APPENDIX

Supplementary Figure Legend

Supplementary Figure 1. Study flow chart. DAPT = Dual Antiplatelet Therapy; RCT = Randomized Controlled Trial.

Supplementary Figure 2. Adjusted risk of ischemic events associated with complex PCI according to DES type. Hazard ratios expressed with non-complex PCI as the reference group. DES = Drug-Eluting Stents; HR = Hazard Ratio; PCI = Percutaneous Coronary Intervention.

Supplementary Figure 3. Effect of long- versus short-term DAPT on the risk of major adverse cardiac events according to procedural complexity in the landmark per-treatment cohort. Incidence rate difference expressed as 100 patient-day of follow-up. HR = Hazard Ratio; IRD = Incidence Rate Difference; MACE = Major Adverse Cardiac Events; PCI = Percutaneous Coronary Intervention.

Supplementary Figure 4. Effect of long- versus short-DAPT across selected angiographic subsets within the complex PCI group. Incidence rate difference expressed as 100 patient-day of follow-up. DAPT = Dual Antiplatelet Therapy; IRD = Incidence Rate Difference; MACE = Major Adverse Cardiac Events; PCI: Percutaneous Coronary Intervention.

Supplementary Table 1: Main Characteristics of Randomized Trials included in Meta-Analysis

Study	N	Primary endpoint	Design	Follow-up	DAPT Duration (Months)	Primary Endpoint Results
RESET	3 months (N=1,059) 12 months (N=1,058)	Cardiac death/MI/ST/TVR/ major bleeding	Non-inferiority	1 year	3 vs.12	Non-inferiority demonstrated
EXCELLENT	6 months (N=722) 12 months (N=721)	Cardiac death/MI/ischemia-driven TVR	Non-inferiority	1 year	6 vs. 12	Non-inferiority demonstrated
PRODIGY	6 months (N=751) 24 months (N=750)	Death/MI/CVA	Superiority	2 years	6 vs. 24	Superiority of 24-month DAPT not demonstrated
OPTIMIZE	3 months (N=1,563) 12 months (N=1,556)	Death/MI/CVA/major bleeding	Non-inferiority	1 year	3 vs. 12	Non-inferiority demonstrated
SECURITY	6 months (N=682) 12 months (N= 717)	Cardiac death/MI/CVA/ST/ major bleeding	Non-inferiority	1 year	6 vs. 12	Non-inferiority demonstrated
ITALIC PLUS	6 months (N=953) 24 months (N=941)	Death/MI/uTVR/CVA/major bleeding	Non-inferiority	2 years	6 vs. 24	Non-inferiority demonstrated

CVA = cerebrovascular accident; DAPT =dual antiplatelet therapy; EXCELLENT =Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting; MI =myocardial infarction;

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 PLUS= Is There A LIfe for DES After Discontinuation of Clopidogrel; ST=stent thrombosis; TVR=target vessel revascularization.

Supplementary Table 2: Inclusion, exclusion criteria and internal validity assessment of randomized trials included in the meta-analysis

Study	Randomization	Major inclusion criteria	Major exclusion criteria	Concealment of allocation treatment	Intention-to-treat analysis	Blinded adjudication of events	One-year follow-up available
EXCELLENT	Index procedure	Clinical or instrumental evidence of myocardial ischemia with at least 1 lesion in native coronary vessel with vessel diameter 2.25 mm to 4.25 mm	MI within 72 hours, LVEF<25%, cardiogenic shock, serum Creatinine>265.2 μmol/L, CTO, left main disease, true bifurcation requiring 2 stents	Yes	Yes	Yes	80%
OPTIMIZE	Index procedure	Stable angina or low risk unstable angina with at least 1 lesion in native coronary vessel≥2.5 mm in diameter	STEMI, scheduled elective surgery within 12 months, in stent restenosis of DES, BMS in nontarget vessel in the last 6 months	Yes	Yes	Yes	98%
PRODIGY	30 days after PCI	Stable angina or	Planned surgery	Yes	Yes	Yes	85%

