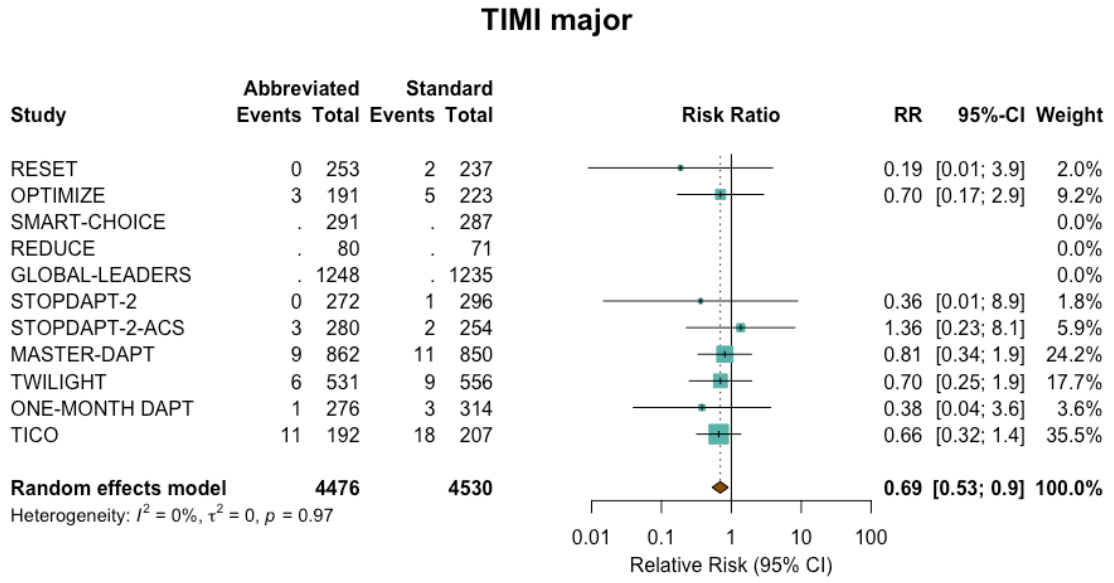
SUPPLEMENTARY FIGURES

Supplementary Figure 1. Study Flow diagram

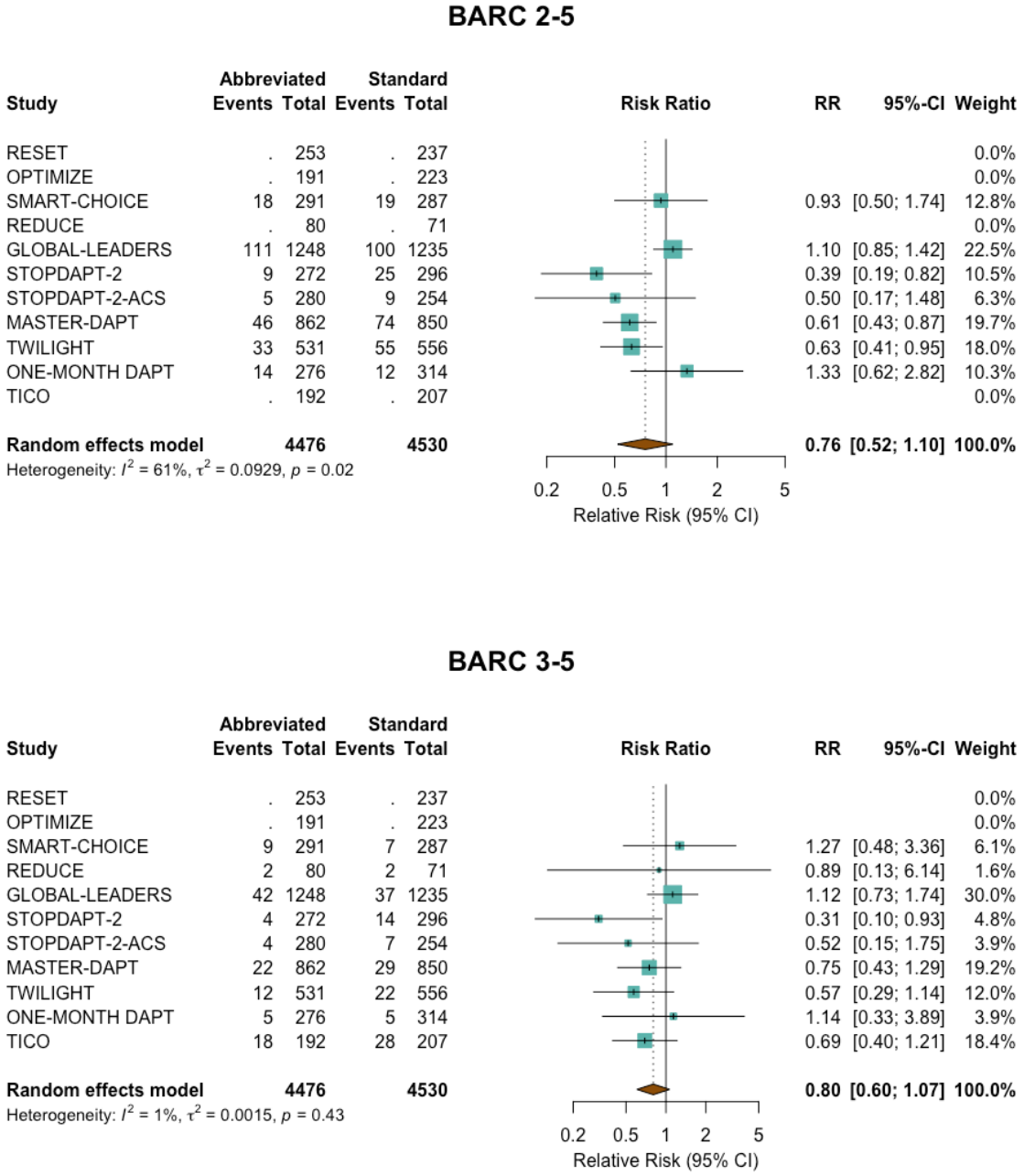


Supplementary Figure 2: Bleeding events according to Thrombosis in Myocardial Infarction (TIMI) definition.

