P2Y12 inhibitor monotherapy or dual antiplatelet therapy after coronary revascularisation: an individual patient-level meta-analysis of randomised controlled trials

Valgimigli et al.

Contents

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Supplementary Methods

Assembled Dataset

IPD were provided for the following variables: physical assessment (gender, age, height, weight, country of randomisation), medical history (diabetes, insulin-treated diabetes, cigarette smoking, hypercholesterolaemia, hypertension, liver disease, peripheral artery disease, previous myocardial infarction, previous percutaneous coronary intervention, previous coronary artery bypass grafting, prior stroke, prior bleeding, history of chronic kidney disease, chronic lung disease), medication on admission (antiplatelet medication on admission), laboratory prior to index percutaneous coronary intervention (creatinine, haemoglobin, white cell count, troponin elevation, CK elevation, CK-MB elevation), procedure information (arterial access, indication for percutaneous coronary intervention), procedural medication (aspirin loading dose, $P2Y_{12}$ loading dose, unfractionated heparin, low molecular weight heparin, glycoprotein IIb/IIIa inhibitors, bivalirudin), angiographic features (left ventricular ejection fraction), intervention (number of vessels treated, number of lesions treated, number of single lesions treated with total stent length >30 mm, post-PCI diameter stenosis, treated vessel [left anterior descending artery, left circumflex artery, right coronary artery, left main], lesion morphology of any target lesions [bifurcation, thrombus, venous or arteria grafts, total occlusion], bifurcation target lesion treated with at least 2 stents, TIMI pre percutaneous coronary intervention, number of implanted stents, diameter of each implanted stent, length of each implanted stent, overlapping stents, total stent length, stent type, minimum diameter of all stents implanted, maximum diameter of all stents implanted, thrombus aspiration), intervention for post-coronary artery bypass grafting patients (number of arterial graft(s), number of venous graft(s), on-pump coronary artery bypass grafting), hospital stay, medication at discharge (aspirin, $P2Y_{12}$ inhibitors, ACE-inhibitors or ATII antagonists, beta-blockers, statins, proton pump inhibitors), duration of participation in the study, reason for end, vital status (dead or alive), date of death, adverse events (bleeding [BARC, TIMI], death [cardiovascular, non-cardiovascular], myocardial infarction [type of myocardial infarction, relation to target vessel], stent thrombosis [timing, possible, probable, definite], stroke [ischaemic, haemorrhagic, not otherwise specified], recurrent adverse events, study medication initiation (ie, at least one dose received), study medication cessation (medication stopped, date of cessation), complete or incomplete fulfillment of enrolment criteria.

Search Strategy

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed			EMBASE		
No.	**Query**	**Results**	**No.**	**Query**	**Results**
#1	coronary artery disease.ab,ti.	85454	#1	'coronary artery disease*':ab,ti AND [embase]/lim	124775
#2	myocardial infarction.ab,ti.	182906	#2	'myocardial infarc*':ab,ti AND [embase]/lim	249971
#3	"acute coronar* syndrom*".ab,ti.	32116	#3	'acute coronary syndrome*':ab,ti AND [embase]/lim	52441
#4	percutaneous coronary intervention.ab,ti.	31832	#4	'percutaneous coronary intervention*':ab,ti AND [embase]/lim	56360
#5	"coronary bypass graft*".ab,ti.	2614	#5	'coronary artery bypass':ti,ab AND [embase]/lim	48135
#6	*Coronary Artery Disease/co, dt, mo, su, th	19940	#6	#1 OR #2 OR #3 OR #4 OR #5	420418
#7	*Myocardial Infarction/co, dt, mo, su, th	51783	#7	'clopidogrel':ti,ab AND [embase]/lim	22791
#8	*Acute Coronary Syndrome/co, dt, mo, su, th	6710	#8	'plavix':ti,ab AND [embase]/lim	768
#9	*Percutaneous Coronary Intervention/ae, co, dt, mo, su, th	2545	#9	#7 OR #8	23210
#10	*Coronary Artery Bypass/ae, mo, th	6737	#10	'prasugrel':ti,ab AND [embase]/lim	4066
#11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	306487	#11	(effient:ti,ab OR efient:ti,ab) AND [embase]/lim	57
#12	clopidogrel.ti,ab.	12753	#12	('cs 747':ti,ab OR ly640315:ti,ab OR hsdb7995:ti,ab) AND [embase]/lim	31
#13	*clopidogrel/	600	#13	#10 OR #11 OR #12	4080
#14	Plavix.mp.	319	#14	'ticagrelor':ti,ab AND [embase]/lim	4917
#15	12 or 13 or 14	12913	#15	(brilinta:ti,ab OR brilique:ti,ab OR possia:ti,ab) AND [embase]/lim	76

#16	prasugrel.ti,ab.	2209	#16	(azd6140:ti,ab OR 'ar c126532xx':ti,ab OR hsdb8306:ti,ab) AND [embase]/lim	88
#17	*prasugrel/	438	#17	#14 OR #15 OR #16	4990
#18	(Effient or Efient).mp.	36	#18	'p2y12':ti,ab AND [embase]/lim	4712
#19	(CS-747 or LY640315 or HSDB7995).mp.	30	#19	#9 OR #13 OR #17 OR #18	27036
#20	16 or 17 or 18 or 19	2248	#20	#6 AND #19	13905
#21	ticagrelor.ti,ab.	2714			
#22	*ticagrelor/	413			
#23	(Brilinta or Brilique or Possia).mp	38			
#24	(AZD6140 or AR-C126532XX or HSDB8306).mp.	63			
#25	21 or 22 or 23 or 24	2782			
#26	P2Y12.ti,ab.	3758			
#27	*Purinergic P2Y Receptor Antagonists/ae, tu, to	716			
#28	26 or 27 (4090)	4090			
#29	15 or 20 or 25 or 28	15936			
#30	11 and 29	8163			

Reference list of included trials

1. Zhao Q, Zhu Y, Xu Z, et al. Effect of Ticagrelor Plus Aspirin, Ticagrelor Alone, or Aspirin Alone on Saphenous Vein Graft Patency 1 Year After Coronary Artery Bypass Grafting. *JAMA* 2018;319:1677–86.
2. Franzone A, McFadden E, Leonardi S, et al. Ticagrelor Alone Versus Dual Antiplatelet Therapy From 1 Month After Drug-Eluting Coronary Stenting. *J Am Coll Cardiol* 2019;74:2223–34.
3. Hahn JY, Song Y Bin, Oh JH, et al. Effect of P2Y12 Inhibitor Monotherapy vs Dual Antiplatelet Therapy on Cardiovascular Events in Patients Undergoing Percutaneous Coronary Intervention. *JAMA* 2019;321:2428–37.
4. Watanabe H, Domei T, Morimoto T, et al. Effect of 1-Month Dual Antiplatelet Therapy Followed by Clopidogrel vs 12-Month Dual Antiplatelet Therapy on Cardiovascular and Bleeding Events in Patients Receiving PCI. *JAMA* 2019;321:2414–27.
5. Kim BK, Hong SJ, Cho YH, et al. Effect of Ticagrelor Monotherapy vs Ticagrelor With Aspirin on Major Bleeding and Cardiovascular Events in Patients With Acute Coronary Syndrome: The TICO Randomized Clinical Trial. *JAMA* 2020;323:2407–16.
6. Mehran R, Baber U, Sharma SK, et al. Ticagrelor with or without Aspirin in High-Risk Patients after PCI. *N Engl J Med* 2019;381:2032–42.

Secondary endpoints

Secondary endpoints included each component of the primary efficacy endpoint, cardiovascular and non-cardiovascular mortality, ischaemic and/or haemorrhagic stroke, definite and/or probable stent thrombosis, bleeding according to BARC (Bleeding Academic Research Consortium) or TIMI (Thrombolysis in Myocardial Infarction) scales, and net adverse events consisting of the composite of the primary efficacy and key safety endpoints.

Further details on data analysis

Baseline and procedural continuous variables were summarised by means and standard deviations or medians and interquartile range, categorical variables by counts and percentages. The randomised groups were compared using Chi-squared or Fisher's exact test for binary and categorical variables and t-test or Wilcoxon test for continuous variables as appropriate.

Sensitivity analyses for superiority were performed in the per-protocol populations of the trials mandating an initial DAPT phase after randomisation in both experimental and control groups,[1–6] patients were left-truncated at the time-point when the protocol specified the change from DAPT to $P2Y_{12}$ inhibitor monotherapy in the experimental group. Data was analysed up to the longest available time-point with protocol-specified $P2Y_{12}$ inhibitor monotherapy in the experimental group and DAPT in the control group.[1–6] Since overall mortality does not require adjudication, a sensitivity analysis restricted to overall mortality was performed including the GLOBAL LEADERS (GLOBAL LEADERS: A Clinical Study Comparing Two Forms of Anti-platelet Therapy After Stent Implantation; NCT01813435)[7] dataset instead of GLASSY (GLOBAL LEADERS Adjudication Sub-Study; NCT03231059).[2] Results for outcomes with time-to-event data were displayed as non-stratified Kaplan-Meier curves for descriptive purposes. Sensitivity analyses were performed considering the same mixed-effect Cox regression approach (i) including the initial DAPT phase in trials with an initial DAPT phase after randomisation in both experimental and control groups, (ii) excluding patients who experienced non-fatal events during the initial DAPT phase, (iii)

including the study period in whom all the trials had available information. The proportional hazard assumption has been verified for each single trial separately and the corresponding p-values have been meta-analysed obtaining a negative overall p-value (p=0.093).

An on-treatment sensitivity analysis was explored for all study outcomes, where patients were truncated at the point they interrupted the study treatment for more than 5 days. For descriptive purposes, we plotted Kaplan-Meier time-to-event curves for the primary ischaemic and key bleeding secondary endpoints; since all trials had a 1:1 randomisation ratio, the curves were not subject to Simpson's paradox.[8] Numbers-needed-to-treat to benefit (NNTBs) were derived from the annualised control group event rate estimated from Poisson regression and the pooled HR.[9]

The per-protocol population was pre-specified and excluded ineligible patients (ie, violating inclusion/exclusion criteria) and/or those who never received allocated treatment strategy. As post-hoc analysis, sex was further analysed with respect to each component of the primary efficacy endpoint and in each trial separately and stratified into categories according to the weight. Pre-specified subgroup analyses of the primary endpoints were based on the same one-step approach mixed-effect Cox regression. In this case, the within-trial and across-trial interactions were separated and based tests for subgroup-by-treatment interactions on within-trial interactions. Analyses were done in Stata Release 16.1 (StataCorp LP, College Station, Texas) and R version 3.6.1 (R Foundation, Vienna, Austria).

Supplementary tables

Supplementary table A. Main characteristics of randomised trials included in the pooled analysis

Trial	N	Follow-up (yrs)	Timing of randomisation	Experimental arm	Control arm	Primary endpoint	Blinded adjudication of events	Industry funded
DACAB	334	1	At index CABG	12-month ticagrelor 90mg twice daily monotherapy	12-month DAPT (ticagrelor 90mg twice daily plus aspirin 100mg once daily)	*Saphenous vein graft patency 1 year after CABG (FitzGibbon grade A)*	Yes	No
GLASSY	7585	2	At index PCI	1-month DAPT (75 to 100mg of aspirin plus 90mg of ticagrelor twice daily) followed by 23-month ticagrelor 90mg twice daily monotherapy	12-month DAPT (75 to 100mg of aspirin plus 75mg of clopidogrel in patients with stable CAD or 90mg of ticagrelor twice daily in patients with ACS) followed by aspirin alone for 12 months	*Coprimary efficacy endpoint*, composite of death, MI, stroke or urgent TVR *Coprimary safety endpoint,* composite of BARC type 3 or 5 bleeding events	Yes	No

SMART-CHOICE	2993	1	At index PCI	100-325mg/d aspirin plus a $P2Y_{12}$ inhibitor for 3 months and thereafter $P2Y_{12}$ inhibitor alone until 1 year	DAPT with 100-325mg/d aspirin plus a $P2Y_{12}$ inhibitor for 12 months	All-cause death, MI, or stroke at 12 months	Yes	No
STOPDAPT-2	3009	1	At index PCI	1-month DAPT with 81-200mg/d aspirin and 75 mg/d clopidogrel or 3,75mg/d prasugrel, followed by 75mg/d clopidogrel monotherapy until 1 year	12 months of DAPT with 81-200mg/d aspirin and 75mg/d clopidogrel	Cardiovascular death, MI, ischaemic or haemorrhagic stroke, definite stent thrombosis, or major or minor bleeding at 12 months	Yes	No
TICO	3056	1	At index PCI	100mg/d aspirin plus ticagrelor 90mg twice daily for 3 months and thereafter ticagrelor monotherapy	12 months of DAPT with 100mg/d aspirin and ticagrelor 90mg twice daily	All-cause death, MI, stent thrombosis, stroke, or TVR	Yes	No

TWILIGHT	6532	1	At 3 months after PCI	Ticagrelor 90mg twice daily plus placebo for 12 months	Ticagrelor 90mg twice daily plus aspirin 81 to 100mg daily for 12 months	First occurrence of BARC type 2, 3, or 5 bleeding between randomisation and 1 year	Yes	No

BARC=Bleeding Academy Research Consortium; CABG=coronary artery bypass surgery; CAD=coronary artery disease; DACAB=Different Antiplatelet Therapy Strategy After Coronary Artery Bypass Graft Surgery; DAPT=dual antiplatelet therapy; GLASSY=GLOBAL LEADERS Adjudication Sub-Study; MI=myocardial infarction; PCI=percutaneous coronary intervention; SMART-CHOICE=Smart Angioplasty Research Team: Comparison Between P2Y12 Antagonist Monotherapy vs Dual Antiplatelet Therapy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents; STOPDAPT-2=Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent; TICO=Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus-eluting Stent for Acute Coronary Syndrome; TVR=target vessel revascularisation; TWILIGHT=Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention.

Supplementary table B. Main inclusion and exclusion criteria in pooled randomised trials

Study	Major inclusion criteria	Major exclusion criteria
DACAB	• Age ≥18 and up to 80 years • Indications for elective CABG surgery	• Cardiogenic shock, haemodynamic instability • Need for urgent revascularisation within 5 days from presentation • Single vessel disease • Two vessel disease with normal left ventricular function (>50%) • Need for concomitant other cardiac surgery (ie, valve replacement) • Need for dual antiplatelet treatment for the patients undergoing CABG after acute coronary syndrome • Contraindication for aspirin and ticagrelor use (ie, known allergy) • History of bleeding diathesis within 3 months prior to presentation • History of significant gastrointestinal bleed within 1 year prior to presentation • History of peptic ulcer without gastrointestinal bleeding in the past 3 years • History of intracranial haemorrhage • History of moderate to severe liver impairment • Patient requiring dialysis • Patient with an increased risk of bradycardia (ie, patients without a pacemaker who have sick sinus syndrome, 2nd or 3rd degree AV block or bradycardia-related syncope) • Need vitamin K antagonist therapy after CABG (ie, persistent atrial fibrillation, mechanical heart valves) • Known, clinically important thrombocytopenia (ie, <100 x 10^9/L) • Known, clinically important anemia (ie, <100 g/L) • Participation in another investigational drug or device study in the last 30 days • Pregnant or lactating female patients Premenopausal women are required to use 2 methods of reliable contraception, one of which must include barrier method

		• Concomitant oral or intravenous therapy with strong CYP3A4 inhibitors, CYP3A4 substrates with narrow therapeutic indices, or strong CYP3A4 inducers which cannot be stopped for the course of the study (strong inhibitors include ketoconazole, itraconazole, voriconazole, telithromycin, clarithromycin, nefazadone, ritonavir, saquinavir, nelfinavir, indinavir, atanazavir, and >1 liter/day of grapefruit juice. Substrates with a narrow therapeutic index include cyclosporine, and quinidine. Strong inducers include rifampin, phenytoin, and carbamazepine) • Active cancer • Life expectancy <12 months • Indication for major surgery (ie, cancer treatment, carotid surgery, cerebral surgery, major vascular surgery)
GLASSY	• Age ≥18 years • Patients with any clinical indication for PCI • Presence of one or more coronary artery stenosis of 50% or more in a native coronary artery or in a saphenous venous or arterial bypass conduit suitable for coronary stent implantation in a vessel with a reference vessel diameter of at least 2.25 millimeter	• Known intolerance to aspirin, $P2Y_{12}$ receptor antagonists, bivalirudin, stainless steel or biolimus • Known intake of a strong cytochrome P3A4 inhibitor • Use of fibrinolytic therapy within 24 hours of PCI • Known severe hepatic impairment • Planned CABG as a staged procedure (hybrid) within 12 months of the index procedure • Planned surgery within 12 months of PCI unless DAPT is maintained throughout the peri-surgical period • Need for oral anticoagulation therapy • PCI for a priori known stent thrombosis • Known overt major bleeding • Known history of intracranial haemorrhage • Known stroke from ischaemic or unknown cause within last 30 days • Known pregnancy at time of randomisation • Inability to provide informed consent • Currently participating in another trial before reaching primary endpoint

