JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER

VOL. 68, NO. 17, 2016
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2016.07.760

Efficacy and Safety of Dual Antiplatelet Therapy After Complex PCI

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ABSTRACT

BACKGROUND Optimal upfront dual antiplatelet therapy (DAPT) duration after complex percutaneous coronary intervention (PCI) with drug-eluting stents (DES) remains unclear.

OBJECTIVES This study investigated the efficacy and safety of long-term (≥12 months) versus short-term (3 or 6 months) DAPT with aspirin and clopidogrel according to PCI complexity.

METHODS The authors pooled patient-level data from 6 randomized controlled trials investigating DAPT durations after PCI. Complex PCI was defined as having at least 1 of the following features: 3 vessels treated, ≥3 stents implanted, ≥3 lesions treated, bifurcation with 2 stents implanted, total stent length >60 mm, or chronic total occlusion. The primary efficacy endpoint was major adverse cardiac events (MACE), defined as the composite of cardiac death, myocardial infarction, or stent thrombosis. The primary safety endpoint was major bleeding. Intention-to-treat was the primary analytic approach.

RESULTS Of 9,577 patients included in the pooled dataset for whom procedural variables were available, 1,680 (17.5%) underwent complex PCI. Overall, 85% of patients received new-generation DES. At a median follow-up time of 392 days (interquartile range: 366 to 710 days), patients who underwent complex PCI had a higher risk of MACE (adjusted hazard ratio [HR]: 1.98; 95% confidence interval [CI]: 1.50 to 2.60; $p < 0.0001$). Compared with short-term DAPT, long-term DAPT yielded significant reductions in MACE in the complex PCI group (adjusted HR: 0.56; 95% CI: 0.35 to 0.89) versus the noncomplex PCI group (adjusted HR: 1.01; 95% CI: 0.75 to 1.35; $p_{interaction} = 0.01$). The magnitude of the benefit with long-term DAPT was progressively greater per increase in procedural complexity. Long-term DAPT was associated with increased risk for major bleeding, which was similar between groups ($p_{interaction} = 0.96$). Results were consistent by per-treatment landmark analysis.

CONCLUSIONS Alongside other established clinical risk factors, procedural complexity is an important parameter to take into account in tailoring upfront duration of DAPT. (J Am Coll Cardiol 2016;68:1851–64)

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)

CAD = coronary artery disease

CTE = coronary thrombotic event

DAPT = dual antiplatelet therapy

DES = drug-eluting stent(s)

MACE = major adverse cardiac event(s)

MI = myocardial infarction

PCI = percutaneous coronary intervention

RCT = randomized controlled trial

ST = stent thrombosis

A period of dual antiplatelet therapy (DAPT) is required after percutaneous coronary intervention (PCI) with drug-eluting stents (DES) (1-3). The pathophysiological rationale for DAPT after DES-PCI is predicated on the need to prevent stent-related thrombotic complications while vascular healing and platform endothelialization are ongoing, a process that seems to last between 1 and 6 months with new-generation DES (1,2,4). Whether to extend DAPT after this mandatory period to provide a broader atherothrombotic risk protection is currently a matter of debate (1). Prolonged DAPT is associated with significant risk reductions in stent- and nonstent-related cardiac ischemic events, counterbalanced by an increased hazard of major bleeding, which is known to be associated with increased morbidity and mortality (1,2,4). The subtle balance between the ongoing risk of ischemia and bleeding requires a careful evaluation of the individual patient's clinical and anatomic profile to identify those patients who might benefit from prolonged and/or higher-potency platelet inhibition and those who might be exposed to an excessive risk of bleeding (5).

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Coronary artery disease (CAD) complexity significantly influences the effectiveness of invasive revascularization strategies and is associated with a higher risk of adverse events, proportional to its severity and burden (5). Patients undergoing PCI with more advanced CAD and challenging subsets of lesions require more complex procedures and remain at increased risk of mid- to long-term adverse ischemic events (5,6). Although initially the U.S. Food and Drug Administration gave on-label indication for DES use in simple, single, de novo coronary lesions in low-risk patients with CAD, many PCIs are currently performed in patients with high-risk clinical and anatomic features. Additionally, several reports linked specific procedural features with a higher risk of short- and long-term coronary thrombosis (7-11). Within this background, patients with advanced CAD undergoing complex revascularization procedures may benefit from more aggressive long-term medical treatments and risk factor control. We therefore hypothesized that compared with a short-term (3 or 6 months) period of DAPT, a longer regimen of DAPT (≥1 year) will reduce the risk of major adverse cardiac events (MACE) to a greater extent after complex percutaneous coronary revascularization.