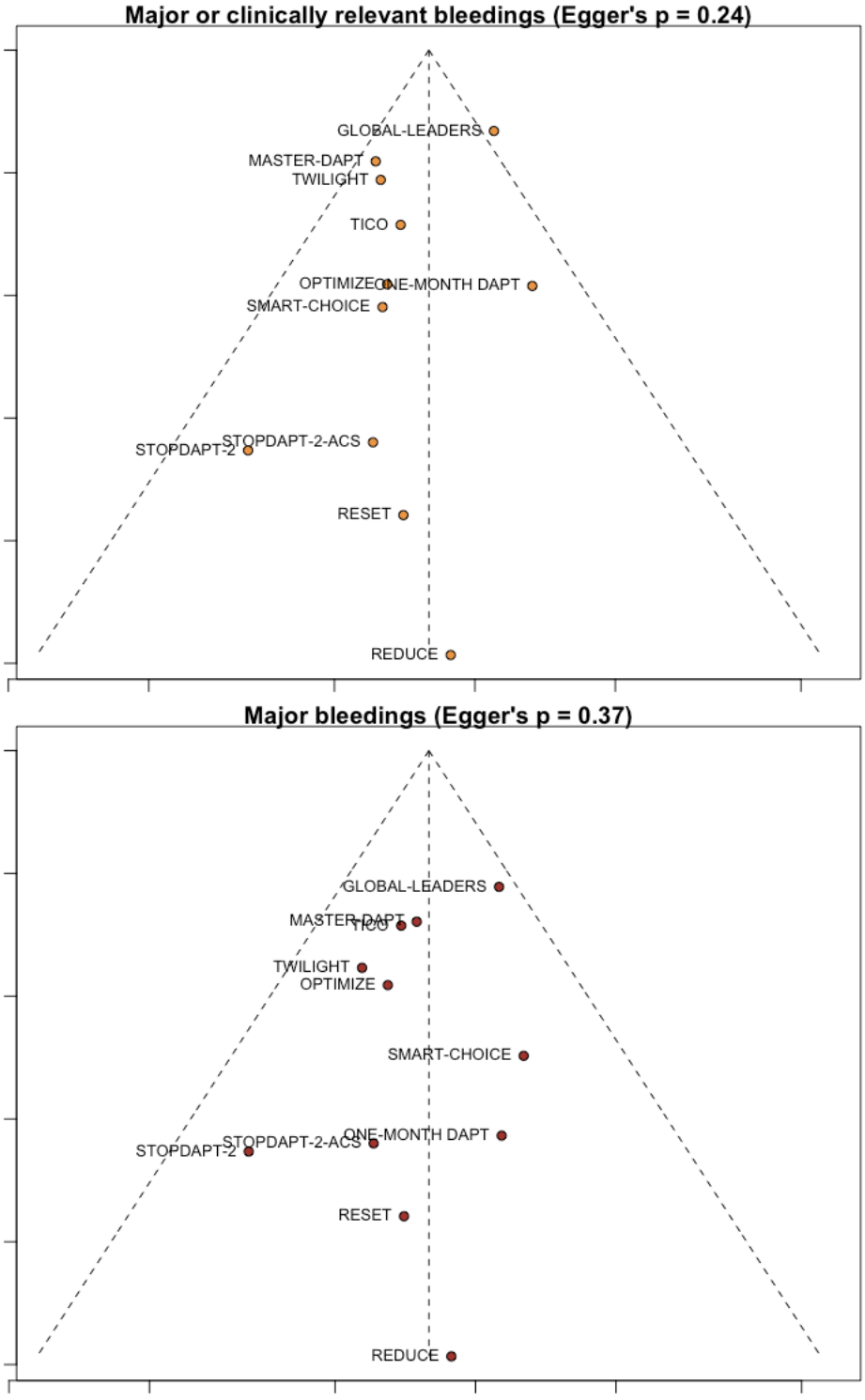


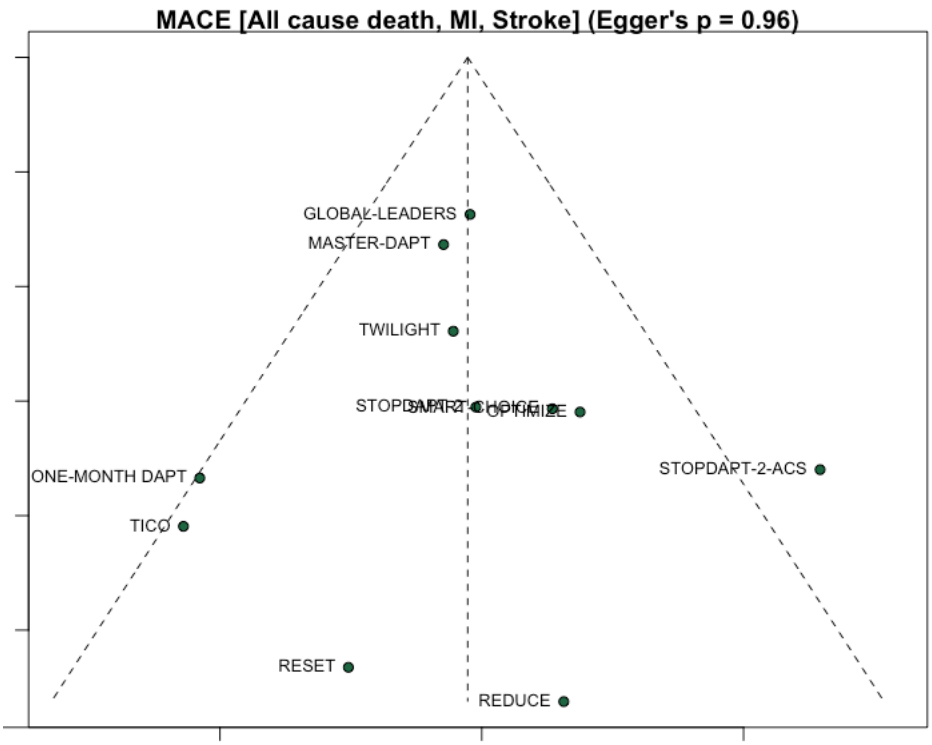


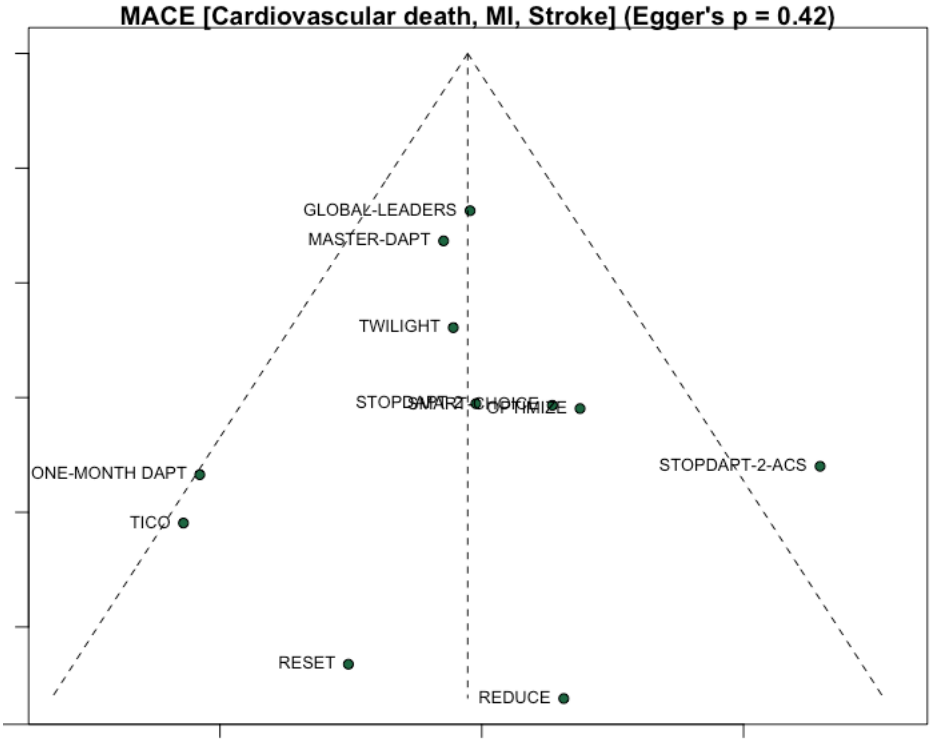
Supplementary Figure 3: Bleeding events according to Bleeding Academic Research Consortium (BARC) definition.