SMART-CHOICE	• Patients must be at least 20 years of age • Patients are able to verbally confirm understandings of risks, benefits and treatment alternatives of receiving PCI and he/she or his/her legally authorised representative provides written informed consent prior to any study-related procedure • Patients should have undergone successful PCI with drug-eluting stent for stable ischaemic heart disease or acute coronary syndrome • Patients must have one or more coronary stenosis of 50% or more in a native coronary artery with a visually estimated diameter of ≥2.25 mm and ≤4.25 mm eligible for stent implantation • Target lesion(s) must be amenable for PCI	• Patients with known hypersensitivity or contraindication to any of the following medications: aspirin, clopidogrel, prasugrel, ticagrelor, everolimus, or sirolimus • Haemodynamic instability or cardiogenic shock • Patients with active pathologic bleeding, including gastrointestinal or genitourinary bleeding • Drug-eluting stent implantation within 12 months before index procedure • Female of childbearing potential, unless a recent pregnancy test is negative, who possibly plan to become pregnant any time after enrolment into this study • Non-cardiac co-morbid conditions are present with life expectancy <2 years or that may result in protocol non-compliance (per site investigator's medical judgment) • Patients who are actively participating in another drug or device investigational study which have not completed the primary endpoint follow-up period
STOPDAPT-2	• Patients who have undergone PCI with the everolimus-eluting cobalt-chromium stent (CoCr-EES, XienceTM) and have not experienced major complications (death, myocardial infarction, stroke, or major	• Patients requiring oral anticoagulants • Patients with medical history of intracranial haemorrhage • Patients who have experienced serious complications (myocardial infarction, stroke, major bleeding) during hospital stay post-PCI) • Patients with drug-eluting stent other than Xience implanted in PCI performed at the time of enrolment • Patients confirmed to have no tolerability to clopidogrel before enrolment

	bleeding) during hospital stay for treatment • Patients who are capable of oral DAPT consisting of aspirin and a $P2Y_{12}$ receptor antagonist	• Patients requiring continuous administration of antiplatelet drugs (PDE3 inhibitors, prostaglandin preparations, etc.) other than aspirin and $P2Y_{12}$ receptor inhibitors (prasugrel, clopidogrel, and ticlopidine) at the time of enrolment
TICO	• Age ≥19 years • Patients who received bioresorbable polymer sirolimus-eluting stent implantation to treat acute coronary syndrome • Provision of informed consent	• Age >80 years • Increased risk of bleeding due to: 1) Any prior event of haemorrhagic stroke; 2) Ischaemic stroke, dementia, or impairment of central nervous system within a year; 3) Traumatic brain injury or brain surgery within the past 6 months; 4) Known intracranial tumor; 5) Documented or suspected aortic dissection; 6) Internal bleeding within the past 6 weeks; 7) Active bleeding or bleeding diathesis; 8) Anemia (haemoglobin ≤8 g/dL) or thrombocytopenia (platelet count <100000/μL); 9) Major surgery or traumatic injury resulting in any impairment of physical activity within the past 3 weeks • Need for oral anticoagulation therapy • Current or potential pregnancy • Life expectancy <1 year • Currently treated with strong cytochrome P4503A4 inhibitors • Moderate to severe hepatic dysfunction (Child-Pugh class B or C) • Increased risk of bradycardia-related symptoms
TWILIGHT	• High-risk patients who have undergone successful elective or urgent PCI with at least one locally approved drug-eluting stent discharged on DAPT with aspirin and ticagrelor of at least 3 months plus one clinical	• Under 18 years of age • Contraindication to aspirin • Contraindication to ticagrelor • Planned surgery within 90 days • Planned coronary revascularisation (surgical or percutaneous) within 90 days • Need for chronic oral anticoagulation • Prior stroke • Dialysis-dependent renal failure • Active bleeding or extreme-risk for major bleeding

	and one angiographic inclusion criteria *Clinical Criteria* • ≥65 years of age • Recent (≥3 days) presentation with acute coronary syndrome with clinical stabilisation and decreasing cardiac enzymes • Established vascular disease defined as previous myocardial infarction, documented PAD, or CAD/PAD revascularisation • Diabetes mellitus treated with medications • Chronic kidney disease defined as an estimated glomerular filtration rate <60 ml/min/1.73m^2 or creatinine clearance <60 ml/min *Angiographic Criteria* • Multivessel coronary artery disease • Target lesion requiring total stent length >30 mm • SYNTAX score ≥23 • Bifurcation lesions with Medina X,X,1 classification requiring at least 2 stents • Left main (≥50%) or proximal LAD (≥70%) lesion • Calcified target lesion requiring atherectomy	• Emergent or salvage PCI or ST-segment elevation myocardial infarction presentation • Liver cirrhosis • Life expectancy <1 year • Unable or unwilling to provide informed consent • Women of childbearing potential (as determined by hospital standard of care) • Fibrinolytic therapy within 24 hours of index PCI • Concomitant therapy with a strong cytochrome P-450 3A inhibitor or inducer • Platelet count <100000 mm^3 • Requiring ongoing treatment with aspirin >325 mg daily

CABG=coronary artery bypass grafting; CAD=coronary artery disease; DAPT=dual antiplatelet therapy; DACAB=Different Antiplatelet Therapy Strategy After Coronary Artery Bypass Graft Surgery; GLASSY=GLOBAL LEADERS Adjudication Sub-Study; LAD=left anterior descending artery; PAD=peripheral artery disease; PCI=percutaneous Coronary Intervention; SMART-

CHOICE=Smart Angioplasty Research Team: Comparison Between P2Y12 Antagonist Monotherapy vs Dual Antiplatelet Therapy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents; STOPDAPT-2=Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent; TICO=Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus-eluting Stent for Acute Coronary Syndrome; TWILIGHT=Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention.

Supplementary table C. Definition of clinical endpoints in randomised trials included in the IPD meta-analysis

Endpoint	DACAB	GLASSY	SMART-CHOICE	STOPDAPT-2	TICO	TWILIGHT
Cardiovascular death	Death due to a cardiovascular aetiology such as are acute MI, sudden cardiac death, heart failure, stroke, cardiovascular procedure, cardiovascular haemorrhage, and other cardiovascular causes such as pulmonary embolism or PAD.	Death due to a cardiovascular aetiology such as are acute MI, sudden cardiac death, heart failure, stroke, cardiovascular procedure, cardiovascular haemorrhage, and other cardiovascular causes such as pulmonary embolism or PAD.				
Cardiac death			Any death due to proximate cardiac cause (ie, MI, low-output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, and all procedure-related deaths, including those related to concomitant treatment.	Any death due to proximate cardiac cause (ie MI, low output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, all procedure related deaths including those related to concomitant treatment. All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established. Any unexpected death even in subjects with coexisting potentially fatal non-cardiac disease (ie, cancer, infection) should be classified as cardiac.	Cardiac death was defined as death due to MI, cardiac perforation or pericardial tamponade; arrhythmia or conduction abnormality stroke within 30 days of the procedure or related to the procedure; death due to a procedural complication; or any case of death in which a cardiac cause was not excluded by a clinical event committee	Any death due to proximate cardiac cause (ie, MI, low-output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, all procedure-related deaths including those related to concomitant treatment, will be classified as cardiac death.

Vascular death			Death caused by non-coronary vascular causes, such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular diseases.	Death due to non-coronary vascular causes such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular cause.	Death caused by non-coronary vascular causes, such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm or other causes.
Noncardiovascular death	Any death that is not thought to be due to a cardiovascular cause.	Any death that is not thought to be due to a cardiovascular cause. The following categories were collected: non-malignant causes, pulmonary, renal, gastrointestinal, hepatobiliary, pancreatic, infection (includes sepsis), non-infectious (ie, systemic inflammatory response syndrome), haemorrhage excluding haemorrhagic strokes and bleeding in the setting of coronary revascularisation.	Any death not covered by the above definitions, such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide, or trauma.	Any death not covered by the above definitions such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide or trauma.	Any death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide or trauma.

Myocardial infarction	Defined based on the third universal definition of MI (Type 1: spontaneous MI; Type 2: MI secondary to an ischaemic imbalance; Type 3: MI resulting in death when biomarker values are unavailable; Type 4a: MI related to PCI; Type 4b: MI related to stent thrombosis; Type 4c: MI related to stent restenosis; Type 5: MI related to CABG).	Defined based on the third universal definition of MI (Type 1: spontaneous MI; Type 2: MI secondary to an ischaemic imbalance; Type 3: MI resulting in death when biomarker values are unavailable; Type 4a: MI related to PCI; Type 4b: MI related to stent thrombosis; Type 4c: MI related to stent restenosis; Type 5: MI related to CABG) with the exception of peri-procedural MI after PCI, which was defined according to the SCAI definition (1. In patients with normal baseline CK-MB: the peak CK-MB measured within 48 hours of the procedure rises to ≥10x the local laboratory ULN, or to ≥5x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB, OR in the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 hours of the PCI rises	MI Classification and Criteria for Diagnosis defined by the Academic Research Consortium (ARC) as follows: Peri procedural PCI: Troponin >3 x URL or CK-MB >3 x URL. Peri-procedural CABG: Troponin >5 x URL or CK-MB >5 x URL. Spontaneous: Troponin >URL or CK-MB >URL. Reinfarction: stable or decreasing values on 2 samples and 20% increase 3 to 6 hours after a second sample diagnose recurrent MI.	As classified by Academic Research Consortium (ARC): However, the sensitivity is too high for the evaluation with Troponin of the peri-procedural MI, thus CK-MB was used.	Defined based on the third universal definition of MI (Type 1: spontaneous MI; Type 2: MI secondary to an ischaemic imbalance; Type 3: MI resulting in death when biomarker values are unavailable, Type 4a: MI related to PCI; Type 4b: MI related to stent thrombosis; Type 4c: MI related to stent restenosis; Type 5: MI related to CABG) with the exception of peri-procedural MI after PCI, which was defined according to the SCAI definition (1.In patients with normal baseline CK-MB: The peak CK-MB measured within 48 hours of the procedure rises to ≥10x the local laboratory ULN, or to ≥5x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB, OR in the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 hours of the PCI rises	Defined according to the third universal definition and includes: Type 1: spontaneous MI; Type 2: MI secondary to an ischaemic imbalance; Type 3: MI resulting in death when biomarker values are unavailable; Type 4a: MI related to PCI; Type 4b: MI related to stent thrombosis; Type 5: MI related to CABG.

to ≥70x the local laboratory ULN, or ≥35x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB; 2. In patients with elevated baseline CK-MB (or cTn) in whom the biomarker levels are stable or falling: the CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level; 3. In patients with elevated CK-MB (or cTn) in whom the biomarker levels have not been shown to be stable or falling: the CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above plus new ST-segment elevation or depression plus signs consistent with a clinically relevant MI, such as new-onset or worsening heart failure or sustained hypotension).

to ≥70x the local laboratory ULN, or ≥35x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB; 2. In patients with elevated baseline CK-MB (or cTn) in whom the biomarker levels are stable or falling: the CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level; 3. In patients with elevated CK-MB (or cTn) in whom the biomarker levels have not been shown to be stable or falling: the CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above plus new ST-segment elevation or depression plus signs consistent with a clinically relevant MI, such as new-onset or worsening heart failure or sustained hypotension).

Stroke	Acute episode of focal or global neurological dysfunction persisting at least 24 hours with presence of acute infarction as demonstrated by imaging.	Acute episode of focal or global neurological dysfunction caused by central nervous system (CNS) vascular injury as a result of haemorrhage or infarction. CNS includes brain, spinal cord and retina. Classified as ischaemic (acute episode of focal cerebral, spinal, or retinal dysfunction caused by CNS infarction. Evidence of infarction is defined as ”Pathological, imaging, or other objective evidence of acute cerebral, spinal cord, or retinal focal ischaemic injury in a defined vascular distribution; or in absence of the above ie, imaging or autopsy unavailable- clinical evidence of cerebral, spinal cord, or retinal focal ischaemic injury is based on symptoms persisting ≥24 hours or until death, and other aetiologies excluded), haemorrhagic (cerebral haemorrhage, stroke caused by intracerebral	Sudden onset of vertigo, numbness, aphasia, dysarthria or central neurologic deficit secondary to vascular lesions of the brain such as haemorrhage, embolism, thrombosis, or rupturing aneurysm, that persists for >72 hours. Haemorrhagic: a stroke with documentation on imaging (ie, CT scan or MRI of haemorrhage in the cerebral parenchyma, or a subdural or subarachnoid haemorrhage). Evidence of haemorrhagic stroke obtained from lumbar puncture, neurosurgery, or autopsy can also confirm the diagnosis. Non-haemorrhagic: a focal neurological deficit that results from a thrombus or embolus (and not due to haemorrhage) that appears and is still partially evident for more than 24 hours. Unknown/no imaging performed: if the type of stroke could not be	Acute onset of a neurological deficit that persists for at least 24 hours and is the result of a disturbance of the cerebral circulation due to ischaemia or haemorrhage. Deficits that last ≤ 24 hours are due to transient ischaemic neurological attack and are not classified in this category.	Sudden onset of vertigo, numbness, aphasia, dysarthria or central neurologic deficit secondary to vascular lesions of the brain such as haemorrhage, embolism, thrombosis, or rupturing aneurysm, that persist for >72 hours. Haemorrhagic: a stroke with documentation on imaging (ie, CT scan or MRI of haemorrhage in the cerebral parenchyma, or a subdural or subarachnoid haemorrhage). Evidence of haemorrhagic stroke obtained from lumbar puncture, neuro surgery, or autopsy can also confirm the diagnosis. Non-haemorrhagic: a focal neurological deficit that results from a thrombus or embolus (and not due to haemorrhage) that appears and is still partially evident for more than 24 hours. Unknown/no imaging performed: if the type of stroke could not be	Acute symptomatic episode of neurological dysfunction, more than 24 hours in duration in the absence of therapeutic intervention or death, due to cerebral, spinal or retinal tissue injury as evidenced by neuroimaging or lumbar puncture. It includes the following sub-classifications: Ischaemic stroke: infarction due to prolonged ischaemia. Causes include (but are not limited to) arterial and venous thrombosis, embolism, and systemic hypoperfusion. Haemorrhagic stroke: caused by a non-traumatic intra-parenchymal, intraventricular or subarachnoid haemorrhage Undetermined: stroke with insufficient information to determine ischaemic or haemorrhagic cause.

		haemorrhage, stroke caused by subarachnoid haemorrhage) or not otherwise specified (episode of acute neurological dysfunction presumed to be caused by ischaemia or haemorrhage, persisting ≥24 hours or until death, but without sufficient evidence to be classified as one of the above).	determined by imaging or other means.		determined by imaging or other means (from lumbar puncture, neuro-surgery, or autopsy).	
Bleeding	Adjudicated according to the TIMI classification	Adjudicated according to the BARC, TIMI and GUSTO classification.	Adjudicated according to the BARC and TIMI classification.	Adjudicated according to the BARC, TIMI and GUSTO classification.	Adjudicated according to the BARC type 3 or 5 and TIMI classification.	Adjudicated according to the BARC, TIMI, GUSTO and ISTH classification.

Stent thrombosis	NA	Defined by the Academic Research Consortium as definite (angiographic or pathological confirmation of stent thrombosis), probable (any unexplained death within the first 30 days. Irrespective of the time after the index procedure, any MI which is related to documented acute ischaemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause) or possible (occurred with any unexplained death from 30 days following intra-coronary stenting until end of trial follow-up).	Defined by the Academic Research Consortium as definite (angiographic or pathological confirmation of stent thrombosis), probable (any unexplained death within the first 30 days. Irrespective of the time after the index procedure, any MI which is related to documented acute ischaemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause) or possible (occurred with any unexplained death from 30 days following intra-coronary stenting until end of trial follow-up).	Defined by the Academic Research Consortium as definite (angiographic or pathological confirmation of stent thrombosis), probable (any unexplained death within the first 30 days. Irrespective of the time after the index procedure, any MI which is related to documented acute ischaemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause) or possible (occurred with any unexplained death from 30 days following intra-coronary stenting until end of trial follow-up).	Defined by the Academic Research Consortium as definite (angiographic or pathological confirmation of stent thrombosis), probable (any unexplained death within the first 30 days. Irrespective of the time after the index procedure, any MI which is related to documented acute ischaemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause) or possible (occurred with any unexplained death from 30 days following intra-coronary stenting until end of trial follow-up).	Classified according to the level of certainty as: Definite stent thrombosis: is highly specific and requires angiographic/pathological confirmation of stent thrombosis in or within 5 mm of the stent in the setting of at least one of the following criteria with a 48-hour time window: acute ischaemic symptoms at rest; new ischaemic ECG changes; typical rise and fall in cardiac biomarkers. Probable stent thrombosis: any unexplained death within the first 30 days following PCI; any MI at any time following PCI that is related to documented acute ischaemia in the territory of the implanted stent, in the absence of angiographic/pathological confirmation of stent thrombosis and no other obvious cause. Possible stent thrombosis: any unexplained death after the first 30 days following PCI until the end of trial follow-up.

