Supplement

Short-term versus long-term dual antiplatelet therapy after drug-eluting stent implantation in elderly patients: a meta-analysis of individual participant data from six randomized trials

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Evaluation of risks of primary outcome in younger (<65 years old) patients before and after time points of 90 or 180 days

It was analyzed whether the hazard ratio was different after time=90 days or 180 days from the hazard ratio prior to those times in younger patients. The formula of hazard function was as follows:

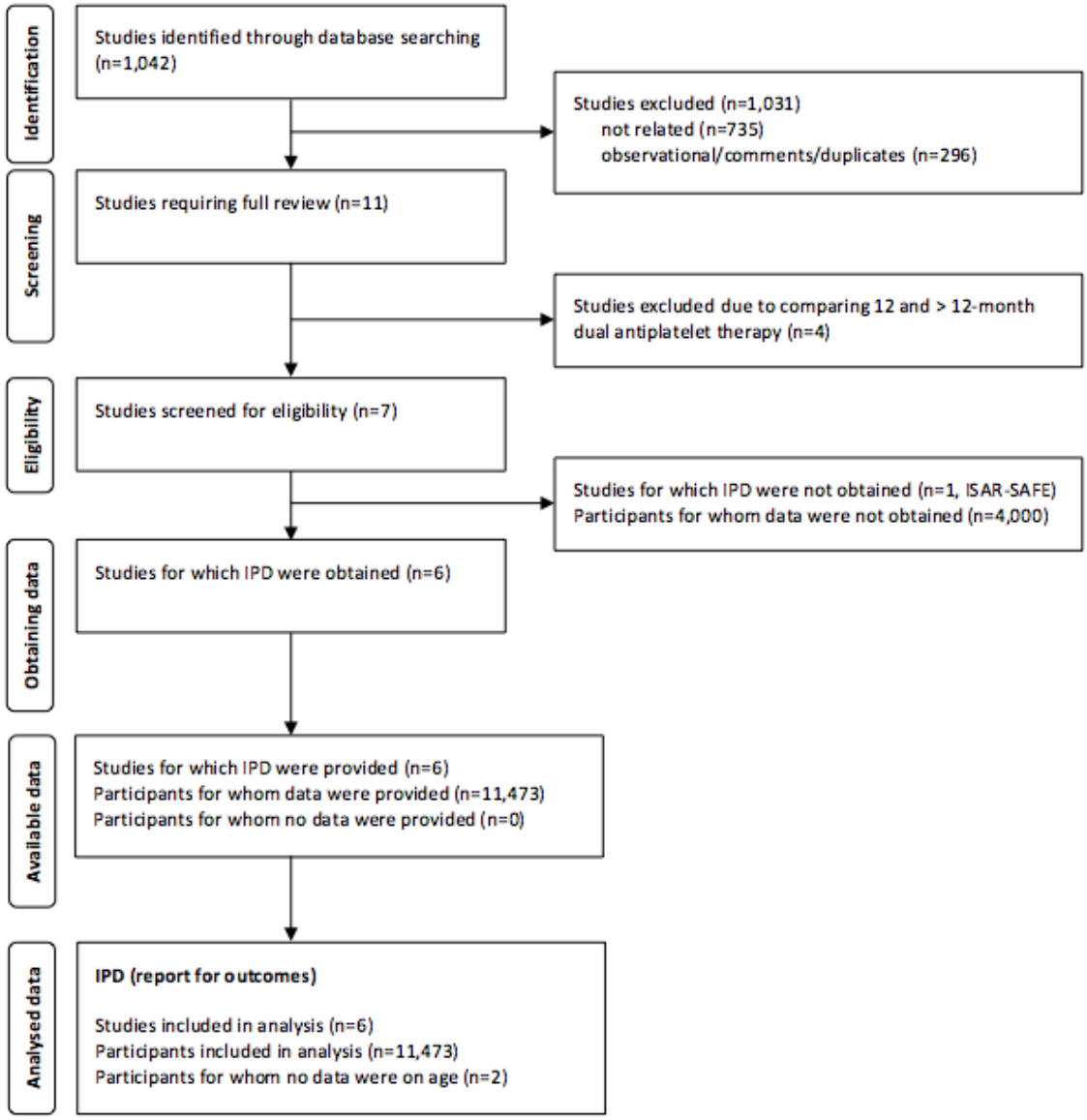
$$h(t, x_1, x_2(t)) = h_0(t) \exp[\beta_1 * x_1 + \beta_2 * x_2(t) + \beta_{confounders} * x_{confounders}]^1$$

,where β_1 and β_2 were the regression coefficients for x_1 and $x_2(t)$, respectively. The x_1 was 1 if a patient was treated with short-term DAPT and 0 if otherwise. The x_2 was 0 if time was less than 90 or 180 days and was equal to x_1 if otherwise. The $\beta_{confounders}$ was the regression coefficient corresponding to confounders that included gender, diabetes mellitus, clinical presentation of acute coronary syndrome, numbers of diseased vessels per patient, and types of drug-eluting stents.