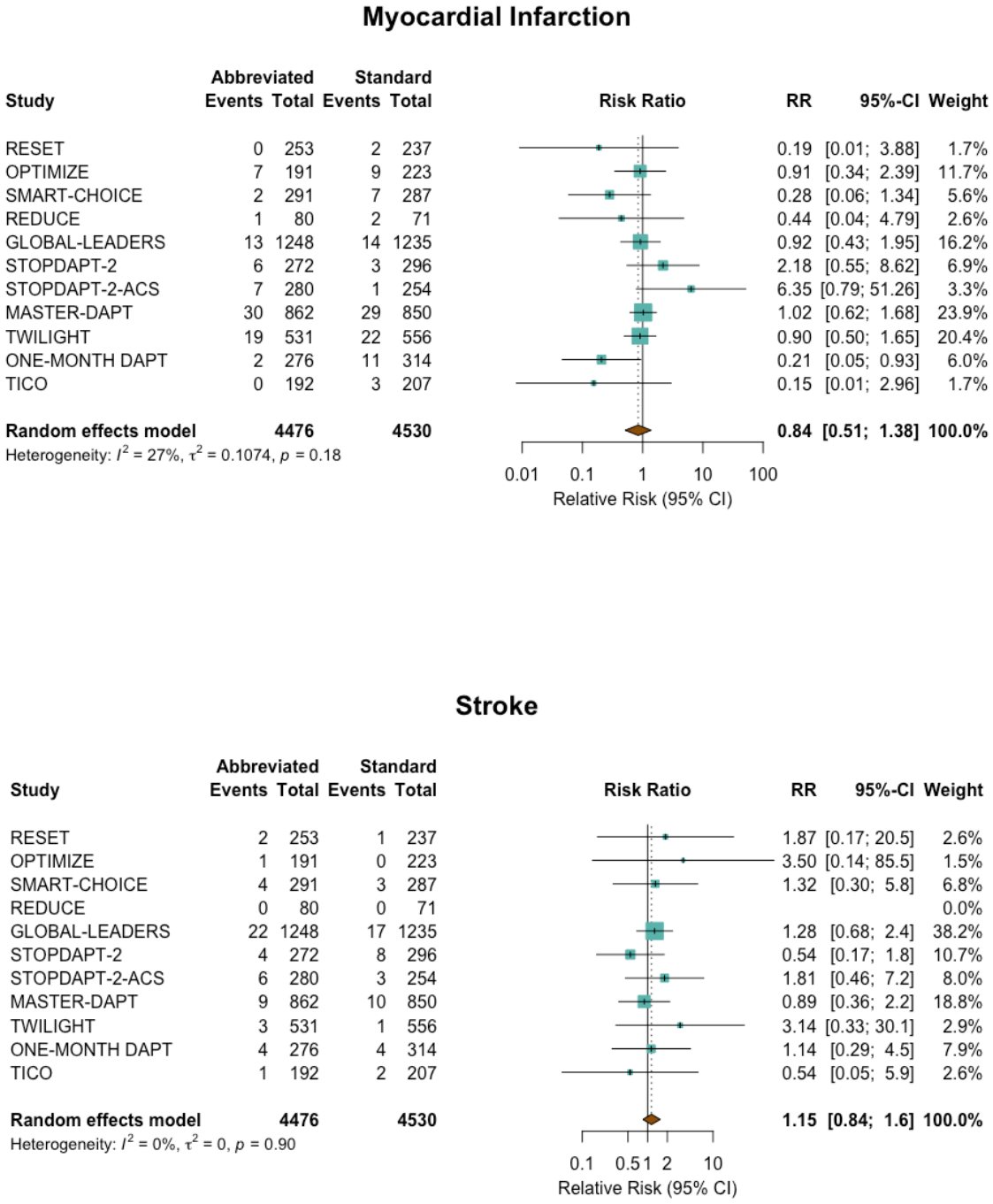
Supplementary Figure 4: Funnel plots for major or clinically relevant non-major bleeding (A), major bleeding (B), major adverse cardiovascular events 1 (C) and major adverse cardiovascular events 2 (D)