ARC=Academic Research Consortium; BARC=Bleeding Academy Research Consortium; CABG=coronary artery bypass grafting; CK-MB=creatine kinase myocardial band; cTn=cardiac Troponin; DACAB=Different Antiplatelet Therapy Strategy After Coronary Artery Bypass Graft Surgery; GLASSY=GLOBAL LEADERS Adjudication Sub-Study; GUSTO=Global Use of Strategies to Open Occluded Coronary Arteries; ISTH=International Society on Thrombosis and Haemostasis; LBBB=left bundle branch block; MI=myocardial infarction; PAD=peripheral artery disease; PCI=percutaneous Coronary Intervention; SMART-CHOICE=Smart Angioplasty Research Team: Comparison Between P2Y12 Antagonist Monotherapy vs Dual Antiplatelet Therapy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents; STOPDAPT-2=Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent; TICO=Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus-eluting Stent for Acute Coronary Syndrome; TIMI=Thrombolysis in Myocardial Infarction; TWILIGHT=Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention; ULN=upper limit of normal.

Supplementary table D. Risk of bias in the included trials as assessed by the Cochrane risk of bias assessment tool

Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
DACAB	P2Y12i monotherapy	DAPT	Death, MI, or stroke	1.26	+	!	+	+	+	!
GLASSY	P2Y12i monotherapy	DAPT	Death, MI, or stroke	32.5	+	!	+	+	+	!
SMART-CHOICE	P2Y12i monotherapy	DAPT	Death, MI, or stroke	8.64	+	!	+	+	+	!
STOPDAPT-2	P2Y12i monotherapy	DAPT	Death, MI, or stroke	11.91	+	!	+	+	+	!
TICO	P2Y12i monotherapy	DAPT	Death, MI, or stroke	5.3	+	!	+	+	+	!
TWILIGHT	P2Y12i monotherapy	DAPT	Death, MI, or stroke	40.38	+	+	+	+	+	+

+ Low risk
! Some concerns
- High risk

D1 Randomisation process
D2 Deviations from the intended interventions
D3 Missing outcome data
D4 Measurement of the outcome
D5 Selection of the reported result

DACAB=Different Antiplatelet Therapy Strategy After Coronary Artery Bypass Graft Surgery; GLASSY=GLOBAL LEADERS Adjudication Sub-Study; SMART-CHOICE=Smart Angioplasty Research Team: Comparison Between P2Y12 Antagonist Monotherapy vs Dual Antiplatelet Therapy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents; STOPDAPT-2=Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent; TICO=Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus-eluting Stent for Acute Coronary Syndrome; TWILIGHT=Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention.

Supplementary table E. Baseline characteristics stratified by trial

	DACAB		GLASSY		SMART-CHOICE		STOPDAPT-2		TICO		TWILIGHT	
	P2Y12i	**DAPT**	**P2Y12i**	**DAPT**	**P2Y12i**	**DAPT**	**P2Y12i**	**DAPT**	**P2Y12i**	**DAPT**	**P2Y12i**	**DAPT**
	N = 166	N = 168	N = 3753	N = 3756	N = 1455	N = 1471	N = 1496	N = 1507	N = 1499	N = 1505	N = 3265	N = 3267
Age, years	63.3 (8.3)	63.5 (8.2)	64.9 (10.3)	64.8 (10.3)	64.6 (10.6)	64.3 (10.7)	68.2 (10.9)	69.1 (10.4)	60.6 (10.8)	61.1 (10.7)	65.2 (10.2)	65.2 (10.3)
Age ≥65 years	74 (45%)	76 (45%)	1968 (52%)	1938 (52%)	766 (53%)	725 (49%)	1006 (67%)	1075 (71%)	567 (38%)	590 (39%)	1713 (53%)	1696 (52%)
Female sex	32 (19%)	34 (20%)	894 (24%)	875 (23%)	389 (27%)	380 (26%)	316 (21%)	355 (24%)	315 (21%)	299 (20%)	771 (24%)	763 (2%)
Height, meters	NA	NA	1.7 (0.1)	1.7 (0.1)	1.6 (0.1)	1.6 (0.1)	1.6 (0.1)	1.6 (0.1)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)
Weight, kg	NA	NA	82.1 (15.3)	82.1 (15.1)	65.9 (11.0)	66.6 (11.4)	65.0 (12.4)	63.9 (12.2)	68.9 (11.6)	68.8 (11.6)	84.3 (19.2)	84.0 (18.8)
BMI, kg/m^2	NA	NA	28.0 (4.5)	27.9 (4.5)	24.5 (3.1)	24.7 (3.2)	24.4 (3.5)	24.2 (3.5)	24.9 (3.2)	25.0 (3.3)	28.9 (5.6)	28.9 (5.6)
Region												
Asia	166 (100%)	168 (100%)	0 (0%)	0 (0%)	1455 (100%)	1471 (100%)	1496 (100%)	1507 (100%)	1499 (100%)	1505 (100%)	530 (16%)	521 (16%)
N. America	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	(0%)	(0.0%)	0 (0%)	(0%)	1484 (46%)	1488 (46%)
W. Europe	0 (0%)	0 (0%)	3002 (80%)	3009 (80%)	0 (0%)	0 (0%)	(0%)	0 (0%)	0 (0%)	(0%)	915 (28%)	922 (28%)
E. Europe	0 (0%)	0 (0%)	751 (20%)	747 (20%)	0 (0%))	0 (0%)	(0%)	0 (0%)	0 (0%)	(0%)	336 (10%)	336 (10%)
Diabetes	75 (45%)	75 (45%)	912 (24%)	892 (24%)	552 (38%)	536 (36%)	584 (39%)	573 (38%)	408 (27%)	407 (27%)	1213 (37%)	1192 (37%)
ID Diabetes	NA	NA	262 (7%)	267 (7%)	30 (5%)	53 (10%)	104 (7%)	98 (7%)	42 (3%)	37 (3%)	308 (9%)	342 (11%)
Current smoker	57 (34%)	59 (35%)	1068 (29%)	1092 (29%)	411 (28%)	356 (24%)	397 (27%)	311 (21%)	545 (36%)	575 (38%)	656 (20%)	744 (23%)
Hypercholesterolaemia	124 (75%)	121 (72%)	2378 (66%)	2454 (68%)	649 (45%)	670 (46%)	1114 (75%)	1127 (75%)	907 (61%)	912 (61%)	2126 (65%)	2113 (65%)
Hypertension	122 (74%)	127 (76%)	2724 (73%)	2712 (72%)	892 (61%)	903 (61%)	1102 (74%)	1115 (74%)	743 (50%)	765 (51%)	2402 (74%)	2398 (73%)
Liver disease	NA	NA	0 (0%)	0 (0%)	NA	NA	6 (1%)	4 (0%)	0 (0%)	0 (0%)	15 (1%)	8 (0%)
PAD	27 16%)	26 (16%)	250 (7%)	297 (8%)	22 (2%)	27 (2%)	96 (6%)	100 (7%)	NA	NA	238 (7%)	240 (7%)
Previous MI	60 (36%)	53 (32%)	860 (23%)	886 (24%)	60 (4%)	65 (4%)	207 (14%)	199 (13%)	62 (4%)	49 (3%)	972 (30%)	965 (30%)
Previous PCI	0 (0%)	0 (0%)	1227 (33%)	1280 (34%)	154 (11%)	170 (12%)	503 (34%)	528 (35%)	134 (9%)	125 (8%)	1422 (44%)	1416 (43%)
Previous CABG	0 (0%)	0 (0%)	204 (5%)	238 (6%)	18 (1%)	10 (1%)	17 (1%)	42 (3%)	8 (1%)	10 (1%)	359 (11%)	344 (11%)
Prior stroke	13 (8%)	26 (16%)	96 (3%)	98 (3%)	95 (7%)	99 (7%)	80 (5%)	105 (7%)	59 (4%)	62 (4%)	0 (0%)	0 (0%)
Prior bleeding	0 (0%)	0 (0%)	26 (1%)	22 (1%)	58 (4%)	54 (4%)	19 (1%)	28 (2%)	2 (0%)	2 (0%)	27 (1.0%)	27 (1%)
History of CKD	3 (2%)	6 (4%)	501 (13%)	489 (13%)	41 (3%)	50 (4%)	521 (35%)	525 (35%)	280 (19%)	314 (21%)	546 (17%)	547 (17%)
Chronic lung disease	5 (3%)	6 (4%)	192 (5%)	199 (5.3%)	NA	NA	40 (3%)	44 (3%)	0 (0%)	0 (0%)	166 (5%)	174 (5%)

Presentation	n = 166	n = 168	n = 3753	n = 3756	n = 1455	n = 1469	n = 1496	n = 1507	n = 1499	n = 1505	n = 3264	n = 326
CCS	63 (38%)	55 (33%)	1844 (49%)	1875 (59%)	613 (42%)	619 (42%)	934 (62%)	925 (61%)	0 (0%)	0 (0%)	1231 (38%)	1180 (36%)
ACS	103 (62%)	113 (67%)	1909 (51%)	1881 (50%)	842 (58%)	850 (58%)	562 (38%)	582 (39%)	1499 (100%)	1505 (100%)	2033 (62%)	2087 (64%)
Unstable angina	97 (94%)	108 (96%)	486 (26%)	498 (27%)	458 (54%)	478 (56%)	192 (34%)	214 (37%)	437 (29%)	482 (32%)	1082 (53%)	1047 (50%)
Non-STEMI	6 (6%)	5 (4%)	750 (39%)	731 (39%)	229 (27%)	226 (27%)	81(14%)	99 (17%)	526 (35%)	478 (32%)	951 (47%)	1040 (50%)
STEMI	0 (0%)	0 (0%)	673 (35%)	652 (35%)	155 (18%)	146 (17%)	289 (51%)	269 (46%)	536 (36%)	545 (36%)	0 (0%)	0 (0%)
Aspirin on admission	151 (91%)	151 (89%)	2338 (62%)	2390 (64%)	289 (20%)	292 (20%)	NA	NA	1442 (96%)	1428 (95%)	2361 (72%)	2340 (72%)
PRECISE-DAPT*	NA	NA	16.6 (8.8)	16.2 (8.5)	17.1 (11.5)	17.1 (11.6)	16.6 (10.7)	17.3 (11.0)	14.6 (8.5)	15.3 (8.9)	17.0 (8.9)	17.0 (9.2)
PRECISE-DAPT score ≥25	NA	NA	591 (17%)	556 (16%)	277 (20%)	278 (19%)	271 (18.2%)	295 (20%)	180 (12%)	195 (13%)	531 (17%)	556 (18%)
Creatinine clearance, ml/min	84.3 (71.9;103.0)	85.2 (72.7;99.8)	83.2 (69.4;97.1)	82.6 (69.0;97.5)	85.6 (70.0;100.9)	84.2 (70.3;99.6)	92.7 (75.2;110.8)	91.7 (75.4;107.2)	89.2 (73.6;104.8)	87.2 (72.6;103.0)	81.0 (68.2;95.3)	81.1 (67.1;96.5)
Haemoglobin, g/dl	13.2 (1.4)	13.1 (1.4)	14.2 (1.5)	14.3 (1.6)	13.8 (2.1)	13.8 (1.8)	13.5 (1.8)	13.5 (3.9)	14.3 (1.7)	14.3 (1.8)	13.9 (1.6)	13.9 (1.7)
LVEF, %	61.0 (7.4)	60.4 (8.5)	52.7 (10.6)	53.4 (10.7)	60.2 (10.7)	60.1 (10.5)	59.8 (10.2)	59.7 (10.6)	54.8 (11.7)	54.6 (12.2)	54.0 (9.4)	53.6 (10.0)

Data expressed as n (%) or means±standard deviations or median [IQR].
*The PRECISE-DAPT score includes 5 items: age, creatinine clearance, white-blood-cell count, haemoglobin, and history of bleeding.
ACS=acute coronary syndrome; BMI=body-mass index; CABG=coronary artery bypass grafting; CCS=chronic coronary syndrome; CKD=chronic kidney disease; g/dl=grams per deciliter; LVEF=left ventricular ejection fraction; MDRD=Modification of Diet in Renal Disease; MI=myocardial infarction; ml/min=milliliter per minute; PAD=peripheral arterial disease; PCI=percutaneous coronary intervention; STEMI=ST-segment elevation myocardial infarction.

Supplementary table F. Procedural characteristics

	Primary study population (N=23308)	$P2Y_{12}$ Inhibitor (N=11634)	Aspirin + $P2Y_{12}$ Inhibitor (N=11674)	Difference (95% CI)	p value
Radial access	n=22941, 6402 (71.5%)	n=11451, 8153 (71.2%)	n=11490, 8249 (71.8%)	-0.6% (-1.8% to 0.6%)	0.319
Femoral access	n=22941, 6344 (27.7%)	n=11451, 3199 (27.9%)	n=11490, 3145 (27.4%)	0.6% (-0.6% to 1.7%)	0.339
Brachial access	n=22941, 221 (1.0%)	n=11451, 112 (1.0%)	n=11490, 109 (0.9%)	0.0% (-0.2% to 0.3%)	0.820
Unfractioned heparin	n=20382, 13349 (65.5%)	n=10179, 6690 (65.7%)	n=10203, 6659 (65.3%)	0.5% (-0.8% to 1.8%)	0.491
LMWH	n=17379, 1163 (6.7%)	n=8683, 567 (6.5%)	n=8696, 596 (6.9%)	-0.3% (-1.1% to 0.4%)	0.393
GP IIb/IIIa inhibitors	n=17379, 861 (5.0%)	n=8683, 417 (4.8%)	n=8696, 444 (5.1%)	-0.3% (-0.9% to 0.3%)	0.357
Bivalirudin	n=20382, 7741 (38.0%)	n=10179, 3872 (38.0%)	n=10203, 3869 (37.9%)	0.1% (-1.2% to 1.5%)	0.861
PCI	**(n=22974)**	**n=11468**	**n=11468**		
Number of vessels treated at index PCI	n=22909	n=11435	n=11474		0.123
One vessel	18874 (82.4%)	9460 (82.7%)	9414 (82.0%)	0.7% (-0.3% to 1.7%)	0.176
Two vessels	3682 (16.1%)	1816 (15.9%)	1866 (16.3%)	-0.4% (-1.3% to 0.6%)	0.439
Three vessels or more	353 (1.5%)	159 (1.4%)	194 (1.7%)	-0.3% (-0.6% to 0.0%)	0.068
Number of lesions treated at index PCI	n=22915	n=11438	n=11477		0.702
One lesion	16660 (72.7%)	8343 (72.9%)	8317 (72.5%)	0.5% (-0.7% to 1.6%)	0.423
Two lesions	4917 (21.5%)	2429 (21.2%)	2488 (21.7%)	-0.4% (-1.5% to 0.6%)	0.421
Three or more lesions	1338 (5.8%)	666 (5.8%)	672 (5.9%)	-0.0% (-0.6% to 0.6%)	0.933
LAD	n=22974, 12283 (53.5%)	n=11468, 6093 (53.1%)	n=11506, 6190 (53.8%)	-0.7% (-2.0% to 0.6%)	0.310
Left circumflex artery	n=22974, 6302 (27.4%)	n=11468, 3145 (27.4%)	n=11506, 3157 (27.4%)	0.0% (-1.2% to 1.1%)	0.981
Right coronary artery	n=22974, 7792 (33.9%)	n=11468, 3890 (33.9%)	n=11506, 3902 (33.9%)	0.0% (-1.2% to 1.2%)	0.990
Left main	n=22974, 724 (3.2%)	n=11468, 349 (3.0%)	n=11506, 375 (3.3%)	-0.2% (-0.7% to 0.2%)	0.349
Venous or arterial graft	n=20048, 230 (1.1%)	n=10013, 109 (1.1%)	n=10035, 121 (1.2%)	0.1% (-0.2% to 0.4%)	0.436
Bifurcation	n=22921, 3580 (15.6%)	n=11440, 1778 (15.5%)	n=11481, 1802 (15.7%)	-0.2% (-1.1% to 0.8%)	0.749
Bifurcation lesion treated with at least 2 stents	n=20048, 664 (3.3%)	n=10013, 330 (3.3%)	n=10035, 334 (3.3%)	-0.0% (-0.5% to 0.5%)	0.897
Thrombus	n=22923, 3106 (13.5%)	n=11441, 1527 (13.3%)	n=11482, 1579 (13.8%)	-0.5% (-1.3% to 0.5%)	0.370
TIMI pre-PCI 0-1	n=18846, 4034 (21.4%)	n=9397, 2052 (21.8%)	n=9449, 1982 (21.0%)	0.9% (-0.3% to 2.0%)	0.150