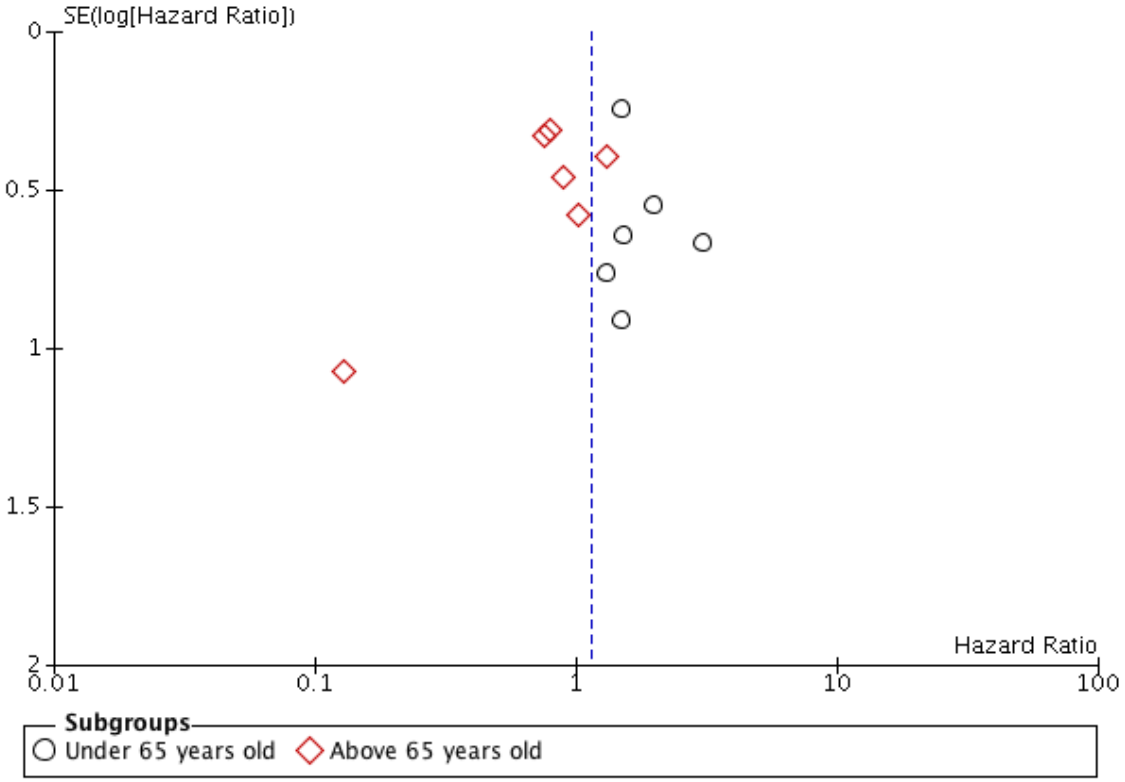
In case with time=90 days, β_1 and β_2 were 0.42083 and 0.27199, respectively. In case with time=180 days, β_1 and β_2 were 0.49258 and 0.08524, respectively. In both cases, β_1 was > 0 and $\beta_1 + \beta_2$ was also > 0, suggesting that hazard ratios persistently increased regardless of the specified time points.

[1]Cantor AB. SAS ® Survival Analysis Techniques for Medical Research, Second Edition. Cary, NC, USA:SAS Institute Inc., 2003:136.