MACE [All cause death, MI, Stroke] (Egger's p = 0.96)
GLOBAL-LEADERS
MASTER-DAPT
TWILIGHT
STOPDAPT-2 CHOICE
OPTIMIZE
ONE-MONTH DAPT
STOPDART-2-ACS
TICO
RESET
REDUCE


MACE [Cardiovascular death, MI, Stroke] (Egger's p = 0.42)
GLOBAL-LEADERS
MASTER-DAPT
TWILIGHT
STOPDAPT-2 CHOICE
OPTIMIZE
ONE-MONTH DAPT
STOPDART-2-ACS
TICO
RESET
REDUCE

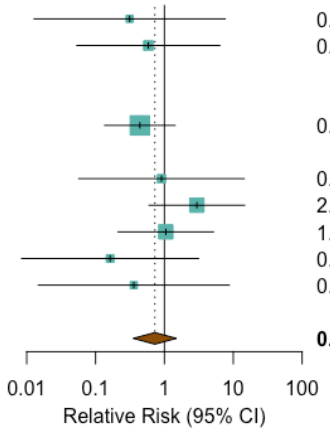
Supplementary Figure 5: Secondary ischemic endpoints explored.



Stent thrombosis (definite)

Study	Abbreviated Events	Abbreviated Total	Standard Events	Standard Total	RR	95%-CI	Weight
RESET	0	253	1	237	0.31	[0.01; 7.6]	4.6%
OPTIMIZE	1	191	2	223	0.58	[0.05; 6.4]	8.2%
SMART-CHOICE	0	291	0	287			0.0%
REDUCE	0	80	0	71			0.0%
GLOBAL-LEADERS	4	1248	9	1235	0.44	[0.14; 1.4]	34.1%
STOPDAPT-2	0	272	0	296			0.0%
STOPDAPT-2-ACS	1	280	1	254	0.91	[0.06; 14.4]	6.2%
MASTER-DAPT	6	862	2	850	2.96	[0.60; 14.6]	18.4%
TWILIGHT	3	531	3	556	1.05	[0.21; 5.2]	18.5%
ONE-MONTH DAPT	0	276	3	314	0.16	[0.01; 3.1]	5.4%
TICO	0	192	1	207	0.36	[0.01; 8.8]	4.6%
Random effects model		**4476**		**4530**	**0.73**	**[0.35; 1.5]**	**100.0%**

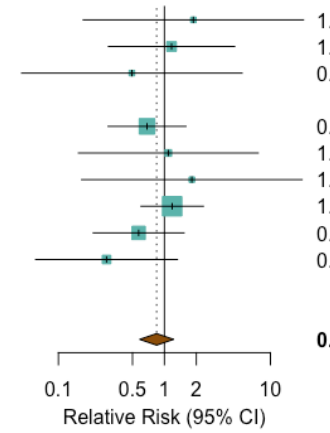
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.62



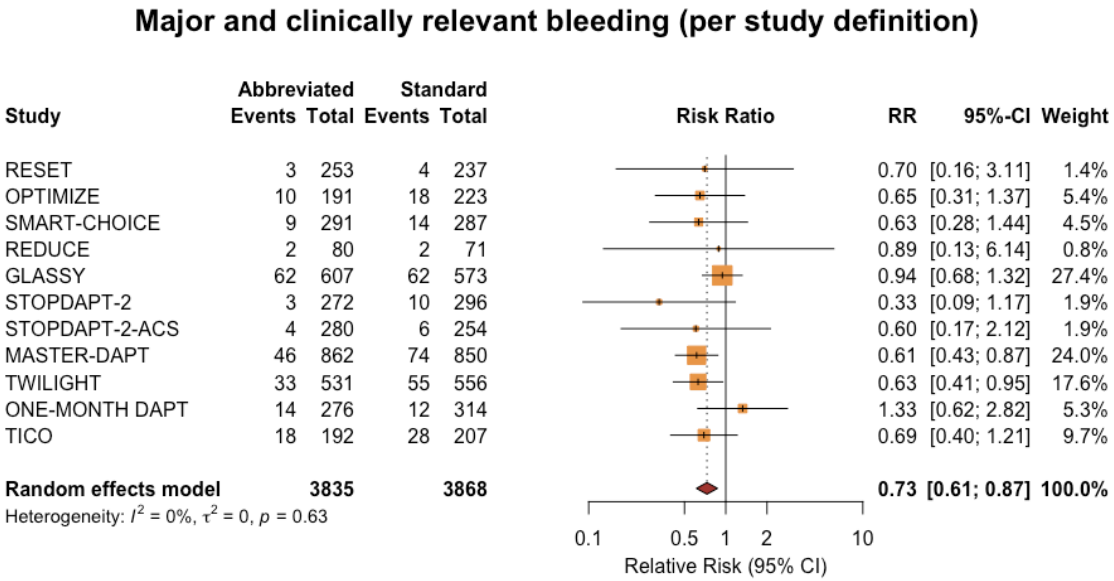
Stent thrombosis (def or prob)