N. of implanted stents	n=16349, 1.0 (1.0 to 2.0)	n=8159, 1.0 (1.0 to 2.0)	n=8190, 1.0 (1.0 to 2.0)	0.01 (-0.02 to 0.03)	0.387
Overlapping stents	n=16442, 4230 (25.7%)	n=8203, 2165 (26.4%)	n=8239, 2065 (25.1%)	1.3% (0.0% to 2.7%)	0.051
Total stent length	n=22879, 28.0 (18.0 to 45.0)	n=11424, 28.0 (18.0 to 46.0)	n=11455, 28.0 (18.0 to 45.0)	0.06 (-0.54 to 0.65)	0.612
New generation DES	n=22881, 22831 (99.8%)	n=11424, 11403 (99.8%)	n=11457, 11428 (99.7%)	0.1% (-0.1% to 0.2%)	0.262
Minimum diameter of all implanted stents (SD)	n=22879, 2.92 (0.48)	n=11424, 2.93 (0.48)	n=11455, 2.92 (0.48)	0.00 (-0.01 to 0.01)	0.947
Maximum diameter of all implanted stents (SD)	n=22879, 3.13 (0.48)	n=11424, 3.13 (0.48)	n=11455, 3.13 (0.48)	0.00 (-0.01 to 0.01)	0.952
Aspirin at randomisation	n=23308, 11674 (50.1%)	n=11634, 0 (0.0%)	n=11674, 11674 (100%)	-100% (-100% to -100%)	<0.001
$P2Y_{12}$ at randomisation	n=23308, 23308 (100.0%)	n=11634, 11634 (100%)	n=11674, 11674 (100%)	0.0% (0.0% to 0.0%)	-
Clopidogrel	n=23308, 6883 (29.5%)	n=11634, 2586 (22.2%)	n=11674, 4297 (36.8%)	-14.6% (-15.7% to -13.4%)	<0.001
Prasugrel	n=23308, 232 (1.0%)	n=11634, 92 (0.8%)	n=11674, 140 (1.2%)	-0.4% (-0.7% to -0.2%)	0.002
Ticagrelor	n=23308, 16193 (69.5%)	n=11634, 8956 (77.0%)	n=11674, 7237 (62.0%)	15.0% (13.8% to 16.2%)	<0.001
ACE-inhibitors or ARBs at randomisation	n=23289, 14901 (64.0%)	n=11623, 7495 (64.5%)	n=11666, 7406 (63.5%)	1.0% (-0.2% to 2.2%)	0.112
ß-blockers at randomisation	n=23292, 16183 (69.5%)	n=11625, 8078 (69.5%)	n=11667, 8105 (69.5%)	0.0% (-1.2% to 1.2%)	0.975
Statins at randomisation	n=22986, 21765 (94.7%)	n=11476, 10866 (94.7%)	n=11510, 10899 (94.7%)	0.0% (-0.6% to 0.6%)	0.981
PPI at randomisation	n=16891, 10013 (59.3%)	n=8433, 5034 (59.7%)	n=8458, 4979 (58.9%)	0.8% (-0.7% to 2.3%)	0.274
CABG	**(n=334)**	**(n=166)**	**(n=168)**		
LIMA	n=334, 285 (85.3%)	n=166, 144 (86.7%)	n=168, 141 (83.9%)	2.8% (-4.8% to 10.4%)	0.467
Number of arterial grafts	n=334, 1.0 (1.0 to 1.0)	n=166, 1.0 (1.0 to 1.0)	n=168, 1.0 (1.0 to 1.0)	0.03 (-0.05 to 0.12)	0.602
Number of venous grafts	n=334, 3.0 (2.0 to 3.0)	n=166, 3.0 (2.0 to 3.0)	n=168, 3.0 (2.0 to 3.0)	0.04 (-0.14 to 0.22)	0.726
On-pump CABG	n=334, 259 (77.5%)	n=166, 130 (78.3%)	n=168, 129 (76.8%)	1.5% (-7.4% to 10.5%)	0.738

Data expressed as n (%) or means±standard deviations or median [IQR]
ACS=acute coronary syndrome; BMI=body-mass index; CABG=coronary artery bypass grafting; CCS=chronic coronary syndrome; CKD=chronic kidney disease; DES=drug-eluting stent; GP=glycoprotein; LAD=left anterior descending artery; LIMA=left internal mammary artery; LMWH=low-molecular-weight heparin; LVEF=left ventricular ejection fraction; MDRD=Modification of Diet in Renal Disease; MI=myocardial infarction; PAD=peripheral arterial disease; PCI=percutaneous coronary intervention; PPI=proton pump inhibitors; STEMI=ST-segment elevation myocardial infarction; TIMI=Thrombolysis in Myocardial Infarction.

Supplementary table G. Procedural characteristics stratified by trial

	DACAB		GLASSY		SMART-CHOICE		STOPDAPT-2		TICO		TWILIGHT	
	P2Y12i	**DAPT**	**P2Y12i**	**DAPT**	**P2Y12i**	**DAPT**	**P2Y12i**	**DAPT**	**P2Y12i**	**DAPT**	**P2Y12i**	**DAPT**
	N = 166	N = 168	N = 3753	N = 3756	N = 1455	N = 1471	N = 1496	N = 1507	N = 1499	N = 1505	N = 3265	N = 3267
Radial access	NA	NA	2728 (73%)	2765 (74%)	1065 (73%)	1074 (73%)	1216 (81%)	1254 (83%)	821 (55%)	851 (56%)	2323 (71.1%)	2305 (70.6%)
Femoral access	NA	NA	998 (27%)	959 (26%)	390 (27%)	397 (27%)	201 (13%)	180 (12%)	678 (45%)	654 (43%)	932 (28%)	955 (29%)
Brachial access	NA	NA	30 (1%)	35 (1%)	0 (0%)	0 (0%)	79 (5%)	73 (5%)	0 (0%)	0 (0%)	3 (0.1%)	1 (0%)
Unfractioned heparin	166 (100%)	168 (100%)	1297 (35%)	1280 (34%)	NA	NA	1496 (100%)	1507 (100%)	930 (62%)	936 (62%)	2801 (86%)	2768 (85%)
LMWH	0 (0%)	0 (0%)	16 (0.4%)	20 (0.5%)	NA	NA	NA	NA	120 (8%)	139 (9%)	431 (13%)	437 (13%)
GP IIb/IIIa inhibitors	0 (0%)	0 (0%)	100 (3%)	109 (3%)	NA	NA	NA	NA	99 (7%)	96 (6%)	218 (7%)	239 (7%)
Bivalirudin	0 (0%)	0 (0%)	3468 (92%)	3446 (92%)	NA	NA	0 (0%)	0 (0%)	0 (0%)	0 (0%)	404 (12%)	423 (13%)
PCI	n = 0	n = 0	n = 3753	n = 3756	n = 1455	n = 1471	n = 1496	n = 1507	n = 1499	n = 1505	n = 3265	n = 3267
N. vessels treated at index PCI	NA	NA	n = 3723	n = 3727	n = 1455	n = 1471	n = 1493	n = 1504	n = 1499	n = 1505	n = 3265	n = 3267
One vessel	NA	NA	3190 (86%)	3177 (85%)	1141 (78%)	1126 (76%)	1420 (95%)	1409 (94%)	1249 (83%)	1242 (82%)	2460 (75%)	2460 (75%)
Two vessels	NA	NA	506 (14%)	517 (14%)	285 (20%)	305 (21%)	68 (5%)	90 (6%)	229 (15%)	239 (16%)	728 (22%)	715 (22%)
Three vessels or more	NA	NA	27 (0.7%)	33 (0.9%)	29 (2%)	40 (3%)	5 (0.3%)	5 (0.3%)	21 (1%)	24 (2%)	77 (2%)	92 (3%)
N. lesions treated at index PCI	n = 0	n = 0	n = 3723	n = 3740	n = 1455	n = 1471	n = 1496	n = 1507	n = 1499	n = 1505	n = 3265	n = 3267
One lesion	NA	NA	2824 (76%)	2818 (76%)	1041 (71%)	1022 (69%)	1339 (89%)	1323 (88%)	1197 (80%)	1197 (79%)	1942 (59%)	1957 (60%)
Two lesions	NA	NA	722 (19%)	711 (19%)	315 (22%)	346 (23%)	141 (9%)	168 (11%)	257 (17%)	257 (17%)	994 (30%)	1006 (31%)
Three or more lesions	NA	NA	177 (5%)	198 (5%)	99 (7%)	103 (7%)	16 (1%)	16 (1%)	45 (3%)	51 (3%)	329 (10%)	304 (9%)
LAD	NA	NA	1712 (46%)	1721 (46%)	877 (60%)	934 (63%)	825 (55%)	853 (57%)	860 (57%)	862 (57%)	1819 (56%)	1820 (56%)
Left circumflex artery	NA	NA	1090 (29%)	1098 (29%)	388 (27%)	370 (25%)	268 (18%)	305 (20%)	345 (23%)	339 (22%)	1054 (32%)	1045 (32%)
Right coronary artery	NA	NA	1288 (34%)	1276 (34%)	509 (35%)	514 (35%)	435 (29%)	409 (27%)	518 (35%)	546 (36%)	1140 (35%)	1157 (35%)
Left main	NA	NA	99 (3%)	107 (3%)	22 (1%)	35 (2%)	43 (3%)	37 (2%)	48 (3%)	44 (3%)	137 (4%)	152 (5%)
Venous or arterial graft	NA	NA	44 (1%)	46 (1%)	0 (0%)	0 (0%)	3 (0.2%)	3 (0.2%)	0 (0%)	0 (0%)	62 (2%)	72 (2%)
Bifurcation	NA	NA	560 (15%)	570 (15%)	192 (13%)	180 (12%)	374 (25%)	392 (26%)	250 (17%)	272 (18%)	402 (12%)	388 (12%)
Bifurcation lesion treated with at least 2 stents	NA	NA	184 (5%)	192 (5%)	NA	NA	9 (0.6%)	7 (0.5%)	28 (2%)	25 (2%)	109 (3%)	110 (3%)
Thrombus	NA	NA	301 (8%)	349 (9%)	108 (7%)	111 (7%)	207 (14%)	203 (13%)	558 (37%)	545 (36%)	353 (11%)	371 (11%)

TIMI pre-PCI 0-1	NA	NA	636 (18%)	655 (18%)	NA	NA	271 (18%)	259 (17%)	694 (46%)	652 (43%)	451 (16%)	416 (15%)
N. of implanted stents	NA	NA	1.0 (1.0;2.0)	1.0 (1.0;2.0)	1.0 (1.0;2.0)	1.0 (1.0;2.0)	1.0 (1.0;1.0)	1.0 (1.0;1.0)	1.0 (1.0;2.0)	1.0 (1.0;2.0)	NA	NA
Overlapping stents	NA	NA	1633 (43%)	1588 (42%)	156 (11%)	134 (9%)	216 (14%)	191 (13%)	160 (11%)	152 (10%)	NA	NA
Total stent length	NA	NA	28.0 (18.0;2.0)	28.0 (18.0;44.0)	32.0 (22.0;48.0)	30.0 (22.0;48.0)	24.0 (18.0;38.0)	28.0 (18.0;38.0)	26.0 (22.0;40.0)	30.0 (22.0;40.0)	33.0 (22.0;50.0)	33.0 (20.0;50.0)
New generation DES	NA	NA	3709 (100%)	3707 (100%)	1455 (100%)	1471 (100%)	1496 (100%)	1507 (100%)	1499 (100%)	1505 (100%)	3244 (99%)	3238 (99%)
Minimum diameter of all implanted stents (SD)	NA	NA	2.9 (0.5)	2.9 (0.5)	3.0 (0.5)	3.0 (0.5)	3.0 (0.5)	3.0 (0.5)	3.1 (0.5)	3.1 (0.4)	2.8 (0.5)	2.8 (0.5)
Maximum diameter of all implanted stents (SD)	NA	NA	3.1 (0.5)	3.1 (0.5)	3.2 (0.5)	3.2 (0.5)	3.1 (0.5)	3.1 (0.4)	3.2 (0.4)	3.2 (0.4)	3.1 (0.5)	3.1 (0.5)
Aspirin	0 (0%)	168 (100%)	0 (0%)	3756 (100%)	0 (0%)	1471 (100%)	0 (0%)	1507 (100%)	0 (0%)	1505 (100%)	0 (0%)	3267 (100%)
$P2Y_{12}$	166 (100%)	168 (100%)	3753 (100%)	3756 (100%)	1455 (100%)	1471 (100%)	1496 (100%)	1507 (100%)	1499 (100%)	1505 (100%)	3265 (100%)	3267 (100%)
Clopidogrel	0 (0%)	0 (0%)	0 (0%)	1722 (46%)	1122 (77%)	1143 (78%)	1464 (98%)	1432 (95%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Prasugrel	0 (0%)	0 (0%)	0 (0%)	0 (0%)	60 (4%)	65 (4%)	32 (2%)	75 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Ticagrelor	166 (100%)	168 (100%)	3753 (100%)	2034 (54%)	273 (19%)	263 (18%)	0 (0%)	0 (0%)	1499 (100%)	1505 (100%)	3265 (100%)	3267 (100%)
ACE-inhibitors or ARBs	98 (59%)	87 (52%)	2283 (61%)	2267 (60%)	831 (57%)	787 (53%)	943 (63%)	957 (63%)	998 (67%)	991 (66%)	2342 (72%)	2317 (71%)
ß-blockers	149 (90%)	153 (91%)	2923 (78%)	2951 (79%)	767 (53%)	769 (52%)	671 (45%)	642 (43%)	990 (66%)	991 (66%)	2578 (79%)	2599 (80%)
Statins	155 (93%)	157 (93%)	3456 (92%)	3463 (92%)	1379 (95%)	1384 (94%)	1314 (98%)	1316 (98%)	1466 (98%)	1477 (98%)	3096 (95%)	3102 (95%)
PPI	108 (65%)	104 (62%)	2069 (55%)	2037 (54%)	NA	NA	1187 (95%)	1191 (94%)	NA	NA	1670 (51%)	1647 (50%)
CABG	n = 166	n = 168	n = 0	n = 0	n = 0	n = 0	n = 0	n = 0	n = 0	n = 0	n = 0	n = 0
LIMA	144 (87%)	141 (84%)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Number of arterial grafts	1.0 (1.0;1.0)	1.0 (1.0;1.0)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Number of venous grafts	3.0 (2.0;3.0)	3.0 (2.0;3.0)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
On-pump CABG	130 (78%)	129 (78%)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Data expressed as n (%) or means±standard deviations or median [IQR]
ACS=acute coronary syndrome; BMI=body-mass index; CABG=coronary artery bypass grafting; CCS=chronic coronary syndrome; CKD=chronic kidney disease; DES=drug-eluting stent; GP=glycoprotein; LAD=left anterior descending artery; LIMA=left internal mammary artery; LMWH=low-molecular-weight heparin; LVEF=left ventricular ejection fraction; MDRD=Modification of Diet in Renal Disease; MI=myocardial infarction; PAD=peripheral arterial disease; PCI=percutaneous coronary intervention; PPI=proton pump inhibitors; STEMI=ST-segment elevation myocardial infarction; TIMI=Thrombolysis in Myocardial Infarction.