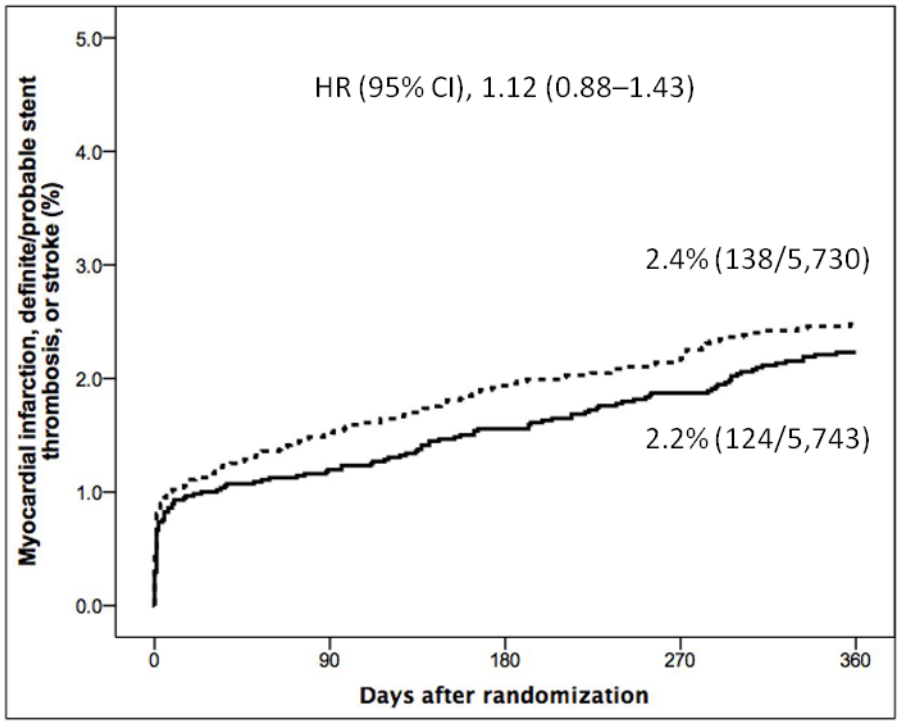
Supplementary Figure 1. Individual participant data (IPD) meta-analysis flow diagram. ISAR-SAFE, Intracoronary Stenting and Antithrombotic Regimen: Safety And EFficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting.

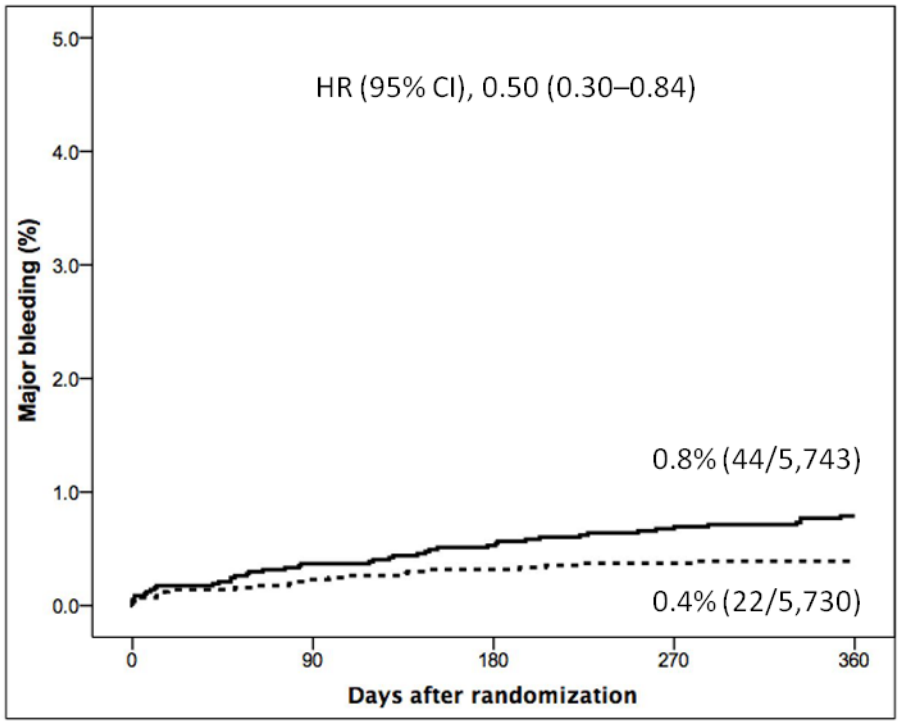


Supplementary Figure 2. Funnel plot of randomized trials included in the individual participant data meta-analysis for the risk of 12-month myocardial infarction, definite/probable stent thrombosis, or stroke. SE, standard error.



Supplementary Figure 3. Events of myocardial infarction, definite/probable stent thrombosis, or stroke (left panel) and major bleeding (right panel) at 12 months, stratified based on short-term (dotted line) and long-term (line) dual antiplatelet therapy (DAPT). The hazard ratio (HR) with 95% confidence interval (CI) is for short-term DAPT, relative to long-term DAPT. Note that 25 and 27 observations were not included because of either missing or invalid values, respectively, for time.