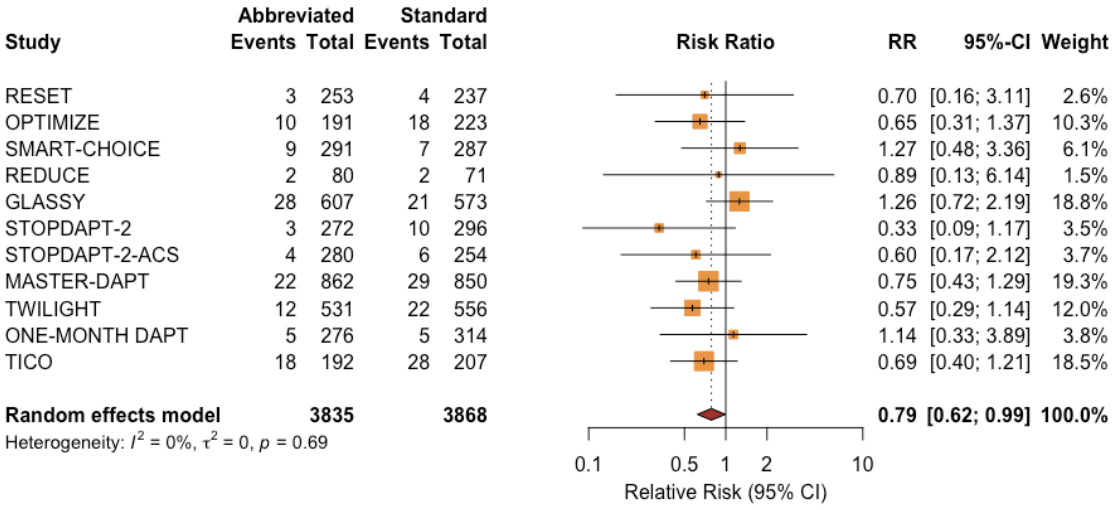
Study	Abbreviated Events	Abbreviated Total	Standard Events	Standard Total	RR	95%-CI	Weight
RESET	2	253	1	237	1.87	[0.17; 20.5]	2.8%
OPTIMIZE	4	191	4	223	1.17	[0.30; 4.6]	8.4%
SMART-CHOICE	1	291	2	287	0.49	[0.04; 5.4]	2.8%
REDUCE	0	80	0	71			0.0%
GLOBAL-LEADERS	9	1248	13	1235	0.69	[0.29; 1.6]	22.1%
STOPDAPT-2	2	272	2	296	1.09	[0.15; 7.7]	4.1%
STOPDAPT-2-ACS	2	280	1	254	1.81	[0.17; 19.9]	2.8%
MASTER-DAPT	18	862	15	850	1.18	[0.60; 2.3]	34.3%
TWILIGHT	6	531	11	556	0.57	[0.21; 1.5]	16.2%
ONE-MONTH DAPT	2	276	8	314	0.28	[0.06; 1.3]	6.7%
TICO	.	192	.	207			0.0%
Random effects model		**4476**		**4530**	**0.84**	**[0.58; 1.2]**	**100.0%**

Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.76



Supplementary Figure 6: Sensitivity analysis including studies with centrally adjudicated events. Major or clinically relevant non-major bleeding (A), major bleeding (B) major adverse cardiovascular events 1 (C) , major adverse cardiovascular events 2 (D) , all-cause death (E) and cardiovascular death (F) are presented.

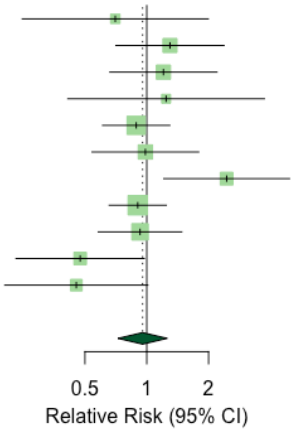




MACE (All cause death, MI, Stroke)