METHODS

STUDY DESIGN. The present study is a post hoc patient-level pooled analysis of randomized controlled trials (RCTs) designed to investigate the efficacy and safety of long-term (≥1 year) versus short-term (3 or 6 months) DAPT in patients undergoing complex or noncomplex PCI. We pooled patient-level data from RCTs comparing short (3 or 6 months) versus long (≥1 year) duration of DAPT. Randomized trials comparing 1 year versus more than 1 year of DAPT were excluded. The study rationale and search strategy were previously reported (4). Briefly, relevant RCTs were searched using MEDLINE, the Cochrane database, the EMBASE database, tctmd, ClinicalTrials, Clinical Trial Results, Cardiosource, and abstracts and presentations from major cardiovascular meetings using the following key words: randomized clinical trial, drug-eluting stent, dual antiplatelet therapy,

Biosensors and Eli Lilly; and has been a consultant for Medtronic and Scitech. Dr. Bhatt has served on the advisory board of Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, and Regado Biosciences; has served on the board of directors of the Boston VA Research Institute and Society of Cardiovascular Patient Care; is chair of the American Heart Association Quality Oversight Committee; has served on the data monitoring committees of Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, and the Population Health Research Institute; has received honoraria from the American College of Cardiology (Senior Associate Editor, *Clinical Trials and News*, ACC.org), Belvoir Publications (Editor-in-Chief, *Harvard Heart Letter*), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (Editor-in-Chief, *Journal of Invasive Cardiology*), *Journal of the American College of Cardiology* (guest editor; associate editor), Population Health Research Institute (clinical trial steering committee), Slack Publications (Chief Medical Editor, *Cardiology Today's Intervention*), the Society of Cardiovascular Patient Care (secretary/treasurer), and WebMD (continuing medical education steering committees); is Deputy Editor of *Clinical Cardiology*; is vice chair of the NCDR-ACTION Registry Steering Committee and VA CART Research and Publications Committee; has received research funding from Amarin, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Forest Laboratories, Ischemix, Medtronic, Pfizer, Roche, Sanofi, and The Medicines Company; has received royalties from Elsevier (Editor, *Cardiovascular Intervention: A Companion to Braunwald's Heart Disease*); has served as site coinvestigator for Biotronik, Boston Scientific, and St. Jude Medical; is a trustee of the American College of Cardiology; and has performed unfunded research for FlowCo, PLx Pharma, and Takeda. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received April 29, 2016; revised manuscript received July 12, 2016, accepted July 26, 2016.

clopidogrel, aspirin, and thienopyridines. The most updated or most inclusive data for a given study were chosen for abstraction. Internal validity of RCTs was assessed by evaluating concealment of allocation, blind adjudication of events, and inclusion of all randomized patients in the analysis (Online Appendix). Patient-level data were obtained from the principal investigators of all qualifying trials and combined in a single pooled database. In addition to the previously included RCTs (n = 4) (12–15), we included the SECURITY (Second Generation Drug-Eluting Stent Implantation Followed by Six- Versus Twelve-Month Dual Antiplatelet Therapy) (16) and the ITALIC (Is There A LIfe for DES After Discontinuation of Clopidogrel) (17) trials. The study flow diagram and characteristics of the included studies are described in Online Tables 1 and 2 and Online Figure 1. The present review was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses statements (18).

STUDY OBJECTIVES AND DEFINITIONS. The objectives of the present study were to: 1) evaluate the effect of procedural complexity on outcomes after contemporary PCI with DES; and 2) investigate the efficacy and safety of long-term (≥1 year) versus short-term (3 or 6 months) DAPT in patients undergoing complex and noncomplex PCI. Complex PCI was defined as a procedure with at least 1 of the following angiographic characteristics: 3 vessels treated, ≥3 stents implanted, ≥3 lesions treated, bifurcation with 2 stents implanted, total stent length >60 mm, or chronic total occlusion as target lesion. Complex PCI was defined on the basis of previously published reports linking features of procedural complexity with ischemic risk and by the clinical judgment of the investigators who conceived this study (Drs. Giustino, Chieffo, and Colombo) (7–11). Short-term DAPT was defined as a randomized DAPT duration ≤6 months (3 or 6 months), whereas long-term DAPT was defined as a randomized DAPT duration ≥12 months.