Supplementary table H. One step mixed-effect Cox regression model for the ITT population including the initial DAPT phase after randomisation in GLASSY, SMART-CHOICE, STOPDAPT-2, and TICO trials

Outcome	$P2Y_{12}$ Inhibitor (N=11747)	Aspirin + $P2Y_{12}$ Inhibitor (N=11762)	HR (95% CI)	Tau^2	p value
Death, MI, or stroke	398 (3.98%)	430 (4.29%)	0.97 (0.84 to 1.11)	0.00	0.644
Death or MI	336 (3.36%)	373 (3.72%)	0.95 (0.82 to 1.10)	0.00	0.477
Death					
All cause	146 (1.26%)	179 (1.54%)	0.82 (0.66 to 1.02)	0.00	0.072
Cardiovascular	93 (0.8%)	126 (1.08%)	0.74 (0.57 to 0.97)	0.00	0.027
Non-cardiovascular	53 (0.46%)	52 (0.45%)	1.02 (0.70 to 1.50)	0.05	0.907
Myocardial infarction	205 (1.78%)	220 (1.91%)	0.93 (0.77 to 1.13)	0.00	0.482
Stroke					
Any	75 (0.65%)	68 (0.59%)	1.11 (0.80 to 1.54)	0.11	0.546
Ischaemic	51 (0.51%)	52 (0.51%)	0.98 (0.67 to 1.45)	0.07	0.932
Haemorrhagic	12 (0.12%)	4 (0.04%)	3.01 (0.97 to 9.32)	0.00	0.057
Stent thrombosis					
Definite	42 (0.37%)	45 (0.39%)	0.93 (0.61 to 1.42)	0.00	0.752
Probable	19 (0.17%)	16 (0.14%)	1.19 (0.61 to 2.31)	0.00	0.608
Possible	27 (0.32%)	48 (0.57%)	0.56 (0.35 to 0.90)	0.00	0.017
Definite or probable	59 (0.51%)	59 (0.51%)	1.00 (0.70 to 1.44)	0.00	0.995
Any	80 (0.81%)	103 (1.04%)	0.78 (0.58 to 1.04)	0.02	0.092
BARC bleeding					
2, 3 or 5	430 (4.41%)	620 (6.42%)	0.61 (0.48 to 0.79)	0.10	<0.001
3 or 5	177 (1.56%)	268 (2.36%)	0.66 (0.55 to 0.80)	0.08	<0.001
5	8 (0.08%)	10 (0.12%)	0.80 (0.32 to 2.03)	0.67	0.642
TIMI bleeding					
Major	85 (0.84%)	128 (1.27%)	0.67 (0.51 to 0.88)	0.19	0.004
Minor	167 (1.67%)	272 (2.72%)	0.61 (0.50 to 0.74)	0.00	<0.001
Major or minor	250 (2.92%)	395 (4.63%)	0.74 (0.50 to 1.11)	0.07	0.143
NACE	544 (4.77%)	652 (5.73%)	0.83 (0.74 to 0.94)	0.00	0.002

P-values are two-sided for superiority.
BARC=Bleeding Academy Research Consortium; CI=confidence interval; HR=hazard ratio; ITT=intention to treat; MI=myocardial infarction; NACE=net adverse clinical events, defined as a composite of all-cause death, myocardial infarction, stroke, or BARC type 3 or 5 bleeding; TIMI=Thrombolysis in Myocardial Infarction.

Supplementary table I. One step mixed-effect Cox regression model for the ITT population excluding patients with MI, ischaemic stroke, or TVR occurring during the initial DAPT phase after randomisation in GLASSY, SMART-CHOICE, STOPDAPT-2 and TICO trials

Outcome	$P2Y_{12}$ Inhibitor (N=11574)	Aspirin + $P2Y_{12}$ Inhibitor (N=11608)	HR (95% CI)	Tau^2	p value
Death, MI, or stroke	301 (2.93%)	331 (3.32%)	0.91 (0.78 to 1.07)	0.00	0.257
Death or MI	257 (2.48%)	293 (2.97%)	0.88 (0.74 to 1.04)	0.00	0.136
Death					
All cause	106 (0.98%)	134 (1.38%)	0.81 (0.62 to 1.04)	0.00	0.099
Cardiovascular	60 (0.56%)	87 (0.88%)	0.70 (0.50 to 0.97)	0.00	0.034
Non-cardiovascular	42 (0.38%)	42 (0.46%)	1.03 (0.67 to 1.58)	0.15	0.895
Myocardial infarction	166 (1.63%)	177 (1.76%)	0.94 (0.76 to 1.16)	0.01	0.572
Stroke					
Any	51 (0.51%)	44 (0.4%)	1.12 (0.75 to 1.68)	0.09	0.585
Ischaemic	38 (0.39%)	35 (0.32%)	1.03 (0.65 to 1.65)	0.07	0.891
Haemorrhagic	6 (0.05%)	2 (0.02%)	2.53 (0.49 to 13.03)	0.00	0.268
Stent thrombosis					
Definite	23 (0.24%)	26 (0.29%)	0.85 (0.48 to 1.50)	0.00	0.568
Probable	6 (0.05%)	6 (0.05%)	0.84 (0.26 to 2.74)	0.00	0.768
Possible	26 (0.26%)	47 (0.51%)	0.55 (0.34 to 0.90)	0.00	0.016
Definite or probable	27 (0.27%)	31 (0.33%)	0.84 (0.50 to 1.41)	0.00	0.512
Any	51 (0.51%)	77 (0.84%)	0.65 (0.46 to 0.93)	0.00	0.018
BARC bleeding					
2, 3 or 5	294 (2.92%)	491 (4.76%)	0.59 (0.51 to 0.69)	0.00	<0.001
3 or 5	97 (0.89%)	195 (1.83%)	0.50 (0.39 to 0.63)	0.03	<0.001
5	3 (0.03%)	5 (0.06%)	0.67 (0.11 to 4.01)	0.00	0.661
TIMI bleeding					
Major	44 (0.45%)	93 (0.95%)	0.47 (0.33 to 0.68)	0.28	<0.001
Minor	136 (1.44%)	241 (2.4%)	0.56 (0.46 to 0.69)	0.00	<0.001
Major or minor	179 (1.89%)	330 (3.34%)	0.54 (0.45 to 0.64)	0.03	<0.001
NACE	382 (3.69%)	495 (4.89%)	0.77 (0.68 to 0.88)	0.02	<0.001

P-values are two-sided for superiority.
BARC=Bleeding Academy Research Consortium; CI=confidence interval; HR=hazard ratio; ITT=intention to treat; MI=myocardial infarction; NACE=net adverse clinical events, defined as a composite of all-cause death, myocardial infarction, stroke, or BARC type 3 or 5 bleeding; TIMI=Thrombolysis in Myocardial Infarction; TVR=target vessel revascularisation.

Supplementary table J. One step mixed-effect Cox regression model for the ITT population excluding patients with MI or ischaemic stroke, occurring during the initial DAPT phase after randomisation in GLASSY, SMART-CHOICE, STOPDAPT-2, and TICO trials

Outcome	$P2Y_{12}$ Inhibitor (N=11585)	Aspirin + $P2Y_{12}$ Inhibitor (N=11623)	HR (95% CI)	Tau^2	p value
Death, MI, or stroke	301 (2.93%)	333 (3.33%)	0.91 (0.78 to 1.06)	0.00	0.227
Death or MI	257 (2.48%)	294 (2.97%)	0.88 (0.74 to 1.04)	0.00	0.126
Death					
All cause	106 (0.98%)	134 (1.38%)	0.81 (0.62 to 1.04)	0.00	0.100
Cardiovascular	60 (0.56%)	87 (0.88%)	0.70 (0.50 to 0.97)	0.00	0.034
Non-cardiovascular	42 (0.38%)	42 (0.46%)	1.03 (0.67 to 1.58)	0.15	0.893
Myocardial infarction	166 (1.63%)	178 (1.77%)	0.94 (0.76 to 1.16)	0.01	0.538
Stroke					
Any	51 (0.51%)	45 (0.41%)	1.10 (0.73 to 1.64)	0.09	0.659
Ischaemic	38 (0.39%)	36 (0.33%)	1.00 (0.63 to 1.59)	0.07	0.984
Haemorrhagic	6 (0.05%)	2 (0.02%)	2.53 (0.49 to 13.03)	0.00	0.268
Stent thrombosis					
Definite	23 (0.24%)	26 (0.29%)	0.85 (0.48 to 1.50)	0.00	0.568
Probable	6 (0.05%)	6 (0.05%)	0.84 (0.26 to 2.74)	0.00	0.769
Possible	26 (0.26%)	47 (0.51%)	0.55 (0.34 to 0.90)	0.00	0.016
Definite or probable	27 (0.27%)	31 (0.33%)	0.84 (0.50 to 1.42)	0.00	0.513
Any	51 (0.51%)	77 (0.84%)	0.65 (0.46 to 0.93)	0.00	0.018
BARC bleeding					
2, 3 or 5	295 (2.92%)	492 (4.77%)	0.60 (0.52 to 0.69)	0.00	<0.001
3 or 5	97 (0.89%)	196 (1.83%)	0.49 (0.39 to 0.63)	0.02	<0.001
5	3 (0.03%)	5 (0.06%)	0.67 (0.11 to 4.01)	0.00	0.661
TIMI bleeding					
Major	44 (0.45%)	93 (0.94%)	0.47 (0.33 to 0.68)	0.28	<0.001
Minor	136 (1.44%)	241 (2.4%)	0.56 (0.46 to 0.69)	0.00	<0.001
Major or minor	179 (1.89%)	330 (3.33%)	0.54 (0.45 to 0.64)	0.03	<0.001
NACE	382 (3.69%)	498 (4.91%)	0.77 (0.67 to 0.88)	0.02	<0.001

P-values are two-sided for superiority.
BARC=Bleeding Academy Research Consortium; CI=confidence interval; HR=hazard ratio; ITT=intention to treat; MI=myocardial infarction; NACE=net adverse clinical events, defined as a composite of all-cause death, myocardial infarction, stroke, or BARC type 3 or 5 bleeding; TIMI=Thrombolysis in Myocardial Infarction.

Supplementary table K. One step mixed-effect Cox regression model for the ITT population excluding patients with BARC type 3 or 5 occurring during the initial DAPT phase after randomisation in GLASSY, SMART-CHOICE, STOPDAPT-2, and TICO trials

Outcome	$P2Y_{12}$ Inhibitor (N=11560)	Aspirin + $P2Y_{12}$ Inhibitor (N=11613)	HR (95% CI)	Tau^2	p value
Death, MI, or stroke	300 (2.93%)	334 (3.34%)	0.9 (0.77 to 1.060)	0.00	0.203
Death or MI	256 (2.48%)	295 (2.98%)	0.87 (0.74 to 1.03)	0.00	0.11
Death					
All cause	105 (0.97%)	134 (1.38%)	0.80 (0.62 to 1.03)	0.00	0.088
Cardiovascular	60 (0.56%)	89 (0.9%)	0.69 (0.49 to 0.95)	0.00	0.024
Non-cardiovascular	42 (0.38%)	42 (0.46%)	1.03 (0.67 to 1.59)	0.15	0.888
Myocardial infarction	166 (1.64%)	180 (1.78%)	0.93 (0.75 to 1.14)	0.01	0.477
Stroke					
Any	51 (0.51%)	45 (0.41%)	1.10 (0.73 to 1.64)	0.09	0.655
Ischaemic	38 (0.39%)	36 (0.33%)	1.01 (0.63 to 1.60)	0.07	0.979
Haemorrhagic	6 (0.05%)	2 (0.02%)	2.53 (0.49 to 13.03)	0.00	0.268
Stent thrombosis					
Definite	23 (0.24%)	26 (0.29%)	0.85 (0.48 to 1.50)	0.00	0.571
Probable	6 (0.05%)	7 (0.06%)	0.72 (0.23 to 2.26)	0.00	0.572
Possible	26 (0.26%)	48 (0.52%)	0.54 (0.34 to 0.88)	0.00	0.012
Definite or probable	27 (0.27%)	32 (0.34%)	0.82 (0.49 to 1.37)	0.00	0.439
Any	51 (0.51%)	79 (0.85%)	0.64 (0.45 to 0.91)	0.00	0.012
BARC bleeding					
2, 3 or 5	294 (2.92%)	492 (4.77%)	0.59 (0.51 to 0.69)	0.00	<0.001
3 or 5	96 (0.88%)	196 (1.83%)	0.49 (0.38 to 0.63)	0.03	<0.001
5	3 (0.03%)	5 (0.06%)	0.67 (0.11 to 4.02)	0.00	0.662
TIMI bleeding					
Major	44 (0.45%)	93 (0.94%)	0.47 (0.33 to 0.68)	0.29	<0.001
Minor	135 (1.43%)	241 (2.4%)	0.56 (0.45 to 0.69)	0.00	<0.001
Major or minor	178 (1.88%)	330 (3.34%)	0.53 (0.44 to 0.64)	0.04	<0.001
NACE	380 (3.68%)	499 (4.92%)	0.76 (0.67 to 0.87)	0.02	<0.001

P-values are two-sided for superiority.
BARC=Bleeding Academy Research Consortium; CI=confidence interval; HR=hazard ratio; ITT=intention to treat; MI=myocardial infarction; NACE=net adverse clinical events, defined as a composite of all-cause death, myocardial infarction, stroke, or BARC type 3 or 5 bleeding; TIMI=Thrombolysis in Myocardial Infarction.

Supplementary table L. One step mixed-effect Cox regression model for the ITT population excluding patients with BARC type 2, 3 or 5 occurring during the initial DAPT phase after randomisation in GLASSY, SMART-CHOICE, STOPDAPT-2, and TICO trials

Outcome	$P2Y_{12}$ Inhibitor (N=11498)	Aspirin + $P2Y_{12}$ Inhibitor (N=11544)	HR (95% CI)	Tau^2	p value
Death, MI, or stroke	295 (2.9%)	329 (3.32%)	0.90 (0.77 to 1.06)	0.00	0.198
Death or MI	252 (2.46%)	290 (2.95%)	0.87 (0.74 to 1.03)	0.00	0.116
Death					
All cause	102 (0.95%)	129 (1.34%)	0.81 (0.62 to 1.05)	0.00	0.108
Cardiovascular	58 (0.55%)	85 (0.86%)	0.69 (0.50 to 0.97)	0.00	0.032
Non-cardiovascular	40 (0.36%)	39 (0.43%)	1.06 (0.68 to 1.65)	0.24	0.799
Myocardial infarction	165 (1.64%)	180 (1.8%)	0.92 (0.75 to 1.14)	0.01	0.444
Stroke					
Any	50 (0.5%)	44 (0.4%)	1.10 (0.73 to 1.65)	0.09	0.654
Ischaemic	37 (0.39%)	35 (0.32%)	1.01 (0.63 to 1.61)	0.07	0.98
Haemorrhagic	6 (0.05%)	2 (0.02%)	2.52 (0.49 to 12.98)	0.00	0.27
Stent thrombosis					
Definite	23 (0.24%)	26 (0.29%)	0.85 (0.48 to 1.50)	0.00	0.572
Probable	6 (0.05%)	6 (0.05%)	0.84 (0.26 to 2.75)	0.00	0.771
Possible	25 (0.25%)	45 (0.5%)	0.56 (0.34 to 0.91)	0.00	0.019
Definite or probable	27 (0.28%)	31 (0.33%)	0.84 (0.50 to 1.42)	0.00	0.517
Any	50 (0.51%)	75 (0.82%)	0.66 (0.46 to 0.94)	0.00	0.022
BARC bleeding					
2, 3 or 5	286 (2.86%)	482 (4.71%)	0.59 (0.51 to 0.68)	0.00	<0.001
3 or 5	93 (0.86%)	190 (1.79%)	0.49 (0.38 to 0.63)	0.03	<0.001
5	3 (0.03%)	5 (0.06%)	0.67 (0.11 to 4.02)	0.00	0.662
TIMI bleeding					
Major	42 (0.44%)	91 (0.93%)	0.46 (0.32 to 0.67)	0.27	<0.001
Minor	135 (1.44%)	236 (2.37%)	0.57 (0.46 to 0.70)	0.00	<0.001
Major or minor	176 (1.87%)	324 (3.3%)	0.54 (0.45 to 0.65)	0.06	<0.001
NACE	372 (3.62%)	490 (4.87%)	0.76 (0.66 to 0.87)	0.02	<0.001

P-values are two-sided for superiority.
BARC=Bleeding Academy Research Consortium; CI=confidence interval; HR=hazard ratio; ITT=intention to treat; MI=myocardial infarction; NACE=net adverse clinical events, defined as a composite of all-cause death, myocardial infarction, stroke, or BARC type 3 or 5 bleeding; TIMI=Thrombolysis in Myocardial Infarction.

Supplementary table M. One step mixed-effect Cox regression model for ITT population excluding patients with MI, stroke, TVR, BARC type 2, 3 or 5 occurring during the initial DAPT phase after randomisation in GLASSY, SMART-CHOICE, STOPDAPT-2, and TICO trials

Outcome	$P2Y_{12}$ Inhibitor (N=11438)	Aspirin + $P2Y_{12}$ Inhibitor (N=11474)	HR (95% CI)	Tau^2	p value
Death, MI, or stroke	293 (2.89%)	321 (3.26%)	0.92 (0.78 to 1.07)	0.00	0.287
Death or MI	250 (2.45%)	283 (2.9%)	0.89 (0.75 to 1.05)	0.00	0.168
Death					
All cause	101 (0.94%)	125 (1.31%)	0.83 (0.63 to 1.07)	0.00	0.152
Cardiovascular	57 (0.54%)	82 (0.84%)	0.71 (0.50 to 0.99)	0.00	0.045
Non-cardiovascular	40 (0.36%)	39 (0.44%)	1.06 (0.68 to 1.65)	0.24	0.802
Myocardial infarction	164 (1.64%)	176 (1.77%)	0.94 (0.76 to 1.16)	0.01	0.539
Stroke					
Any	50 (0.5%)	43 (0.39%)	1.12 (0.74 to 1.69)	0.09	0.582
Ischaemic	37 (0.39%)	34 (0.31%)	1.03 (0.65 to 1.66)	0.07	0.888
Haemorrhagic	6 (0.05%)	2 (0.02%)	2.52 (0.49 to 13.0)	0.00	0.269
Stent thrombosis					
Definite	23 (0.24%)	26 (0.29%)	0.85 (0.48 to 1.5)	0.00	0.57
Probable	6 (0.05%)	5 (0.04%)	1.00 (0.29 to 3.47)	0.00	0.994
Possible	24 (0.24%)	44 (0.49%)	0.55 (0.33 to 0.9)	0.00	0.018
Definite or probable	27 (0.28%)	30 (0.32%)	0.87 (0.51 to 1.47)	0.00	0.601
Any	49 (0.5%)	73 (0.81%)	0.66 (0.46 to 0.95)	0.00	0.025
BARC bleeding					
2, 3 or 5	285 (2.86%)	480 (4.72%)	0.59 (0.51 to 0.68)	0.00	<0.001
3 or 5	93 (0.87%)	188 (1.78%)	0.49 (0.39 to 0.63)	0.03	<0.001
5	3 (0.03%)	5 (0.06%)	0.67 (0.11 to 4.01)	0.00	0.66
TIMI bleeding					
Major	42 (0.44%)	91 (0.94%)	0.46 (0.32 to 0.67)	0.27	<0.001
Minor	135 (1.44%)	235 (2.37%)	0.57 (0.46 to 0.71)	0.00	<0.001
Major or minor	176 (1.88%)	323 (3.31%)	0.54 (0.45 to 0.65)	0.05	<0.001
NACE	370 (3.62%)	480 (4.8%)	0.77 (0.67 to 0.88)	0.02	<0.001

P-values are two-sided for superiority.