Study	Abbreviated Events	Abbreviated Total	Standard Events	Standard Total	RR	95%-CI	Weight
RESET	6	253	8	237	0.70	[0.25; 1.99]	4.0%
OPTIMIZE	20	191	18	223	1.30	[0.71; 2.38]	9.0%
SMART-CHOICE	22	291	18	287	1.21	[0.66; 2.20]	9.2%
REDUCE	7	80	5	71	1.24	[0.41; 3.74]	3.6%
GLASSY	48	607	51	573	0.89	[0.61; 1.30]	15.1%
STOPDAPT-2	19	272	21	296	0.98	[0.54; 1.79]	9.2%
STOPDAPT-2-ACS	27	280	10	254	2.45	[1.21; 4.96]	7.4%
MASTER-DAPT	66	862	72	850	0.90	[0.66; 1.25]	17.1%
TWILIGHT	31	531	35	556	0.93	[0.58; 1.48]	12.3%
ONE-MONTH DAPT	10	276	24	314	0.47	[0.23; 0.97]	7.1%
TICO	8	192	19	207	0.45	[0.20; 1.01]	6.1%
Random effects model		**3835**		**3868**	**0.95**	**[0.72; 1.26]**	**100.0%**

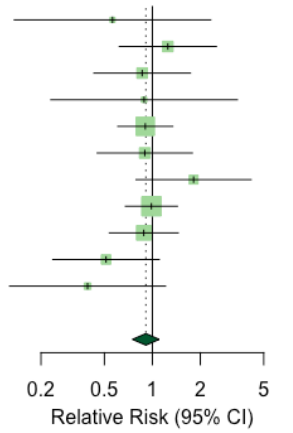
Heterogeneity: I^2 = 38%, τ^2 = 0.0511, p = 0.10



MACE (CV death, MI, Stroke)

Study	Abbreviated Events	Abbreviated Total	Standard Events	Standard Total	RR	95%-CI	Weight
RESET	3	253	5	237	0.56	[0.14; 2.3]	1.7%
OPTIMIZE	15	191	14	223	1.25	[0.62; 2.5]	7.1%
SMART-CHOICE	14	291	16	287	0.86	[0.43; 1.7]	7.2%
REDUCE	4	80	4	71	0.89	[0.23; 3.4]	1.9%
GLASSY	44	607	46	573	0.90	[0.61; 1.3]	22.2%
STOPDAPT-2	14	272	17	296	0.90	[0.45; 1.8]	7.4%
STOPDAPT-2-ACS	16	280	8	254	1.81	[0.79; 4.2]	5.1%
MASTER-DAPT	51	862	51	850	0.99	[0.68; 1.4]	24.7%
TWILIGHT	27	531	32	556	0.88	[0.54; 1.4]	14.1%
ONE-MONTH DAPT	9	276	20	314	0.51	[0.24; 1.1]	5.9%
TICO	4	192	11	207	0.39	[0.13; 1.2]	2.8%
Random effects model		**3835**		**3868**	**0.91**	**[0.75; 1.1]**	**100.0%**

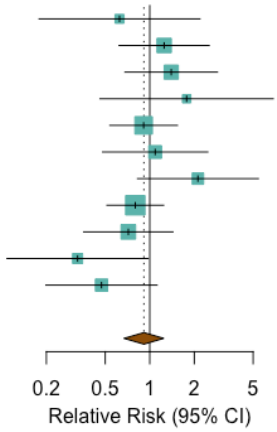
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.59



All-cause death

Study	Abbreviated Events	Abbreviated Total	Standard Events	Standard Total	RR	95%-CI	Weight
RESET	4	253	6	237	0.62	[0.18; 2.19]	4.0%
OPTIMIZE	15	191	14	223	1.25	[0.62; 2.52]	10.4%
SMART-CHOICE	17	291	12	287	1.40	[0.68; 2.87]	10.0%
REDUCE	6	80	3	71	1.77	[0.46; 6.84]	3.5%
GLASSY	26	607	27	573	0.91	[0.54; 1.54]	15.4%
STOPDAPT-2	11	272	11	296	1.09	[0.48; 2.47]	8.2%
STOPDAPT-2-ACS	14	280	6	254	2.12	[0.83; 5.42]	6.5%
MASTER-DAPT	34	862	42	850	0.80	[0.51; 1.24]	18.8%
TWILIGHT	13	531	19	556	0.72	[0.36; 1.44]	10.6%
ONE-MONTH DAPT	4	276	14	314	0.33	[0.11; 0.98]	5.0%
TICO	7	192	16	207	0.47	[0.20; 1.12]	7.5%
Random effects model		**3835**		**3868**	**0.91**	**[0.67; 1.25]**	**100.0%**

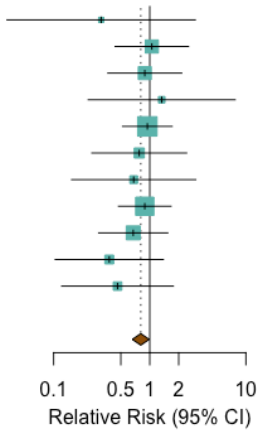
Heterogeneity: I^2 = 24%, τ^2 = 0.0449, p = 0.22