		acute coronary syndrome including STEMI with at least 1 lesion in native coronary vessel≥2.25 mm in diameter	within 24 months, history of bleeding, concomitant need of oral anticoagulant therapy				
RESET	Index procedure	Stable angina or acute MI with more than 50% diameter stenosis in a coronary artery	Cardiogenic shock, STEMI within 48 hours, LVEF<40%, previous stent thrombosis, CTO	Yes	Yes	Yes	95.3%
SECURITY	Index procedure	Stable angina Unstable angina Stenosis more than 70 % in a coronary artery	STEMI within 48 hours, LVEF < 30%, NSTEMI within 6 months, unprotected left main disease, in stent restenosis, SVG	Yes	Yes	Yes	96.5%
ITALIC PLUS	Index procedure	Stable Angina Unstable angina ACS	Left main intervention, STEMI, Prior DES less than 1 year,	Yes	Yes	Yes	99%

	major surgery within the preceding 6 weeks; evidence of active gastrointestinal or urogenital bleeding

ACS = Acute Coronary Syndrome; CTO = Chronic Total Occlusion; DES = Drug-Eluting Stent; LVEF = Left Ventricular Ejection Fraction; NSTEMI = Non-ST-segment Elevation Myocardial Infarction; PCI = Percutaneous Coronary Intervention; STEMI = ST-segment Elevation Myocardial Infarction; SVG = Saphenous Vein Graft;

Supplementary Table 3. Definition of clinical endpoints in each randomized trial included in the meta-analysis

	OPTIMIZE	RESET	EXCELLENT	PRODIGY	ITALIC	SECURITY
Cardiac death	Any death unless a definite non-cardiovascular cause could be established.	Any death unless a definite non-cardiovascular cause could be established.	Any death unless a definite non-cardiovascular cause could be established.	Any death unless a definite non-cardiovascular cause could be established.	Any death unless a definite non-cardiovascular cause could be established.	Any death without a noncardiac cause.
Myocardial infarction	-Periprocedural: rise in CPK-MB or troponin> 3 times ULN within 48 hours after PCI or >5 times ULN, with new Q wave/LBBB after CABG. -Spontaneous: any CK-MB or troponin rise	Typical symptoms, with EKG changes and a rise in CPK-MB> 3 times the ULN range or troponinT/troponin-I more than the 99th percentile of the ULN, unrelated to an interventional procedure	-Periop rise in CK-MB or troponin> 3 times ULN within 48 hours after PCI -Spontaneous: typical symptoms combined with a CPK-MB fraction or troponin T/troponin>	Rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile ULN and with at least one of the following: -Symptoms of ischemia. -Typical EKG changes -New	- Development of new pathological Q waves in 2 or more contiguous leads with elevated creatine kinase (CK), CK-MB, or troponin levels. -Greater than 2-fold CK elevation with elevated CK-MB or troponin without new	-Troponin T/I or CK MB above the upper normal limit associated with at least 1 ischemic symptom -New Q waves -Typical EKG changes

	greater than the ULN.		than the ULN.	pathological Q waves -Evidence of new loss of viable myocardium	pathological Q wave.	
Stroke	Acute neurological event with duration≥24 hours with confirmation by either computed tomography or magnetic resonance imaging or pathological confirmation.	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.	New neurological deficit ending in death or lasting longer than 24 h confirmed by a neurologist and by CT scan.	Any new neurological deficit lasting >24 h confirmed by CT scan .
Target vessel revascularization	A new percutaneous or surgical coronary re-	Repeat PCI or CABG of the target vessel due to ischemic symptoms	Defined as repeat PCI or CABG of the target vessel.	Defined as repeat PCI or CABG of the target vessel.	Repeat coronary revascularization (PCI or surgery) of the target	Defined as repeat PCI or CABG of the target vessel.