BARC=Bleeding Academy Research Consortium; CI=confidence interval; HR=hazard ratio; ITT=intention to treat; MI=myocardial infarction; NACE=net adverse clinical events, defined as a composite of all-cause death, myocardial infarction, stroke, or BARC type 3 or 5 bleeding; TIMI=Thrombolysis in Myocardial Infarction; TVR=target vessel revascularisation.

Supplementary table N. One step mixed-effect Cox regression model in the on-treatment populations

	Intention to treat population					Per-protocol population				
Outcome	**$P2Y_{12}$ Inhibitor (N=10135)**	**Aspirin + $P2Y_{12}$ Inhibitor (N=10169)**	**HR (95% CI)**	**Tau^2**	**p value**	**$P2Y_{12}$ Inhibitor (N=9455)**	**Aspirin + $P2Y_{12}$ Inhibitor (N=9898)**	**HR (95% CI)**	**Tau^2**	**p value**
Death, MI, or stroke	254 (2.91%)	248 (2.98%)	1.01 (0.85 to 1.2)	0.00	0.919	239 (2.89%)	239 (2.92%)	1.02 (0.85 to 1.22)	0.00	0.859
Death or MI	215 (2.46%)	222 (2.68%)	0.95 (0.79 to 1.15)	0.00	0.608	205 (2.47%)	218 (2.68%)	0.95 (0.79 to 1.15)	0.00	0.62
Death										
All cause	77 (0.82%)	88 (1.08%)	0.88 (0.65 to 1.2)	0.05	0.433	77 (0.87%)	84 (1.05%)	0.97 (0.71 to 1.32)	0.13	0.842
Cardiovascular	49 (0.53%)	66 (0.82%)	0.74 (0.51 to 1.07)	0.00	0.114	49 (0.56%)	62 (0.78%)	0.82 (0.56 to 1.20)	0.00	0.308
Non-cardiovascular	28 (0.29%)	22 (0.26%)	1.33 (0.75 to 2.34)	0.46	0.324	28 (0.31%)	22 (0.26%)	1.40 (0.79 to 2.47)	0.52	0.245
Myocardial infarction	150 (1.75%)	144 (1.71%)	1.02 (0.81 to 1.28)	0.00	0.86	140 (1.73%)	143 (1.73%)	0.98 (0.78 to 1.24)	0.00	0.878
Stroke										
Any	44 (0.5%)	29 (0.32%)	1.44 (0.89 to 2.3)	0.00	0.135	39 (0.47%)	24 (0.27%)	1.59 (0.95 to 2.66)	0.00	0.077
Ischaemic	35 (0.41%)	25 (0.28%)	1.31 (0.78 to 2.20)	0.00	0.314	32 (0.4%)	20 (0.23%)	1.41 (0.79 to 2.50)	0.00	0.24
Haemorrhagic	5 (0.05%)	2 (0.02%)	1.98 (0.36 to 10.81)	0.00	0.431	4 (0.04%)	2 (0.02%)	1.66 (0.28 to 9.96)	0.00	0.58
Stent thrombosis										
Definite	20 (0.25%)	20 (0.28%)	0.97 (0.52 to 1.80)	0.00	0.92	16 (0.21%)	20 (0.28%)	0.82 (0.42 to 1.59)	0.00	0.552
Probable	5 (0.05%)	5 (0.05%)	0.60 (0.14 to 2.52)	0.77	0.488	-	-	-	-	-
Possible	22 (0.24%)	40 (0.53%)	0.54 (0.32 to 0.91)	0.00	0.02	22 (0.25%)	40 (0.54%)	0.55 (0.32 to 0.92)	0.00	0.023
Definite or probable	23 (0.28%)	24 (0.32%)	0.89 (0.50 to 1.59)	0.00	0.704	19 (0.25%)	24 (0.32%)	0.77 (0.41 to 1.43)	0.00	0.404
Any	45 (0.52%)	64 (0.85%)	0.67 (0.46 to 0.99)	0.00	0.042	41 (0.5%)	64 (0.86%)	0.62 (0.42 to 0.92)	0.00	0.017

BARC bleeding										
2, 3 or 5	262 (3.05%)	430 (4.97%)	0.60 (0.51 to 0.69)	0.00	<0.001	249 (3.05%)	416 (4.9%)	0.61 (0.52 to 0.71)	0.00	<0.001
3 or 5	74 (0.8%)	126 (1.44%)	0.58 (0.43 to 0.77)	0.00	<0.001	71 (0.81%)	117 (1.37%)	0.62 (0.46 to 0.84)	0.02	0.002
5	-	-	-	-	-	-	-	-	-	-
TIMI bleeding										
Major	35 (0.41%)	59 (0.79%)	0.58 (0.38 to 0.89)	0.00	0.012	35 (0.43%)	54 (0.75%)	0.65 (0.42 to 0.99)	0.02	0.045
Minor	111 (1.39%)	185 (2.21%)	0.58 (0.46 to 0.73)	0.00	<0.001	110 (1.44%)	179 (2.18%)	0.59 (0.46 to 0.75)	0.03	<0.001
Major or minor	146 (1.8%)	242 (2.99%)	0.58 (0.47 to 0.71)	0.04	<0.001	145 (1.88%)	232 (2.93%)	0.60 (0.49 to 0.74)	0.10	<0.001
NACE	316 (3.59%)	360 (4.27%)	0.86 (0.74 to 1.01)	0.00	0.06	299 (3.59%)	342 (4.14%)	0.89 (0.76 to 1.04)	0.00	0.142

P-values are two-sided for superiority.
BARC=Bleeding Academy Research Consortium; CI=confidence interval; HR=hazard ratio; MI=myocardial infarction; NACE=net adverse clinical events, defined as a composite of all-cause death, myocardial infarction, stroke, or BARC type 3 or 5 bleeding; TIMI=Thrombolysis in Myocardial Infarction.

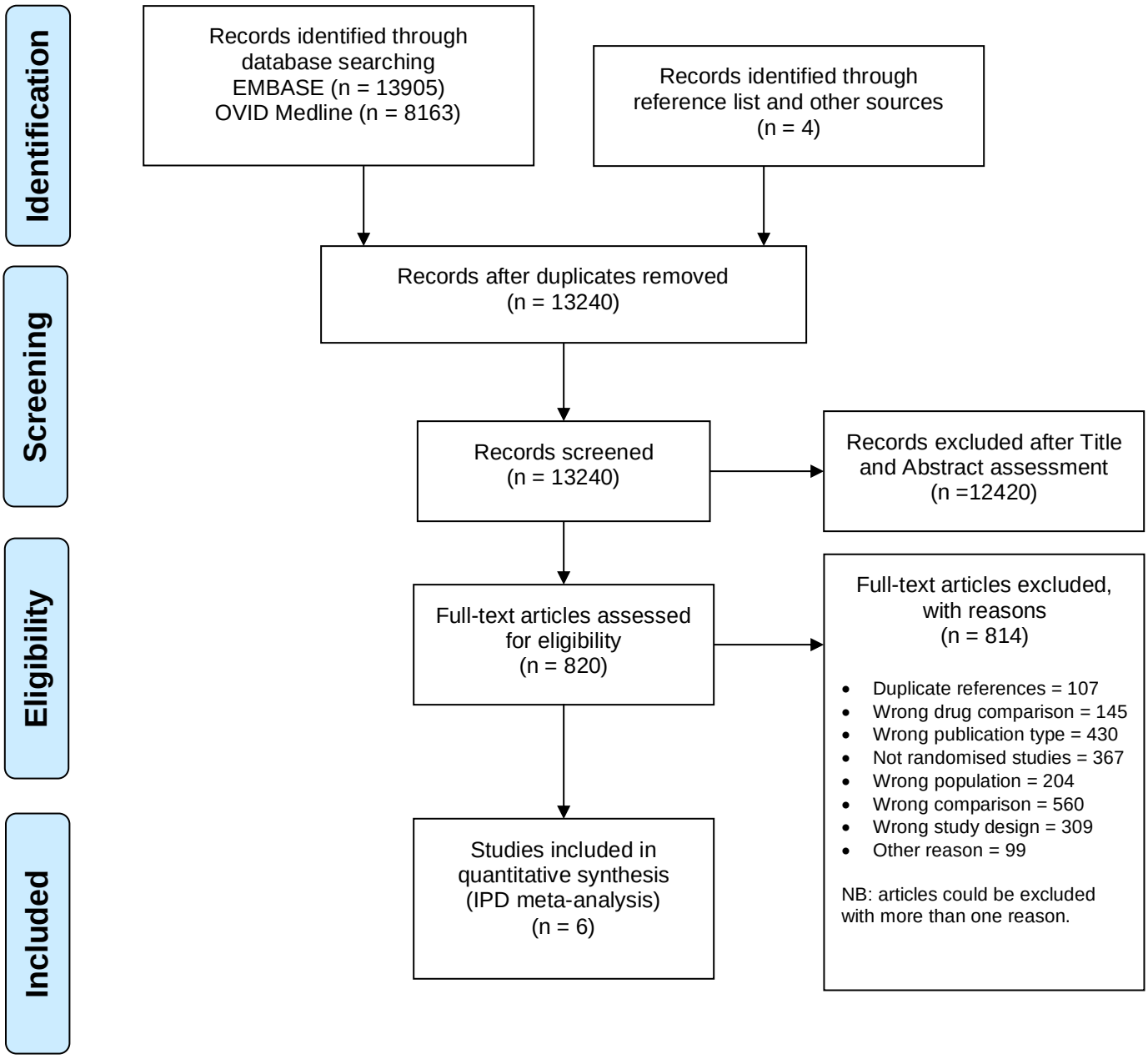
Supplementary table O. One step mixed-effect Cox regression model for ITT population right censoring events 9 months after the start of $P2Y_{12}$ inhibitor monotherapy in the experimental groups

Outcome	$P2Y_{12}$ Inhibitor (N=11634)	Aspirin + $P2Y_{12}$ Inhibitor (N=11674)	HR (95% CI)	Tau^2	p value
Death, MI, or stroke	259 (2.28%)	284 (2.49%)	0.92 (0.77 to 1.08)	0.00	0.312
Death or MI	221 (1.94%)	249 (2.18%)	0.89 (0.74 to 1.07)	0.00	0.213
Death					
All cause	98 (0.86%)	111 (0.97%)	0.90 (0.69 to 1.19)	0.00	0.466
Cardiovascular	55 (0.48%)	75 (0.65%)	0.75 (0.53 to 1.06)	0.00	0.101
Non-cardiovascular	39 (0.34%)	31 (0.27%)	1.31 (0.81 to 2.10)	0.01	0.27
Myocardial infarction	137 (1.2%)	153 (1.34%)	0.90 (0.71 to 1.13)	0.01	0.364
Stroke					
Any	43 (0.37%)	41 (0.36%)	1.01 (0.65 to 1.55)	0.00	0.978
Ischaemic	30 (0.26%)	32 (0.28%)	0.88 (0.53 to 1.46)	0.00	0.621
Haemorrhagic	6 (0.05%)	2 (0.02%)	2.52 (0.49 to 13.0)	0.00	0.269
Stent thrombosis					
Definite	17 (0.15%)	19 (0.17%)	0.84 (0.43 to 1.64)	0.00	0.618
Probable	6 (0.05%)	7 (0.06%)	0.72 (0.23 to 2.26)	0.00	0.571
Possible	24 (0.21%)	38 (0.33%)	0.63 (0.38 to 1.06)	0.00	0.08
Definite or probable	21 (0.18%)	25 (0.22%)	0.80 (0.45 to 1.44)	0.00	0.463
Any	43 (0.38%)	62 (0.54%)	0.68 (0.46 to 1.01)	0.00	0.053
BARC bleeding					
2, 3 or 5	242 (2.13%)	432 (3.83%)	0.56 (0.48 to 0.65)	0.03	<0.001
3 or 5	85 (0.75%)	180 (1.58%)	0.47 (0.36 to 0.61)	0.02	<0.001
5	3 (0.03%)	5 (0.06%)	0.67 (0.11 to 4.02)	0.00	0.662
TIMI bleeding					
Major	34 (0.3%)	81 (0.71%)	0.42 (0.28 to 0.63)	0.34	<0.001
Minor	103 (0.9%)	211 (1.85%)	0.48 (0.38 to 0.61)	0.00	<0.001
Major or minor	137 (1.2%)	288 (2.53%)	0.47 (0.38 to 0.58)	0.02	<0.001
NACE	332 (2.93%)	441 (3.89%)	0.75 (0.65 to 0.87)	0.02	<0.001

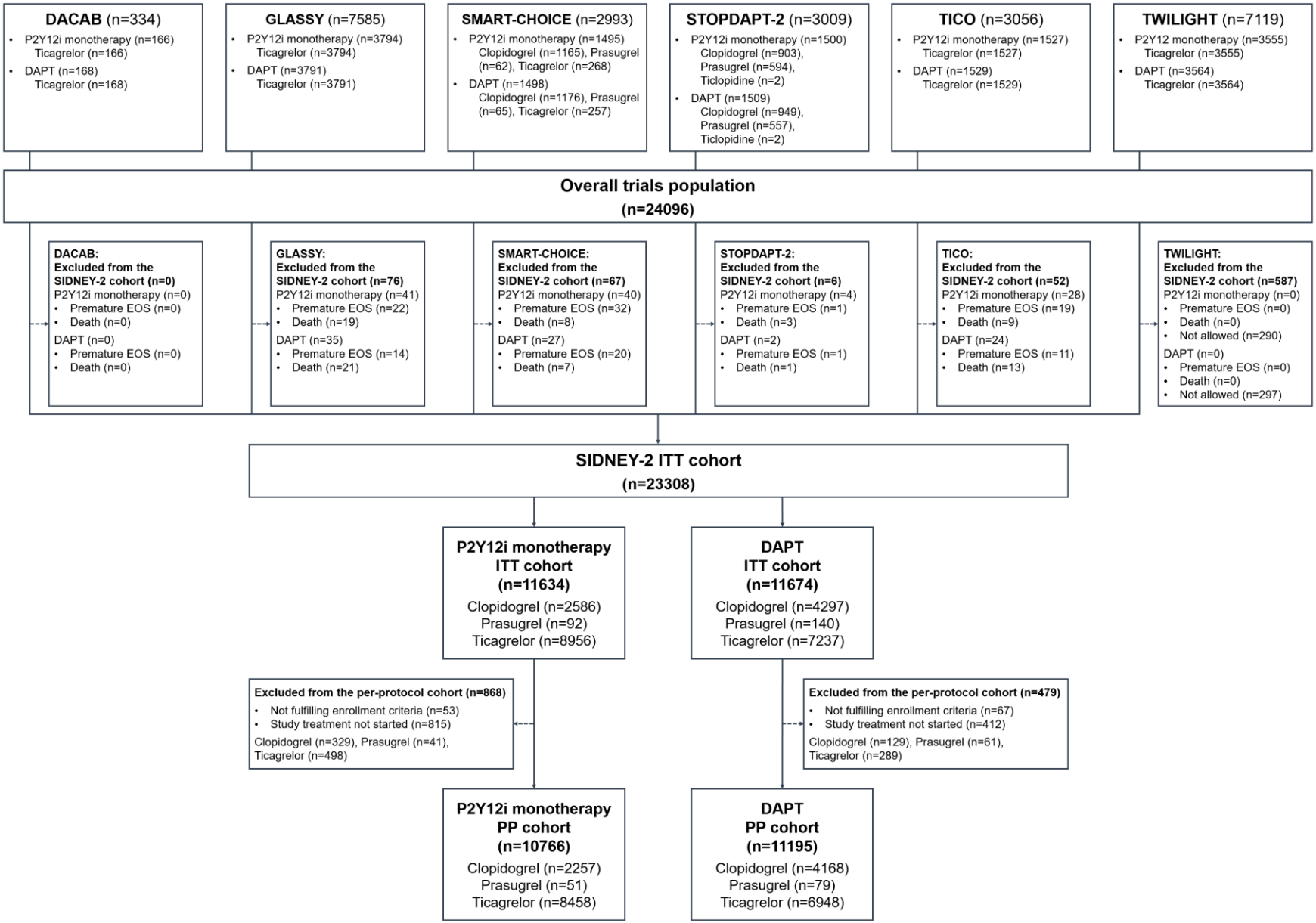
P-values are two-sided for superiority.
BARC=Bleeding Academy Research Consortium; CI=confidence interval; HR=hazard ratio; ITT=intention to treat; MI=myocardial infarction; NACE=net adverse clinical events, defined as a composite of all-cause death, myocardial infarction, stroke, or BARC type 3 or 5 bleeding; TIMI=Thrombolysis in Myocardial Infarction.