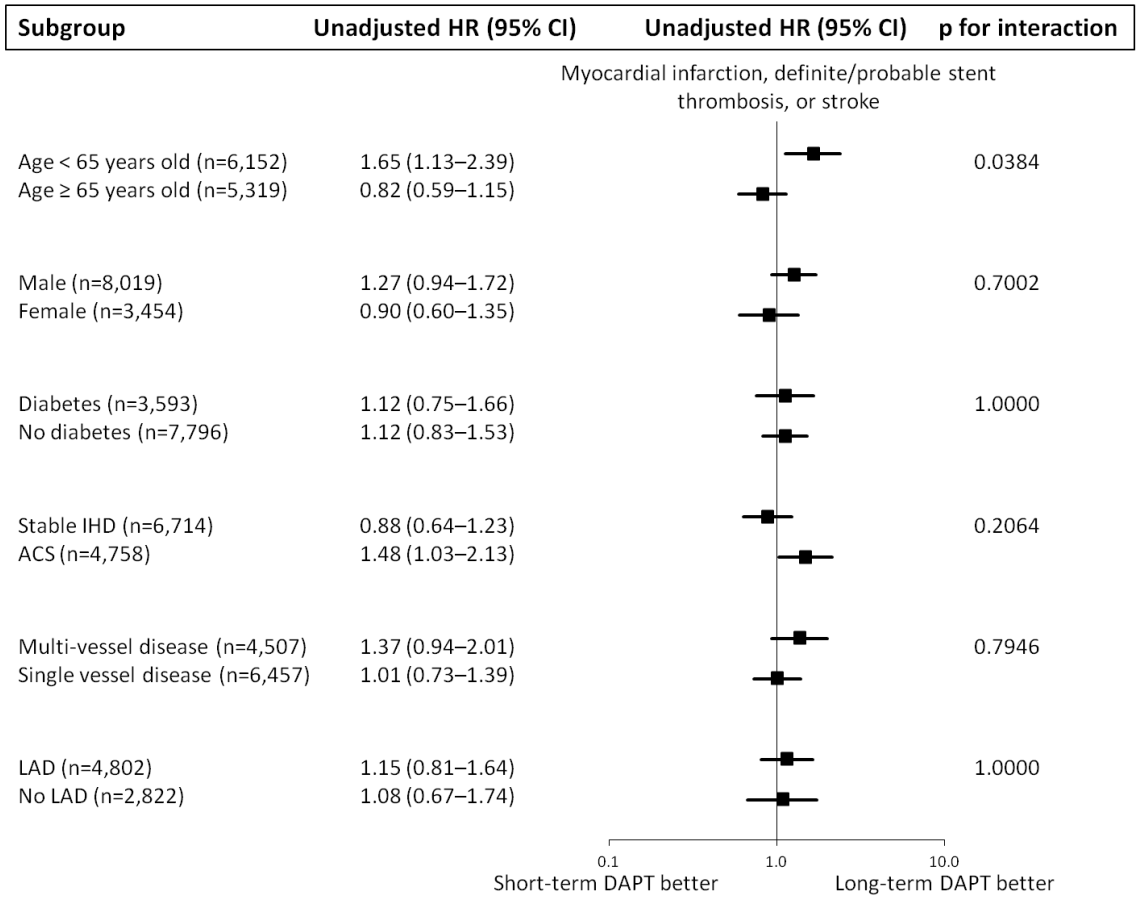




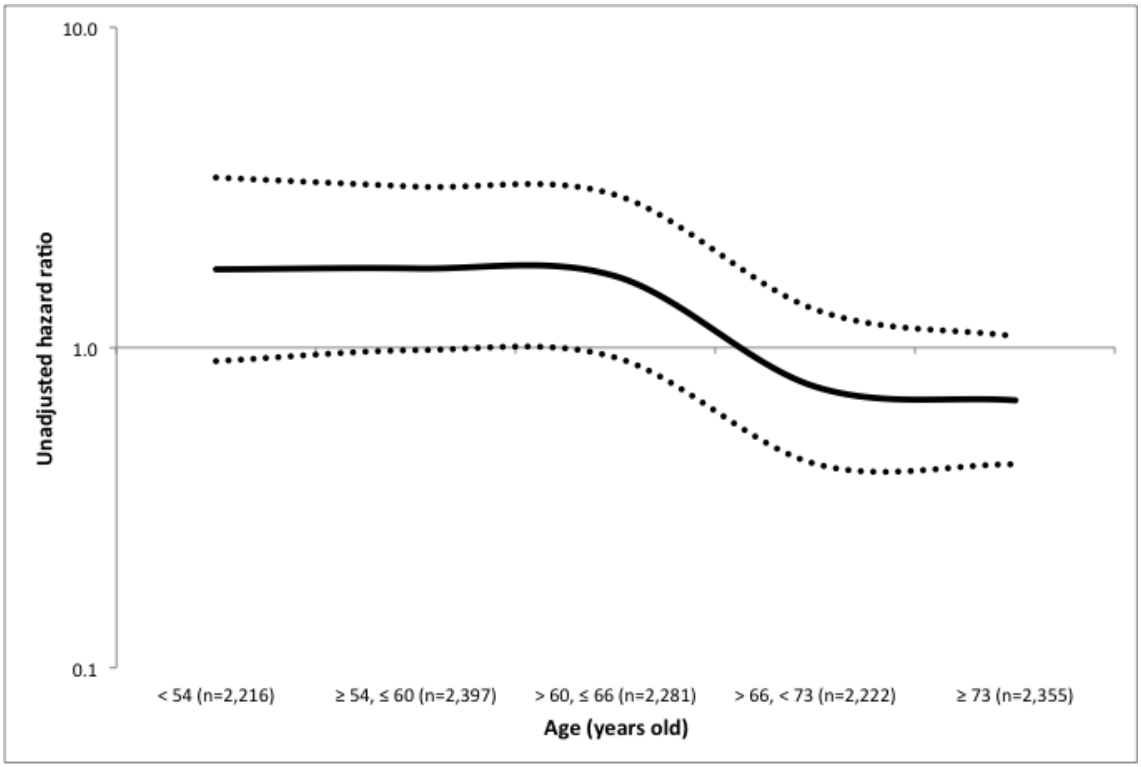
No. at risk					
Short	5,731	5,601	5,471	5,365	4,876
Long	5,717	5,574	5,455	5,361	4,896

No. at risk					
Short	5,731	5,643	5,521	5,419	4,937
Long	5,715	5.639	5,535	5,448	4,991

Supplementary Figure 4. Prespecified subgroups and duration of dual antiplatelet therapy (DAPT). ACS, acute coronary syndrome; CI, confidence interval; HR, hazard ratio; IHD, ischemic heart disease; LAD, left anterior descending artery.



Supplementary Figure 5. The 12-month risk for myocardial infarction, definite/probable stent thrombosis, or stroke in patients treated with short-term dual antiplatelet therapy (versus long-term), according to the quintile of age. Unadjusted hazard ratio and 95% confidence interval were represented as line and dotted line, respectively.



Supplementary Table 1. Main characteristics of randomized trials included in the meta-analysis

Study	Design	DAPT duration (n)	Primary outcome	Follow-up	Results
RESET	Non-inferiority	3 months (1,059) vs. 12 months (1,058)	Cardiac death/MI/ST/TVR/bleeding	12 months	Non-inferiority demonstrated
EXCELLENT	Non-inferiority	6 months (722) vs. 12 months (721)	Cardiac death/MI/ischemia-driven TVR	12 months	Non-inferiority demonstrated