	intervention of a target vessel.	or positive stress test and angiographic minimal lumen diameter stenosis ≥50%, or angiographic diameter stenosis ≥70% without ischemic symptoms or positive stress test.			vessel.	
Stent thrombosis	ARC criteria	ARC criteria	ARC criteria	ARC criteria	ARC criteria	ARC criteria
Bleeding	REPLACE criteria	TIMI criteria	TIMI criteria	TIMI and BARC criteria	TIMI criteria	BARC criteria

CPK-MB = creatine phosphokinase myocardial band; ULN = upper limit of normal; LBB = left bundle branch block; PCI = percutaneous coronary intervention, CABG = coronary artery bypass grafting; EKG = electrocardiography; NA = not available; ARC = Academic Research Consortium; REPLACE = Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events; TIMI = thrombolysis in Myocardial Infarction; BARC = Bleeding Academic Research Consortium.

Supplementary Table 4. Overlap between components of complex PCI.

	≥ 3 vessels treated	≥ 3 stents implanted	≥ 3 lesions treated	Bifurcation with 2 stents	Stent length > 60 mm	Chronic total occlusion
Chronic total occlusion	11.4%	5.5%	5.3%	5.6%	5.8%	
Stent length > 60 mm	84.5%	79.1%	84.4%	19.1%		24.1%
Bifurcation with 2 stents	62.1%	23.4%	20.0%		24.7%	37.8%
≥ 3 lesions treated	44.1%	23.3%		4.9%	21.1%	5.5%
≥ 3 stents implanted	100.0%		100.0%	12.0%	75.9%	15.5%
≥ 3 vessels treated		16.2%	30.3%	2.7%	18.3%	2.2%

Results reported as % of patients.

Supplementary Table 5. Predictors of major adverse cardiac events and coronary thrombotic events in all randomized patients.

Major adverse cardiac events	**Adjusted HR† (95% CI)**	**Beta coefficient**	**p-value**
High-risk acute coronary syndrome*	2.40 (1.76 – 3.28)	0.88	<0.0001
Complex PCI	1.90 (1.40 – 2.58)	0.64	<0.0001
Prior revascularization‖	1.82 (1.33 – 2.49)	0.60	<0.0001
Early-generation DES	1.56 (1.09 – 2.25)	0.45	0.02
Female sex	1.49 (1.13 – 1.99)	0.40	0.006
Diabetes mellitus	1.40 (1.07 – 1.85)	0.34	0.02
Left ventricular ejection fraction (per 10% decrease)	1.28 (1.14 - 1.44)	0.25	<0.0001
Age (per year increase)	1.04 (1.02 – 1.05)	0.04	<0.0001
Coronary thrombotic events	**Adjusted HR† (95% CI)**	**Beta coefficient**	**p-value**
Prior revascularization‖	2.30 (1.60 – 3.31)	0.83	<0.0001
Complex PCI	2.19 (1.55 – 3.09)	0.78	<0.0001
High-risk acute coronary syndrome*	1.80 (1.24 – 2.61)	0.59	0.002
Prior myocardial infarction	1.57 (1.08 – 2.28)	0.45	0.02
Female sex	1.53 (1.10 – 2.14)	0.43	0.01
Diabetes mellitus	1.38 (0.99 – 1.91)	0.32	0.055
Age	1.02 (1.00 – 1.04)	0.02	0.008
Definite or probable stent thrombosis	**Adjusted HR†**	**Beta**	**p-value**