Supplementary figures

Supplementary figure A. PRISMA Flow Diagram for the Systematic Review



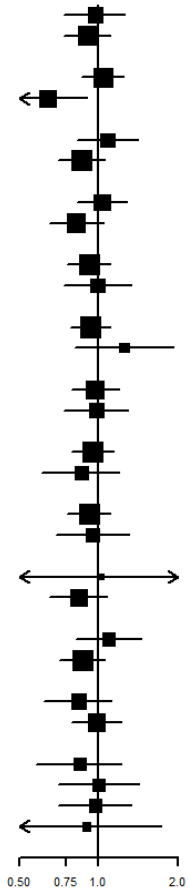
Supplementary figure B. SIDNEY-2 flow-chart



DACAB=Different Antiplatelet Therapy Strategy After Coronary Artery Bypass Graft Surgery; DAPT=dual antiplatelet therapy; EOS=end of study; GLASSY=GLOBAL LEADERS Adjudication Sub-Study; ITT=intention to treat; PP=per-protocol; SMART-CHOICE=Smart Angioplasty Research Team: Comparison Between P2Y12 Antagonist Monotherapy vs Dual Antiplatelet Therapy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents; STOPDAPT-2=Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent; TICO=Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus-eluting Stent for Acute Coronary Syndrome; TWILIGHT=Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention.

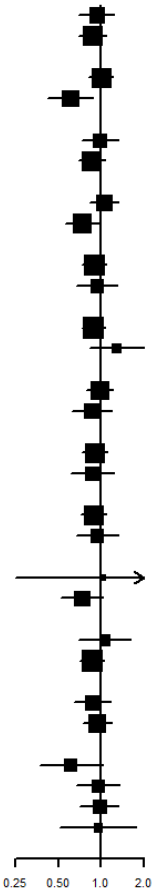
Supplementary figure C. Subgroup analyses for the primary endpoint of all-cause death, myocardial infarction, or stroke in the per-protocol population

	P2Y12i monotherapy (N=10766)	DAPT (N=11195)	HR (95% CI)	p value for interaction
Age				
<65 years	104/5160 (2.3%)	111/5377 (2.5%)	0.97 (0.74-1.26)	0.520
≥ 65 years	179/5606 (3.5%)	204/5818 (3.9%)	0.91 (0.74-1.11)	
Sex				
Male	232/8288 (3.1%)	232/8612 (3.1%)	1.04 (0.86-1.24)	0.012
Female	51/2478 (2.2%)	83/2583 (3.5%)	0.64 (0.45-0.90)	
Clinical presentation				
Stable CAD	109/4325 (2.8%)	105/4521 (2.6%)	1.08 (0.83-1.41)	0.290
ACS	174/6440 (3.0%)	210/6672 (3.6%)	0.86 (0.70-1.05)	
Diabetes				
No	158/7327 (2.4%)	161/7690 (2.3%)	1.03 (0.83-1.28)	0.110
Yes	125/3435 (4.0%)	154/3505 (5.1%)	0.82 (0.65-1.04)	
History of CKD				
No	194/8878 (2.4%)	220/9268 (2.8%)	0.92 (0.76-1.11)	0.810
Yes	87/1748 (5.4%)	91/1797 (5.5%)	0.99 (0.74-1.33)	
Peripheral artery disease				
No	229/8841 (2.8%)	254/9216 (3.0%)	0.93 (0.78-1.11)	0.210
Yes	44/595 (7.7%)	40/666 (7.0%)	1.25 (0.81-1.91)	
High bleeding risk				
PRECISE DAPT <25	176/8453 (2.4%)	188/8817 (2.5%)	0.97 (0.79-1.19)	0.920
PRECISE DAPT ≥ 25	95/1686 (6.0%)	103/1767 (6.4%)	0.98 (0.74-1.29)	
Complex PCI				
No	212/8578 (2.7%)	233/8993 (3.0%)	0.95 (0.79-1.14)	0.640
Yes	65/2009 (3.6%)	77/2028 (4.2%)	0.86 (0.61-1.19)	
PCI of left main or LAD				
No	201/6981 (3.2%)	228/7307 (3.6%)	0.92 (0.76-1.11)	0.980
Yes	75/3711 (2.2%)	81/3819 (2.4%)	0.95 (0.69-1.3)	
Type of revascularisation				
CABG	4/166 (2.4%)	4/168 (2.4%)	1.02 (0.25-4.07)	0.800
PCI	279/10600 (2.9%)	311/11027 (3.2%)	0.84 (0.65-1.07)	
P2Y12 inhibitor in control group*				
Clopidogrel	92/3817 (2.5%)	93/4178 (2.4%)	1.09 (0.82-1.45)	0.270
Newer P2Y12i	191/6949 (3.0%)	222/7017 (3.5%)	0.87 (0.71-1.05)	
Use of proton-pump inhibitors				
No	81/3274 (2.6%)	101/3428 (3.2%)	0.84 (0.62-1.12)	0.400
Yes	162/4788 (3.5%)	166/4839 (3.6%)	0.98 (0.79-1.22)	
Region**				
Asia	74/4536 (1.8%)	88/4776 (2.2%)	0.85 (0.58-1.22)	0.213
North Europa	62/1471 (4.3%)	62/1468 (4.3%)	1.00 (0.70-1.42)	
Western Europe	109/3702 (3.0%)	123/3875 (3.2%)	0.97 (0.70-1.33)	
Eastern Europe	38/1057 (3.6%)	42/1076 (4.5%)	0.90 (0.47-1.73)	



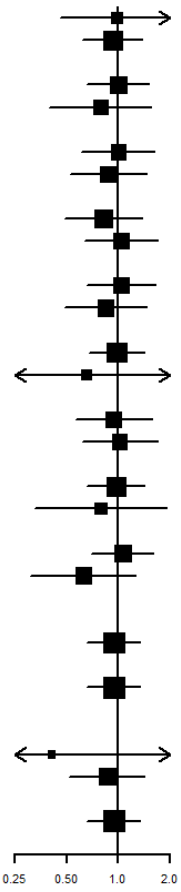
Supplementary figure D. Subgroup analyses for the primary endpoint of all-cause death, myocardial infarction, or stroke for monotherapy with a newer $P2Y_{12}$ inhibitor in the experimental arm in the intention to treat population

Experimental only with Newer P2Y12i	P2Y12i monotherapy (N=9016)	DAPT (N=9024)	HR (95% CI)	p value for interaction
Age				
< 65 years	96/4569 (2.3%)	105/4614 (2.6%)	0.93 (0.70-1.22)	0.640
≥ 65 years	147/4447 (3.6%)	168/4410 (4.1%)	0.87 (0.70-1.08)	
Sex				
Male	199/6951 (3.2%)	202/7005 (3.3%)	1.00 (0.82-1.21)	0.019
Female	44/2065 (2.2%)	71/2019 (3.7%)	0.61 (0.42-0.88)	
Clinical presentation				
Stable CAD	85/3170 (2.8%)	86/3140 (2.9%)	0.98 (0.73-1.32)	0.630
ACS	158/5845 (3.0%)	187/5884 (3.7%)	0.85 (0.69-1.06)	
Diabetes				
No	144/6293 (2.5%)	140/6350 (2.4%)	1.04 (0.83-1.32)	0.029
Yes	99/2722 (3.9%)	133/2674 (5.5%)	0.73 (0.56-0.95)	
History of CKD				
No	173/7538 (2.5%)	195/7530 (2.9%)	0.89 (0.73-1.09)	0.760
Yes	68/1336 (5.6%)	73/1360 (5.9%)	0.93 (0.67-1.30)	
Peripheral artery disease				
No	187/6980 (2.8%)	211/6939 (3.2%)	0.88 (0.73-1.07)	0.120
Yes	43/518 (8.6%)	37/565 (7.4%)	1.28 (0.83-1.99)	
High bleeding risk				
PRECISE DAPT < 25	162/7056 (2.6%)	169/7092 (2.7%)	0.97 (0.78-1.20)	0.480
PRECISE DAPT ≥ 25	68/1344 (5.3%)	80/1347 (6.4%)	0.85 (0.62-1.18)	
Complex PCI				
No	177/6993 (2.8%)	198/7038 (3.2%)	0.90 (0.73-1.10)	0.800
Yes	60/1840 (3.6%)	69/1802 (4.1%)	0.86 (0.61-1.22)	
PCI of left main or proximal LAD				
No	170/5907 (3.2%)	195/5935 (3.7%)	0.88 (0.72-1.08)	0.880
Yes	66/3029 (2.3%)	70/3010 (2.6%)	0.93 (0.67-1.31)	
Type of revascularisation				
CABG	4/166 (2.4%)	4/168 (2.4%)	1.02 (0.25-4.07)	0.680
PCI	239/8850 (3.0%)	269/8856 (3.4%)	0.73 (0.52-1.03)	
P2Y12 inhibitor in control group*				
Clopidogrel	43/1678 (2.6%)	42/1716 (2.5%)	1.05 (0.69-1.61)	0.330
Newer P2Y12i	200/7338 (3.0%)	231/7308 (3.5%)	0.86 (0.71-1.04)	
Use of proton-pump inhibitors				
No	86/3337 (2.7%)	101/3403 (3.2%)	0.87 (0.65-1.16)	0.660
Yes	140/3847 (3.7%)	146/3788 (4.0%)	0.94 (0.75-1.19)	
Region**				
Asia	24/2528 (1.0%)	39/2522 (1.8%)	0.61 (0.37-1.02)	0.140
North America	62/1484 (4.2%)	65/1488 (4.4%)	0.95 (0.67-1.35)	
Western Europe	117/3917 (3.0%)	127/3931 (3.2%)	0.97 (0.71-1.31)	
Eastern Europe	40/1087 (3.7%)	42/1083 (4.5%)	0.95 (0.51-1.76)	



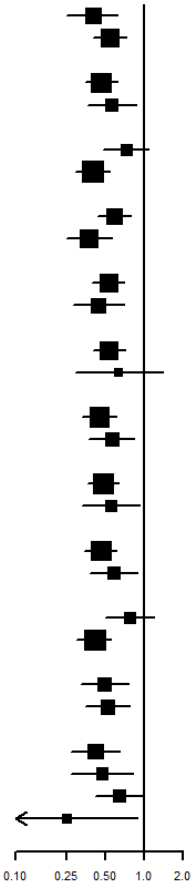
Supplementary figure E. Subgroup analyses for the primary endpoint of all-cause death, myocardial infarction, or stroke for monotherapy with clopidogrel in the experimental arm in the intention to treat population

Experimental only with Clopidogrel	P2Y12i monotherapy (N=2618)	DAPT (N=2650)	HR (95% CI)	p value for interaction
Age				
< 65 years	14/971 (1.6%)	14/960 (1.8%)	0.98 (0.46-2.05)	0.880
≥ 65 years	46/1647 (3.0%)	51/1690 (3.2%)	0.93 (0.62-1.38)	
Sex				
Male	45/1966 (2.4%)	45/1963 (2.5%)	1.00 (0.66-1.51)	0.550
Female	15/652 (2.7%)	20/687 (3.3%)	0.79 (0.40-1.54)	
Clinical presentation				
Stable CAD	32/1515 (2.2%)	32/1514 (2.4%)	1.00 (0.61-1.63)	0.700
ACS	28/1103 (2.9%)	33/1134 (3.2%)	0.88 (0.53-1.46)	
Diabetes				
No	26/1593 (1.7%)	33/1649 (2.1%)	0.82 (0.49-1.37)	0.500
Yes	34/1022 (3.7%)	32/1001 (3.7%)	1.04 (0.64-1.69)	
History of CKD				
No	37/2061 (1.9%)	36/2079 (1.9%)	1.04 (0.66-1.65)	0.550
Yes	23/556 (4.3%)	29/571 (5.3%)	0.84 (0.49-1.46)	
Peripheral artery disease				
No	56/2501 (2.4%)	58/2524 (2.6%)	0.98 (0.68-1.41)	0.480
Yes	4/115 (3.5%)	7/125 (5.7%)	0.65 (0.19-2.22)	
High bleeding risk				
PRECISE DAPT < 25	30/2065 (1.5%)	32/2074 (1.7%)	0.94 (0.57-1.56)	0.830
PRECISE DAPT ≥ 25	30/506 (6.7%)	31/533 (6.4%)	1.02 (0.62-1.69)	
Complex PCI				
No	51/2318 (2.4%)	54/2362 (2.5%)	0.97 (0.66-1.42)	0.650
Yes	9/300 (3.1%)	11/288 (4.4%)	0.79 (0.33-1.90)	
PCI of left main or proximal LAD				
No	46/1660 (3.0%)	44/1675 (2.9%)	1.06 (0.70-1.60)	0.200
Yes	13/956 (1.4%)	21/972 (2.5%)	0.63 (0.31-1.25)	
Type of revascularisation				
CABG				
PCI	60/2618 (2.5%)	65/2650 (2.7%)	0.94 (0.66-1.33)	
P2Y12 inhibitor in control group*				
Clopidogrel	60/2618 (2.5%)	65/2650 (2.7%)	0.94 (0.66-1.33)	
Newer P2Y12i				
Use of proton-pump inhibitors				
No	1/62 (1.6%)	3/76 (4.1%)	0.41 (0.04-3.92)	0.540
Yes	29/1187 (2.5%)	34/1191 (2.9%)	0.86 (0.52-1.41)	
Region**				
Asia	60/2618 (2.5%)	65/2650 (2.7%)	0.94 (0.66-1.33)	



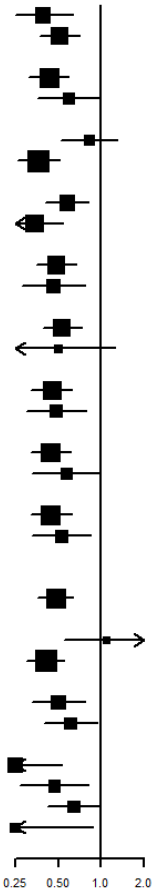
Supplementary figure F. Subgroup analyses for the key safety endpoint of Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding in the intention to treat population

	P2Y12i monotherapy (N=11468)	DAPT (N=11506)	HR (95% CI)	p value for interaction
Age				
< 65 years	27/5448 (0.5%)	68/5482 (1.4%)	0.40 (0.25-0.62)	0.290
≥ 65 years	70/6020 (1.2%)	129/6024 (2.3%)	0.54 (0.40-0.72)	
Sex				
Male	66/8783 (0.8%)	143/8834 (1.8%)	0.46 (0.35-0.62)	0.520
Female	31/2685 (1.2%)	54/2672 (2.1%)	0.56 (0.36-0.87)	
Clinical presentation				
Stable CAD	42/4622 (1.0%)	58/4599 (1.3%)	0.72 (0.48-1.07)	0.057
ACS	55/6845 (0.8%)	139/6905 (2.2%)	0.40 (0.29-0.54)	
Diabetes				
No	65/7795 (0.9%)	113/7906 (1.6%)	0.58 (0.43-0.79)	0.089
Yes	32/3669 (0.9%)	84/3600 (2.4%)	0.37 (0.25-0.56)	
History of CKD				
No	71/9436 (0.8%)	135/9447 (1.6%)	0.53 (0.39-0.70)	0.830
Yes	26/1889 (1.4%)	60/1925 (3.2%)	0.44 (0.28-0.70)	
Peripheral artery disease				
No	74/9342 (0.8%)	138/9321 (1.6%)	0.53 (0.40-0.71)	0.600
Yes	10/606 (1.7%)	17/664 (2.6%)	0.63 (0.29-1.38)	
High bleeding risk				
PRECISE DAPT < 25	58/9121 (0.7%)	130/9166 (1.6%)	0.45 (0.33-0.61)	0.490
PRECISE DAPT ≥ 25	35/1850 (2.0%)	64/1880 (3.6%)	0.56 (0.37-0.84)	
Complex PCI				
No	74/9311 (0.8%)	156/9400 (1.8%)	0.48 (0.36-0.63)	0.730
Yes	23/2140 (1.1%)	41/2090 (2.2%)	0.55 (0.33-0.92)	
PCI of left main or LAD				
No	62/7565 (0.9%)	137/7607 (1.9%)	0.46 (0.34-0.61)	0.330
Yes	34/3831 (0.9%)	58/3827 (1.6%)	0.58 (0.38-0.88)	
P2Y12 inhibitor in control group*				
Clopidogrel	36/4296 (0.9%)	48/4366 (1.2%)	0.77 (0.50-1.18)	0.018
Newer P2Y12i	61/7172 (0.9%)	149/7140 (2.2%)	0.41 (0.30-0.55)	
Use of proton-pump inhibitors				
No	31/3341 (0.9%)	64/3415 (2.0%)	0.49 (0.32-0.76)	0.570
Yes	38/4926 (0.8%)	72/4875 (1.5%)	0.52 (0.35-0.77)	
Region**				
Asia	38/4980 (0.8%)	87/5004 (1.9%)	0.42 (0.27-0.65)	0.655
North Europa	18/1484 (1.2%)	38/1488 (2.6%)	0.47 (0.27-0.82)	
Western Europe	38/3917 (1.0%)	60/3931 (1.6%)	0.64 (0.42-0.95)	
Eastern Europe	3/1087 (0.3%)	12/1083 (1.3%)	0.25 (0.07-0.88)	