PRODIGY	Superiority	6 months (751) vs. 24 months (750)	Death/MI/cerebrovascular accident	24 months	Superiority of 24-month DAPT not demonstrated
OPTIMIZE	Non-inferiority	3 months (n=1,563) vs. 12 months (n=1,556)	Death/MI/stroke/major bleeding	12 months	Non-inferiority demonstrated
SECURITY	Non-inferiority	6 months (682) vs. 12 months (717)	Cardiac death/MI/ST/stroke/major bleeding	12 months	Non-inferiority demonstrated
ITALIC	Non-inferiority	6 months (953) vs. 24 months (941)	Death/MI/urgent TVR/stroke/major bleeding	24 months	Non-inferiority demonstrated

Trials: EXCELLENT, Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting; OPTIMIZE, Optimized Duration of Clopidogrel Therapy Following Treatment With the Zotarolimus-Eluting Stent in Real-World Clinical Practice; PRODIGY, Prolonging Dual Antiplatelet Treatment After Grading Stent- Induced Intimal Hyperplasia Study; RESET, REal Safety and Efficacy of a 3-month dual antiplatelet Therapy following E-ZES implantation; SECURITY, Second Generation Drug-Eluting Stent Implantation Followed by Six- Versus Twelve-Month Dual Antiplatelet Therapy; ITALIC, Is There A LIfe for DES After Discontinuation of Clopidogrel.