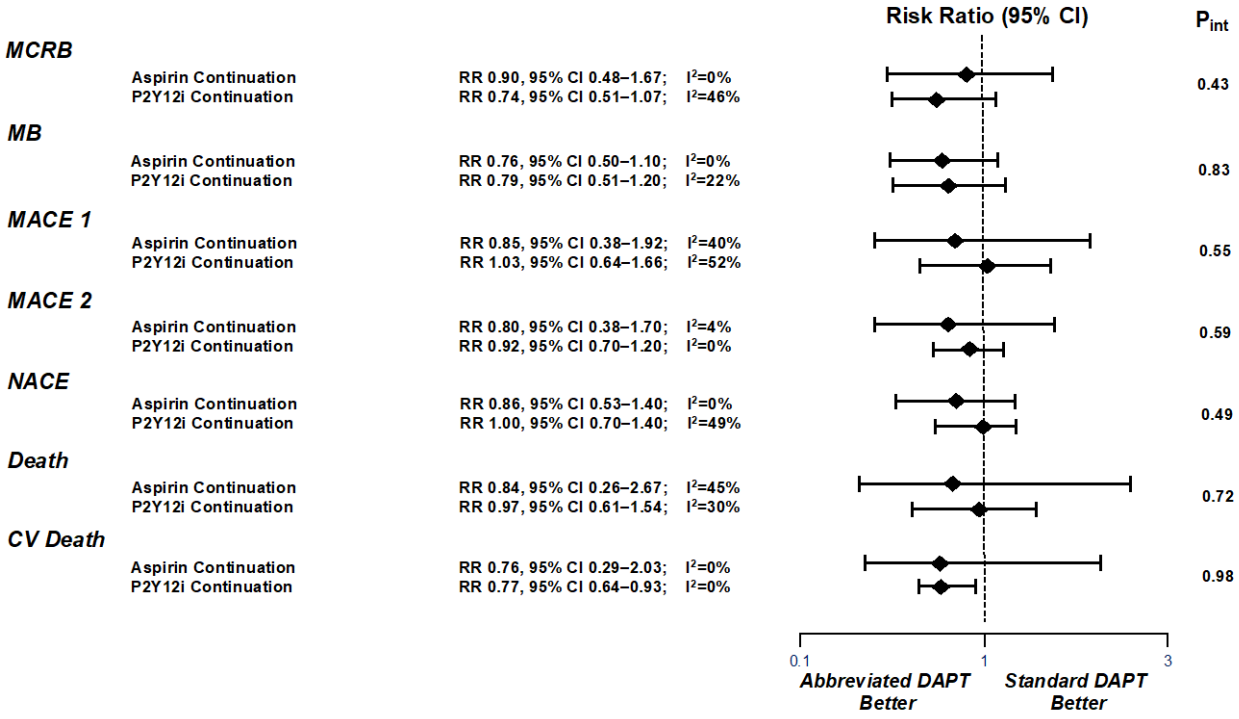
Cardiovascular death

Study	Abbreviated Events	Abbreviated Total	Standard Events	Standard Total	RR	95%-CI	Weight
RESET	1	253	3	237	0.31	[0.03; 2.98]	1.6%
OPTIMIZE	9	191	10	223	1.05	[0.44; 2.53]	10.5%
SMART-CHOICE	9	291	10	287	0.89	[0.37; 2.15]	10.4%
REDUCE	3	80	2	71	1.33	[0.23; 7.74]	2.6%
GLASSY	21	607	21	573	0.94	[0.52; 1.71]	23.1%
STOPDAPT-2	5	272	7	296	0.78	[0.25; 2.42]	6.3%
STOPDAPT-2-ACS	3	280	4	254	0.68	[0.15; 3.01]	3.7%
MASTER-DAPT	18	862	20	850	0.89	[0.47; 1.67]	20.5%
TWILIGHT	9	531	14	556	0.67	[0.29; 1.54]	11.9%
ONE-MONTH DAPT	3	276	9	314	0.38	[0.10; 1.39]	4.8%
TICO	3	192	7	207	0.46	[0.12; 1.76]	4.5%
Random effects model		**3835**		**3868**	**0.81**	**[0.66; 0.99]**	**100.0%**

Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.95



Supplementary Figure 7: Subgroup analysis based on the type of antiplatelet therapy continuation after short DAPT withdrawal. Treatment effects and interaction p values are presented for subgroups of patients continuing antiplatelet monotherapy with aspirin or P2Y12 inhibitor after short DAPT withdrawal.



Supplementary Figure 8: Subgroup analysis based on the type of drug eluting stent implanted. Treatment effects and interaction p values are presented for subgroups of patients treated with durable polymer or bioresorbable/no-polymer drug eluting stent in the experimental arm.