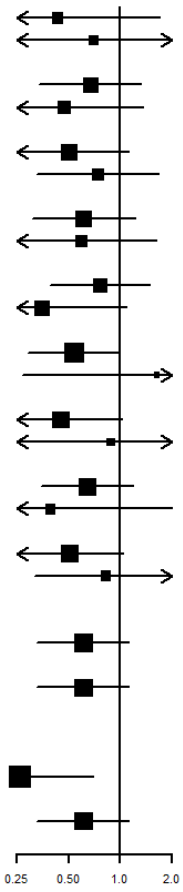
Supplementary figure G. Subgroup analyses for the key safety endpoint of Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding for monotherapy with a newer $P2Y_{12}$ inhibitor in the experimental arm in the intention to treat population

Experimental only with Newer P2Y12i	P2Y12i monotherapy (N=9016)	DAPT (N=9024)	HR (95% CI)	p value for interaction
Age				
< 65 years	24/4569 (0.5%)	61/4614 (1.4%)	0.39 (0.25-0.63)	0.460
≥ 65 years	54/4447 (1.3%)	104/4410 (2.5%)	0.51 (0.37-0.71)	
Sex				
Male	52/6951 (0.8%)	122/7005 (1.9%)	0.43 (0.31-0.59)	0.310
Female	26/2065 (1.3%)	43/2019 (2.2%)	0.59 (0.36-0.95)	
Clinical presentation				
Stable CAD	33/3170 (1.1%)	40/3140 (1.3%)	0.82 (0.52-1.30)	0.023
ACS	45/5845 (0.8%)	125/5884 (2.3%)	0.36 (0.26-0.51)	
Diabetes				
No	52/6293 (0.9%)	91/6350 (1.6%)	0.58 (0.41-0.81)	0.083
Yes	26/2722 (1.0%)	74/2674 (2.9%)	0.34 (0.22-0.54)	
History of CKD				
No	56/7538 (0.8%)	115/7530 (1.6%)	0.48 (0.35-0.67)	0.920
Yes	22/1336 (1.8%)	48/1360 (3.6%)	0.46 (0.28-0.77)	
Peripheral artery disease				
No	58/6980 (0.8%)	108/6939 (1.6%)	0.53 (0.39-0.73)	0.870
Yes	7/518 (1.4%)	15/565 (2.7%)	0.50 (0.20-1.24)	
High bleeding risk				
PRECISE DAPT < 25	50/7056 (0.7%)	112/7092 (1.7%)	0.45 (0.32-0.62)	0.880
PRECISE DAPT ≥ 25	24/1344 (1.9%)	50/1347 (3.8%)	0.48 (0.30-0.79)	
Complex PCI				
No	57/6993 (0.9%)	129/7038 (1.9%)	0.44 (0.32-0.61)	0.470
Yes	21/1840 (1.2%)	36/1802 (2.2%)	0.57 (0.33-0.98)	
PCI of left main or proximal LAD				
No	51/5907 (0.9%)	115/5935 (2.1%)	0.44 (0.32-0.62)	0.500
Yes	26/3029 (0.9%)	48/3010 (1.7%)	0.53 (0.33-0.85)	
Type of revascularisation				
CABG	0/166 (%)	0/168 (%)	1.00 (1.00-1.00)	1.000
PCI	78/8850 (0.9%)	165/8856 (2.0%)	0.48 (0.36-0.64)	
P2Y12 inhibitor in control group*				
Clopidogrel	17/1678 (1.0%)	16/1716 (0.9%)	1.09 (0.55-2.16)	0.007
Newer P2Y12i	61/7338 (0.9%)	149/7308 (2.1%)	0.41 (0.30-0.55)	
Use of proton-pump inhibitors				
No	31/3337 (0.9%)	63/3403 (1.9%)	0.50 (0.33-0.77)	0.550
Yes	33/3847 (0.9%)	53/3788 (1.4%)	0.61 (0.40-0.94)	
Region**				
Asia	19/2528 (0.9%)	55/2522 (2.4%)	0.25 (0.12-0.53)	0.221
North America	18/1484 (1.2%)	38/1488 (2.6%)	0.47 (0.27-0.82)	
Western Europe	38/3917 (1.0%)	60/3931 (1.6%)	0.64 (0.42-0.95)	
Eastern Europe	3/1087 (0.3%)	12/1083 (1.3%)	0.25 (0.07-0.88)	

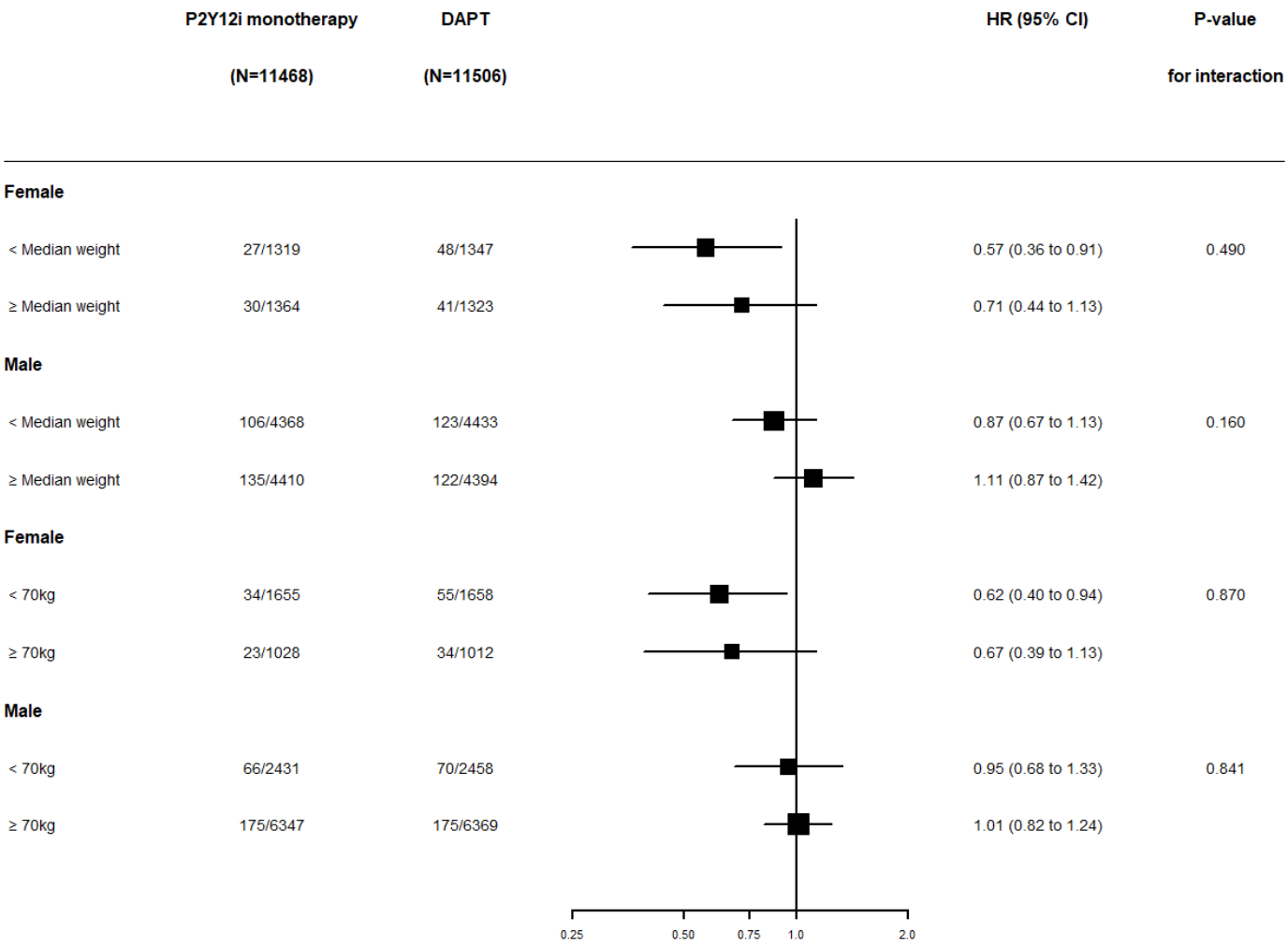


Supplementary figure H. Subgroup analyses for the key safety endpoint of Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding for monotherapy with clopidogrel in the experimental arm in the intention to treat population

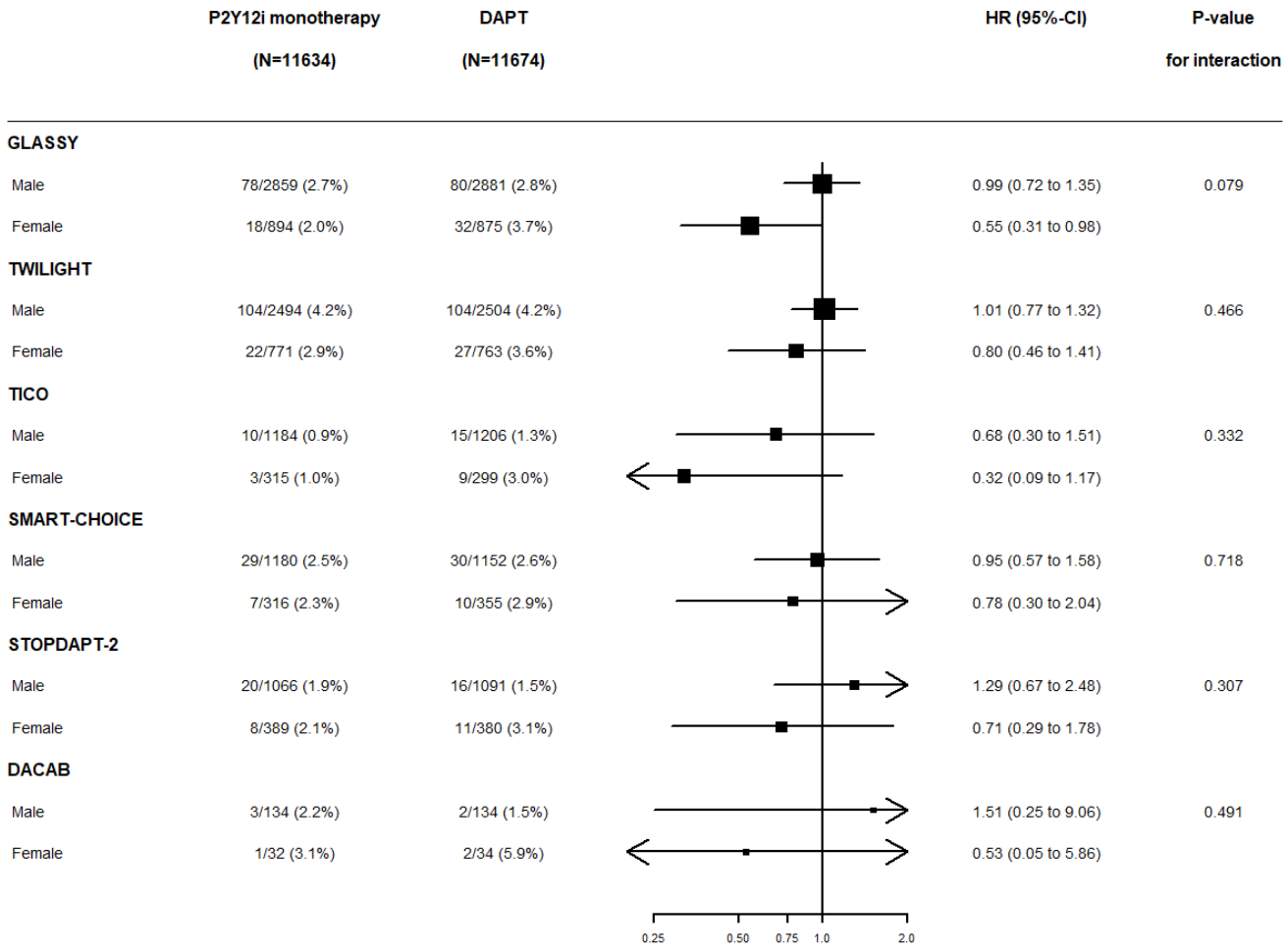
Experimental only with Clopidogrel	P2Y12i monotherapy (N=2618)	DAPT (N=2650)	HR (95% CI)	p value for interaction
Age				
< 65 years	3/971 (0.3%)	7/960 (0.8%)	0.43 (0.11-1.68)	0.440
≥ 65 years	16/1647 (1.1%)	25/1690 (1.6%)	0.70 (0.22-2.22)	
Sex				
Male	14/1966 (0.8%)	21/1963 (1.2%)	0.67 (0.34-1.32)	0.470
Female	5/652 (0.8%)	11/687 (1.7%)	0.47 (0.16-1.35)	
Clinical presentation				
Stable CAD	9/1515 (0.7%)	18/1514 (1.3%)	0.50 (0.22-1.11)	0.650
ACS	10/1103 (1.0%)	14/1134 (1.3%)	0.74 (0.33-1.66)	
Diabetes				
No	13/1593 (0.9%)	22/1649 (1.5%)	0.61 (0.31-1.22)	0.950
Yes	6/1022 (0.6%)	10/1001 (1.0%)	0.59 (0.21-1.61)	
History of CKD				
No	15/2061 (0.8%)	20/2079 (1.1%)	0.76 (0.39-1.48)	0.810
Yes	4/556 (0.7%)	12/571 (2.1%)	0.35 (0.11-1.08)	
Peripheral artery disease				
No	16/2501 (0.7%)	30/2524 (1.3%)	0.54 (0.29-0.99)	0.130
Yes	3/115 (2.6%)	2/125 (1.6%)	1.62 (0.27-9.74)	
High bleeding risk				
PRECISE DAPT < 25	8/2065 (0.4%)	18/2074 (1.0%)	0.45 (0.19-1.03)	0.330
PRECISE DAPT ≥ 25	11/506 (2.3%)	14/533 (2.8%)	0.88 (0.23-3.37)	
Complex PCI				
No	17/2318 (0.8%)	27/2362 (1.2%)	0.64 (0.35-1.18)	0.420
Yes	2/300 (0.7%)	5/288 (2.4%)	0.39 (0.08-2.00)	
PCI of left main or proximal LAD				
No	11/1660 (0.7%)	22/1675 (1.4%)	0.51 (0.24-1.04)	0.480
Yes	8/956 (0.9%)	10/972 (1.1%)	0.82 (0.32-2.07)	
Type of revascularisation				
CABG				
PCI	19/2618 (0.8%)	32/2650 (1.3%)	0.61 (0.33-1.11)	
P2Y12 inhibitor in control group*				
Clopidogrel	19/2618 (0.8%)	32/2650 (1.3%)	0.61 (0.33-1.11)	
Newer P2Y12i				
Use of proton-pump inhibitors				
No	0/62 (%)	1/76 (1.3%)	0.00 (0.00-Inf)	1.000
Yes	5/1187 (0.4%)	19/1191 (1.6%)	0.26 (0.10-0.70)	
Region**				
Asia	19/2618 (0.8%)	32/2650 (1.3%)	0.61 (0.33-1.11)	



Supplementary figure I. Treatment-by-weight interaction for the primary efficacy endpoint of all-cause death, cardiovascular death, myocardial infarction, or stroke stratified by sex in the intention to treat population



Supplementary figure J. Treatment-by-sex interaction testing for the primary outcome for each trial



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