DAPT, dual antiplatelet therapy; MI, myocardial infarction; ST, stent thrombosis; TVR, target-vessel revascularization.

Supplementary Table 2. Inclusion/exclusion criteria and internal validity of randomized trials included in the meta-analysis

Study	Major inclusion criteria	Major exclusion criteria	Randomization	Concealment of allocation treatment	Intention-to-treat analysis	Blinded adjudication of events
RESET	Angina or acute MI with > 50% stenosis in a coronary artery	STEMI within 48 hours, LVEF < 40%, left main disease, bifurcation (2 stents), CTO, restenosis	Index procedure	Yes	Yes	Yes
EXCELLENT	Myocardial ischemia with > 50% stenosis in a native coronary vessel or significant stenosis of > 75%	MI within 72 hours, LVEF < 25%, left main disease, bifurcation (2 stents), CTO	Index procedure	Yes	Yes	Yes
PRODIGY	Stable angina or acute coronary syndrome with ≥ 50% stenosis	No limit for clinical presentation or lesion complexity	30 days after PCI	Yes	Yes	Yes
OPTIMIZE	Angina or recent MI with > 50% stenosis in a native vessel	Acute MI, drug-eluting stent restenosis, SVG	Index procedure	Yes	Yes	Yes
SECURITY	Silent ischemia or angina with ≥ 70% stenosis in a native coronary artery	STEMI within 48 hours, non-STEMI within 6 months, LVEF ≤ 30%, left main disease, restenosis, SVG	Index procedure	Yes	Yes	Yes
ITALIC	PCI with at least 1 everolimus-eluting stent	Primary PCI for acute MI, left main disease	Index procedure	Yes	Yes	Yes

Trials: EXCELLENT, Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting; OPTIMIZE, Optimized Duration of Clopidogrel Therapy Following Treatment With the Zotarolimus-Eluting Stent in Real-World Clinical Practice; PRODIGY, Prolonging Dual Antiplatelet Treatment After Grading Stent- Induced Intimal Hyperplasia Study; RESET, REal Safety and Efficacy of a 3-month dual antiplatelet Therapy following E-ZES implantation; SECURITY, Second Generation Drug-Eluting Stent Implantation Followed by Six- Versus Twelve-Month Dual Antiplatelet Therapy; ITALIC, Is There A LIfe for DES After Discontinuation of Clopidogrel.

CTO, chronic total occlusion; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; SVG, saphenous vein graft.

Supplementary Table 3. Risk of bias in randomized trials included in the meta-analysis

	RESET	EXCELLENT	PRODIGY	OPTIMIZE	SECURITY	ITALIC
Random sequence generation	Low	Low	Low	Low	Low	Low
Allocation concealment	Low	Low	Low	Low	Low	Low
Blinding of participants and personnel	High	High	High	High	High	High
Blinding of outcome assessment	Low	Low	Low	Low	Low	Low
Incomplete outcome data	Low	Low	Low	Low	Low	Low
Selective reporting	Low	Low	Low	Low	Low	Low

Trials: EXCELLENT, Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting; OPTIMIZE, Optimized Duration of Clopidogrel Therapy Following Treatment With the Zotarolimus-Eluting Stent in Real-World Clinical Practice; PRODIGY, Prolonging Dual Antiplatelet Treatment After Grading Stent- Induced Intimal Hyperplasia Study; RESET, REal Safety and Efficacy of a 3-month dual antiplatelet Therapy following E-ZES implantation; SECURITY, Second Generation Drug-Eluting Stent Implantation Followed by Six- Versus Twelve-Month Dual Antiplatelet Therapy; ITALIC, Is There A LIfe for DES After Discontinuation of Clopidogrel.