	(95% CI)	coefficient	
Prior revascularization‖	3.83 (2.15 – 6.82)	1.34	<0.0001
Early-generation DES	3.54 (1.82 – 6.89)	1.27	<0.0001
High-risk acute coronary syndrome*	3.43 (1.84 – 6.40)	1.23	<0.0001
Diabetes mellitus	1.82 (1.02 – 3.25)	0.60	0.04
Complex PCI	1.80 (0.94 – 3.42)	0.59	0.07
Myocardial infarction	**Adjusted HR† (95% CI)**	**Beta coefficient**	**p-value**
Prior revascularization‖	2.25 (1.55 – 3.27)	0.81	<0.0001
Complex PCI	2.18 (1.54 – 3.10)	0.78	<0.0001
High-risk acute coronary syndrome*	1.82 (1.25 – 2.65)	0.60	0.002
Prior myocardial infarction	1.65 (1.13 – 2.41)	0.50	0.01
Female sex	1.63 (1.16 – 2.29)	0.49	0.005
Diabetes mellitus	1.45 (1.04 – 2.01)	0.37	0.03
Left ventricular ejection fraction (per 10% decrease)	1.16 (1.00 – 1.34)	0.15	0.04

*Includes non-ST-segment elevation myocardial infarction or ST-segment elevation myocardial infarction. †The following covariates have been included in the Cox regression multivariable model: for major adverse cardiac events, coronary thrombotic events and myocardial infarction (age, sex, prior revascularization, prior myocardial infarction, hypertension, diabetes mellitus, high-risk acute coronary syndrome, current smoking, stent type, complex percutaneous coronary intervention and left ventricular ejection fraction), for definite or probable stent thrombosis (high-risk acute coronary syndrome, diabetes mellitus, left ventricular ejection fraction, DES generation, and prior revascularization). ‖Include prior percutaneous coronary intervention or prior coronary artery by-pass graft surgery.

Supplementary Table 6. Baseline clinical and procedural characteristics according to PCI complexity and randomized assignment to long- or short-dual antiplatelet therapy.

	Complex PCI (n = 1,680)		p-value	Non-Complex PCI (n = 7,897)		p-value
	Long-DAPT (n = 854)	Short-DAPT (n = 826)		Long-DAPT (n = 3,946)	Short-DAPT (n = 3,951)	
Age	63.7 ± 11.0	63.6 ± 10.5	0.94	63.5 ± 10.6	63.3 ± 10.4	0.53
Male gender	580 (67.9)	574 (69.5)	0.49	2665 (67.5)	2680 (67.8)	0.78
Clinical history						
Hypertension	640 (75.0)	612 (74.1)	0.66	2966 (75.4)	2948 (74.8)	0.55
Diabetes mellitus	295 (34.5)	307 (37.2)	0.26	1227 (31.2)	1203 (30.5)	0.52
Dyslipidemia	557 (65.9)	534 (65.1)	0.73	2448 (63.0)	2426 (62.3)	0.49
Current smoking	190 (25.2)	201 (27.8)	0.26	839 (25.6)	882 (26.7)	0.32
Prior myocardial infarction	165 (19.3)	179 (21.7)	0.24	816 (20.8)	803 (20.5)	0.72
Prior percutaneous coronary intervention	105 (12.3)	116 (14.0)	0.29	563 (14.3)	595 (15.1)	0.32
Prior coronary artery by-pass graft	32 (3.8)	50 (6.1)	0.07	247 (6.3)	167 (5.0)	0.02
Prior stroke	30 (4.6)	38 (6.2)	0.20	91 (3.4)	101 (3.7)	0.55
Clinical presentation			0.53			0.58
Stable coronary artery disease	443 (51.9)	441 (53.4)		2262 (57.3)	2241 (56.7)	
Acute coronary syndrome	411 (48.1)	385 (46.6)		1683 (42.7)	1710 (43.3)	