Supplementary Table 4. Definitions of outcomes in randomized trials included in the meta-analysis

	RESET	EXCELLENT	PRODIGY	OPTIMIZE	SECURITY	ITALIC
Cardiac death	Any death unless a definite non-cardiovascular cause could be established	Any death unless a definite non-cardiac cause could be established	Any death unless an unequivocal non-cardiovascular cause could be established	Any unknown causes of death or death that cannot be clearly attributed to a non-cardiac cause	Any death without a non-cardiac cause	Any death unless an unequivocal non-cardiac cause could be established
MI	A presence of clinical symptoms, electrocardiographic change or abnormal imaging findings of MI combined with an increase in CK-MB to greater than 3 times the upper limit of the normal range or troponin-T/troponin-I more than the 99th percentile of the upper normal limit, unrelated to an interventional procedure	-For 48 hours an increase of cardiac enzyme 3 times above the upper limit of normal in stable patients. a subsequent increase of 2-fold from baseline values in patients with elevated baseline levels of cardiac enzyme -After 48 hours presence of clinical signs of MI combined with an increase of cardiac enzyme higher than the upper limit of normal	Following universal definition of MI[1]	Following historical extended World Health Organization definition[2]	Cardiac enzyme elevation above the upper normal limit associated with at least 1 ischemic symptom Development of Q waves on the electro-cardiogram Electrocardiogram changes indicative of ischemia or coronary artery intervention	-Q-wave MI recurrence of symptoms and/or development of new pathological Q waves in 2 or more contiguous leads with elevated creatine kinase, CK-MB, or troponin levels -Non–Q-wave MI >2-fold creatine kinase elevation with elevated CK-MB or troponin without new pathological Q waves
Stroke or cerebrovascular accident	A sudden onset of vertigo, numbness, aphasia, or dysarthria resulting from vascular lesions of the brain, including hemorrhage, embolism, thrombosis, or rupturing aneurysm	New neurological deficit confirmed by a neurologist and on imaging	New neurological deficit confirmed by a neurologist and on imaging	Acute neurological event with duration ≥ 24 hours with confirmation by either computed tomography or magnetic resonance imaging or pathological study	New neurological deficit lasting >24 h associated with neuroimaging evidence (computed tomography or magnetic resonance imaging)	New neurological deficit ending in death or lasting longer than 24 h, diagnosed as stroke by a physician
Stent thrombosis	ARC	ARC	ARC	ARC	ARC	ARC

Bleeding	TIMI	TIMI	TIMI and BARC	REPLACE-2 and GUSTO	BARC	TIMI

Trials: EXCELLENT, Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting; OPTIMIZE, Optimized Duration of Clopidogrel Therapy Following Treatment With the Zotarolimus-Eluting Stent in Real-World Clinical Practice; PRODIGY, Prolonging Dual Antiplatelet Treatment After Grading Stent- Induced Intimal Hyperplasia Study; RESET, REal Safety and Efficacy of a 3-month dual antiplatelet Therapy following E-ZES implantation; SECURITY, Second Generation Drug-Eluting Stent Implantation Followed by Six- Versus Twelve-Month Dual Antiplatelet Therapy; ITALIC, Is There A LIfe for DES After Discontinuation of Clopidogrel.

ARC, Academic Research Consortium; BARC, Bleeding Academic Research Consortium; CK-MB, creatine kinase-myocardial band; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; MI, myocardial infarction; REPLACE, Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events; TIMI, thrombolysis in myocardial infarction.

[1]Thygesen K, Alpert JS, White HD, Jaffe AS, Apple FS, Galvani M, Katus HA, Newby LK, Ravkilde J, Chaitman B, Clemmensen PM, Dellborg M, Hod H, Porela P, Underwood R, Bax JJ, Beller GA, Bonow R, Van der Wall EE, Bassand JP, Wijns W, Ferguson TB, Steg PG, Uretsky BF, Williams DO, Armstrong PW, Antman EM, Fox KA, Hamm CW, Ohman EM, Simoons ML, Poole-Wilson PA, Gurfinkel EP, Lopez-Sendon JL, Pais P, Mendis S, Zhu JR, Wallentin LC, Fernandez-Aviles F, Fox KM, Parkhomenko AN, Priori SG, Tendera M, Voipio-Pulkki LM, Vahanian A, Camm AJ, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck- Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Widimsky P, Zamorano JL, Morais J, Brener S, Harrington R, Morrow D, Lim M, Martinez-Rios MA, Steinhubl S, Levine GN, Gibler WB, Goff D, Tubaro M, Dudek D, Al-Attar N. Universal definition of myocardial infarction. *Circulation*. 2007;116:2634 –2653.

[2]Vranckx P, Cutlip DE, Mehran R, Kint PP, Silber S, Windecker S, Serruys PW. Myocardial infarction adjudication in contemporary all-comer stent trials: balancing sensitivity and specificity. Addendum to the historical MI definitions used in stent studies. *EuroIntervention* 2010;5:871-874.