High-risk acute coronary syndrome*	161 (18.9)	139 (16.8)		631 (16.0)	640 (16.2)	
Angiographic and procedural characteristics						
Num. of diseased vessels per patient	1.9 ± 0.8	1.9 ± 0.8	0.79	1.47 ± 0.69	1.46 ± 0.68	0.78
Num. of vessels stented per patient	1.5 ± 0.7	1.5 ± 0.7	0.48	1.15 ± 0.36	1.14 ± 0.35	0.69
Num. of lesions stented per patient	1.8 ± 0.8	1.8 ± 0.9	0.78	1.19 ± 0.39	1.19 ± 0.39	0.96
Num. of stents implanted per patient	2.5 ± 1.2	2.5 ± 1.3	0.48	1.29 ± 0.46	1.28 ± 0.45	0.40
Any bifurcation treated	340 (61.3)	318 (64.4)	0.30	-	-	-
Any chronic total occlusion treated	84 (12.8)	98 (16.0)	0.11	-	-	-
Target vessels						
Left main	25 (5.0)	24 (5.1)	0.97	51 (1.8)	55 (1.9)	0.74
Left anterior descending artery	577 (80.4)	542 (76.9)	0.11	1806 (58.6)	1877 (60.2)	0.21
Left circumflex artery	329 (53.7)	307 (53.4)	0.92	830 (27.9)	809 (27.1)	0.48
Right coronary artery	309 (53.4)	309 (55.9)	0.40	981 (32.8)	993 (32.6)	0.90
Type of drug-eluting stent implanted†			0.46			< 0.0001
Old-generation drug-eluting stent	129 (15.6)	114 (14.3)		633 (16.2)	309 (7.9)	
New-generation drug-eluting stent	700 (84.4)	686 (85.8)		3274 (83.8)	3600 (92.1)	

Results reported as n (%) or mean ± standard deviation. DAPT = Dual antiplatelet therapy.

*Includes non-ST-segment elevation myocardial infarction or ST-segment elevation myocardial infarction.

†Old-generation DES includes sirolimus-eluting stent and paclitaxel-eluting stents; new-generation DES include everolimus-eluting stent, zotarolimus-eluting stents and biolimus-eluting stents.

Supplementary Table 7. Effect of long- versus short-term DAPT on the risk of ischemic events according to DES generation in the complex PCI cohort.

Endpoint	DES generation	Adjusted HR (95% CI)	P for interaction
Major adverse cardiac events	Early-generation	0.35 (0.07 – 1.68)	0.12
	New-generation	0.76 (0.45 – 1.28)	
Coronary thrombotic events	Early-generation	0.48 (0.09 – 2.42)	0.38
	New-generation	0.69 (0.38 – 1.26)	
Definite or probable stent thrombosis	Early-generation	-*	-*
	New-generation	0.70 (0.20 – 2.50)	
Myocardial infarction	Early-generation	0.48 (0.09 – 2.42)	0.39
	New-generation	0.77 (0.41 – 1.44)	
Cardiac death	Early-generation	-*	-*
	New-generation	1.29 (0.55 – 3.08)	

Early-generation DES includes sirolimus-eluting and paclitaxel-eluting DES. New-generation DES includes everolimus-eluting, biolimus-eluting, zotarolimus-eluting and new-generation sirolimus-eluting DES.

*Not estimable because of too low number of events.

Supplementary Table 8. Inter-trial heterogeneity assessment.

Endpoint	Breslow-Day Test p-value	I^2 test*	Cox model $p_{interaction}$†
Major adverse cardiac events	0.71	0%	0.51
Cardiac death	0.95	0%	0.65
Myocardial infarction	0.68	0%	0.95
Definite or probable stent thrombosis	0.52	0%	0.43
Coronary thrombotic event‡	0.78	0%	0.61
All-cause mortality	0.87	0%	0.51
Non-cardiac death	0.91	0%	0.77
Stroke	0.54	0%	0.69
Target vessel revascularization	0.99	0%	0.73
Bleeding			
Major bleeding	0.76	0%	0.58
Minor bleeding	0.84	0%	0.92
Any bleeding	0.82	0%	0.71