Supplementary Table 5. Baseline characteristics according to duration of dual antiplatelet therapy (DAPT) after implantation of drug-eluting stent in randomized trials

	≤ 6-month DAPT (n=5,730)	12-month DAPT (n=5,743)	p
Age (years)	63.1 (10.6)	63.2 (10.7)	0.5356
Weight (kg)	71.9 (14.1)	72.0 (14.2)	0.8270
Male	70.3% (4,029 / 5,730)	69.5% (3,990 / 5,743)	0.3277
Medically treated hypertension	78.1% (4,466 / 5,722)	78.6% (4,507 / 5,732)	0.4519
Medically treated diabetes	31.4% (1,784 / 5,688)	31.7% (1,809 / 5,701)	0.6735
Medically treated dyslipidemia	63.9% (3,599 / 5,632)	64.5% (3,634 / 5,637)	0.5322
Current smoker	22.6% (1,117 / 4,946)	21.7% (1,073 / 4,939)	0.3039
Prior myocardial infarction	21.9% (1,129 / 5,166)	21.7% (1,121 / 5,157)	0.8855
Prior percutaneous coronary intervention	18.3% (948 / 5,187)	17.0% (879 / 5,172)	0.0872
Prior coronary bypass surgery	6.0% (312 / 5,188)	6.3% (325 / 5,167)	0.5589
Left ventricular ejection fraction < 40%	8.1% (396 / 4,862)	7.7% (375 / 4,870)	0.4168
Hemoglobin (g/dL)	13.7 (1.6)	13.7 (1.6)	0.7783
Clinical diagnosis			0.8057
Stable ischemic heart disease	58.4% (3,347 / 5,730)	58.6% (3,367 / 5,742)	
Acute coronary syndrome	41.6% (2,383 / 5,730)	41.4% (2,375 / 5,742)	
Unstable angina	1,604	1,582	
Non-ST elevation myocardial infarction	459	485	
ST elevation myocardial infarction	320	308	
Clopidogrel at discharge	99.6% (3,966 / 3,982)	99.7% (3,997 / 4,008)	0.3267
No. of diseased vessels	1.6 (0.8)	1.6 (0.8)	0.9848
No. of stented vessels	1.2 (0.4)	1.2 (0.4)	0.6926
Stented coronary artery			
Left main	2.3% (79 / 3,374)	2.3% (77 / 3,367)	0.8816
Left anterior descending artery	63.3% (2,419 / 3,824)	62.7% (2,383 / 3,800)	0.6204
Left circumflex artery	31.4% (1,116 / 3,557)	32.3% (1,159 / 3,584)	0.3823
Right coronary artery	36.2% (1,302 / 3,599)	36.1% (1,290 / 3,575)	0.9348
No. of stented lesions	1.3 (0.5)	1.3 (0.5)	0.7510
No. of implanted stents	1.5 (0.8)	1.5 (0.8)	0.5860
Types of drug-eluting stents			<0.0001
First-generation	7.5% (423 / 5,662)	13.4% (762 / 5,679)	
Sirolimus-eluting stent	164	505	
Paclitaxel-eluting stent	259	257	
Next-generation	92.5% (5,239 / 5,662)	86.6% (4,917 / 5,679)	
Zotarolimus-eluting stent	3,155	2,570	
Everolimus-eluting stent	1,854	2,118	
Biolimus-eluting stent	230	229	

Smallest device diameter > 3.0 mm	33.6% (848 / 2,522)	33.2% (839 / 2,524)	0.7729
Total stent length (mm)	35.4 (24.3)	35.9 (23.9)	0.5134

Data are presented as mean (standard deviation), number, or percentage.

Supplementary Table 6. The risk of myocardial infarction (MI), definite/probable stent thrombosis (ST), or stroke in short-term and long-term dual antiplatelet therapy (DAPT), grouped by patients' age of 75 years old

	< 75 years old				≥ 75 years old				
	≤ 6-month DAPT	12-month DAPT	Unadjusted HR (95% CI)	p	≤ 6-month DAPT	12-month DAPT	Unadjusted HR (95% CI)	p	p for interaction
MI, definite/probable ST, or stroke	2.3% (114 / 4,890)	2.0% (96 / 4,865)	1.19 (0.90-1.56)	0.2192	2.9% (24 / 838)	3.2% (28 / 878)	0.88 (0.51-1.52)	0.6389	0.3558

CI, confidence interval; HR, hazard ratio.