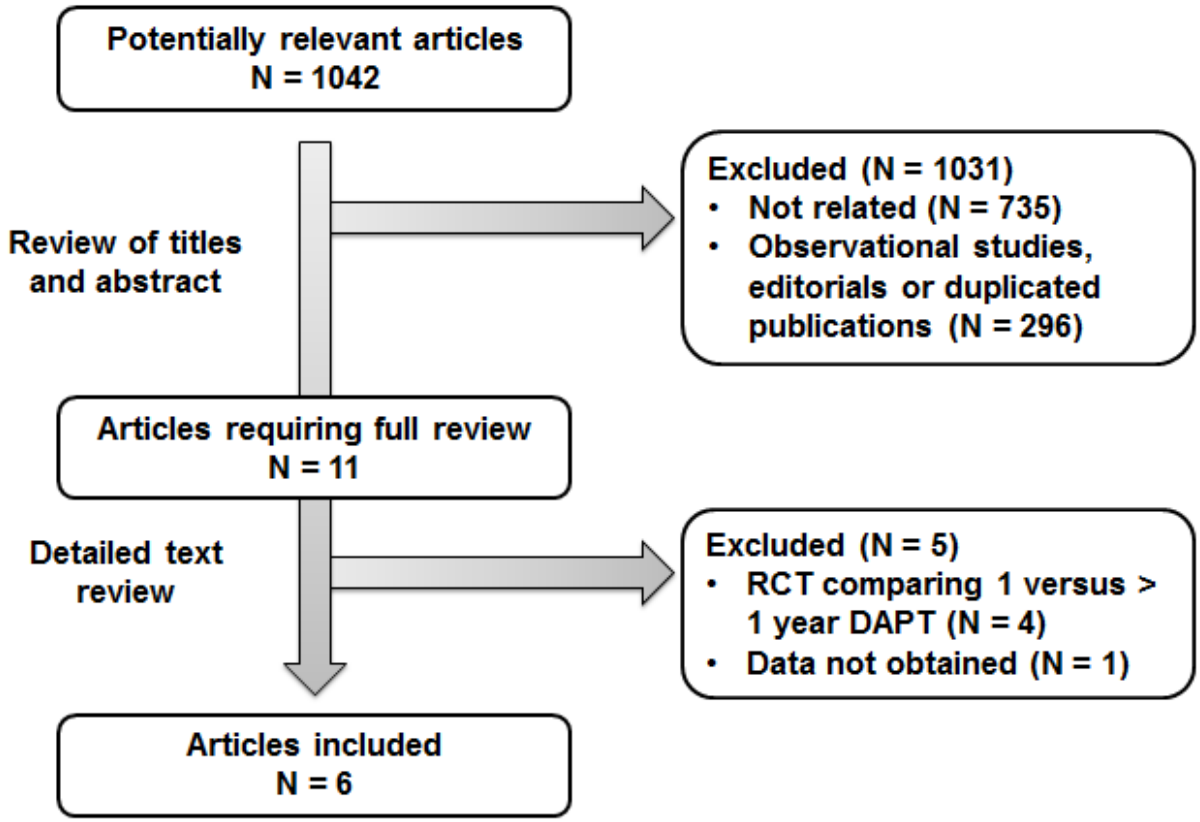
*Values of < 25%, ≥ 25% to > 50%, and > 50% represent none or mild, moderate, and severe heterogeneity, respectively

†Interaction term between trial identifier * randomized DAPT treatment duration.

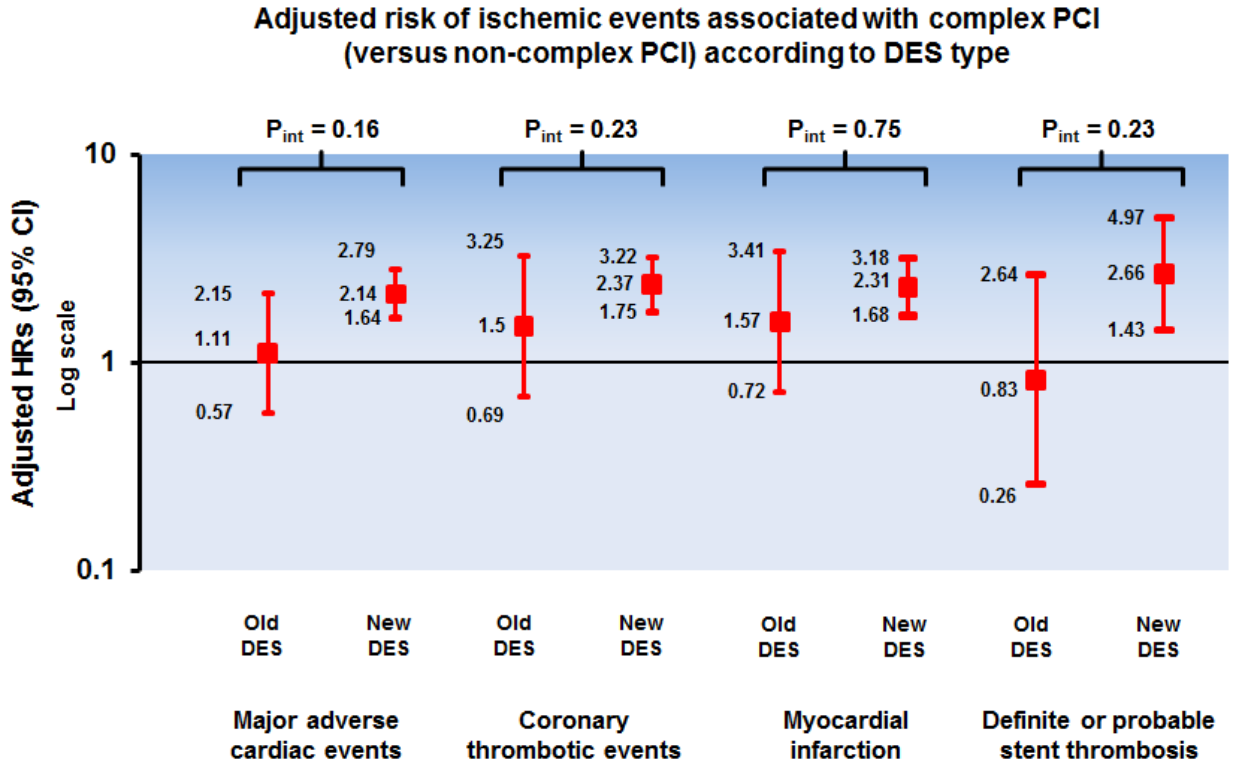
Supplementary Table 9. Risk of bias across studies for the primary efficacy and safety endpoint.

Type of bias	PRODIGY	RESET	EXCELLENT	OPTIMIZE	SECURITY	ITALIC
Selection bias						
Random sequence generation	Low-risk	Low-risk	Low-risk	Low-risk	Low-risk	Low-risk
Allocation concealment	Low-risk	Low-risk	Low-risk	Low-risk	Low-risk	Low-risk
Performance bias						
Blinding of participants and personnel	High-risk	High-risk	High-risk	High-risk	High-risk	High-risk
Detection bias						
Blinding of outcome assessment	Intermediate-risk	Intermediate-risk	Intermediate-risk	Intermediate-risk	Intermediate-risk	Intermediate-risk
Attrition bias						
Incomplete outcome data	Low-risk	Low-risk	Low-risk	Low-risk	Low-risk	Low-risk
Reporting bias						
Selective reporting	Low-risk	Low-risk	Low-risk	Low-risk	Low-risk	Low-risk

Supplementary Figure 1.

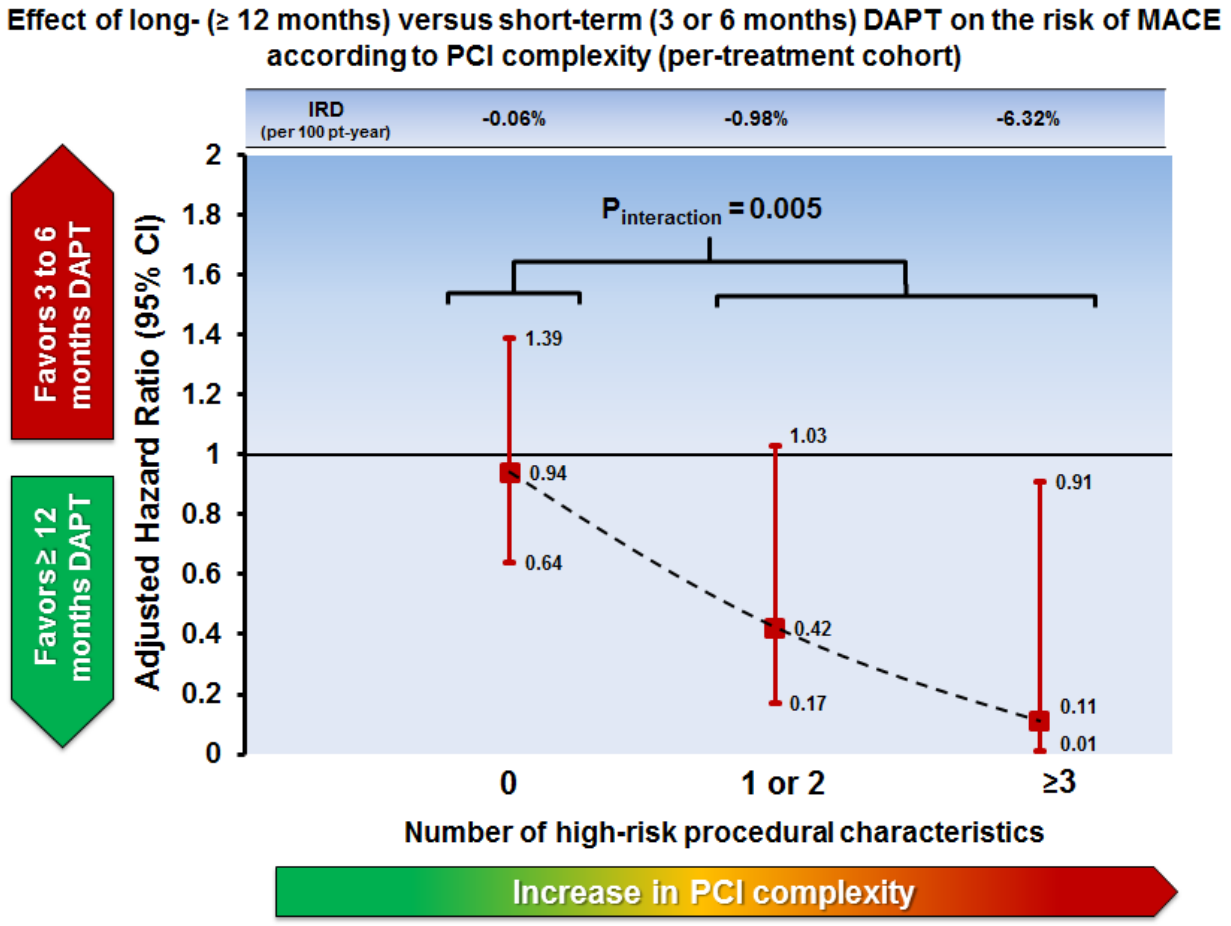


Supplementary Figure 2.



Old DES includes sirolimus-eluting stent or paclitaxel-eluting stent. New DES includes everolimus-eluting stent, zotarolimus-eluting stent or biolimus-eluting stent.

Supplementary Figure 3.



Supplementary Figure 4.