The primary efficacy endpoint was MACE, defined as the composite of cardiac death, myocardial infarction (MI), or definite or probable stent thrombosis (ST) at median time of follow-up. The primary safety endpoint was major bleeding at median time of follow-up. The endpoint definitions as applied in each trial were incorporated. Bleeding was defined according to the TIMI (Thrombolysis In Myocardial Infarction) criteria in 4 trials (12,14,15,19), the BARC (Bleeding Academic Research Consortium) criteria in 1 trial, and the REPLACE (Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events) criteria in 1 trial (13). Secondary endpoints were the rates of all-cause mortality, cardiac mortality, noncardiac mortality, MI, definite or probable ST, coronary thrombotic events (CTEs) (defined as the composite of MI or definite or probable ST), target vessel revascularization, minor bleeding, and any bleeding. In each trial, a blinded clinical events committee adjudicated events (Online Table 2). Endpoint definitions in each included trial are reported in Online Table 3.

STATISTICAL ANALYSIS. Individual patient data was pooled in a single dataset and analyzed with a single-stage approach. The intention-to-treat population was used for the analyses, including all patients according to randomized treatment arm assignment (long- vs. short-term DAPT). Categorical variables are reported as counts and percentages and were compared by the Cochrane-Mantel-Haenszel test, using trial identifier as the stratification variable. Continuous variables are reported as mean ± SD and were compared with 2-way analysis of variance, using trial identifier as the stratification variable. A simple Cox regression model was used to generate cumulative hazard function curves at median time of follow-up for descriptive purposes. Incidence rates and incidence rate differences for the main study endpoints (MACE, CTE, and major bleeding) are reported as 100 patient-days of follow-up.

The adjusted effect of "complex PCI" was estimated with multivariable Cox regression modeling, including "complex PCI" as either a categorical or a continuous (per increase in number of complex PCI features) covariate in the Cox model, stratified by trial identifier. Additionally, to evaluate the effect of the individual complex PCI components on ischemic outcomes, each was included as a separate predictor in the multivariable Cox model. Besides complex PCI, the following covariates were used as candidates for the Cox regression multivariable model: age, sex, prior revascularization (PCI or coronary artery bypass graft), prior MI, hypertension, diabetes mellitus, high-risk acute coronary syndrome (ACS) (including non-ST-segment elevation MI or ST-segment elevation myocardial infarction), current smoking, and stent type. The adjusted effect of complex versus noncomplex PCI was also evaluated according to DES generation (early-generation vs. new-generation) for the main ischemic endpoints. Multicollinearity was evaluated by a visual inspection of correlation matrix and estimation of the variance inflation factor, with >10 used as a threshold to define significant multicollinearity. The proportionality assumption for the Cox models was verified using the Schoenfeld residuals method. Effect estimates are reported with adjusted hazard ratios (HRs) and 95% confidence intervals (CIs).

TABLE 1 Baseline Characteristics in All Randomized Patients According to PCI Complexity

	Complex PCI (n = 1,680)	Noncomplex PCI (n = 7,897)	p Value
Age, yrs	63.6 ± 10.8	63.4 ± 10.5	0.36
Male	1,154 (68.7)	5,345 (67.7)	0.16
Clinical history			
Hypertension	1,252 (74.6)	5,914 (75.1)	0.74
Diabetes mellitus	602 (35.8)	2,430 (30.8)	0.006
Dyslipidemia	1,091 (65.5)	4,874 (62.6)	0.59
Current smoking	391 (26.5)	1,721 (26.1)	0.90
Prior MI	344 (20.5)	1,619 (20.6)	0.88
Prior PCI	221 (13.2)	1,158 (14.7)	0.44
Prior coronary artery bypass graft	82 (4.9)	444 (5.6)	0.65
Prior stroke	68 (5.4)	192 (3.5)	0.31
Clinical presentation			0.37
Stable CAD	884 (52.6)	4,503 (57.0)	
ACS*	796 (47.4)	3,393 (43.0)	
High-risk ACS†	300 (17.9)	1,271 (16.1)	
Angiographic and procedural characteristics			
Number of diseased vessels/patient	1.9 ± 0.8	1.5 ± 0.7	—
Number of vessels stented/patient‡	1.5 ± 0.7	1.2 ± 0.4	—
Number of lesions stented/patient‡	1.8 ± 0.8	1.2 ± 0.4	—
Number of stents implanted/patient‡	2.5 ± 1.2	1.3 ± 0.5	—
Any bifurcation treated with 2 stents‡	658 (16.2)	—	—
Any chronic total occlusion treated‡	182 (2.7)	—	—
Target vessels			
Left main	49 (5.1)	106 (1.8)	<0.0001
Left anterior descending artery	1,119 (78.6)	3,683 (59.4)	<0.0001
Left circumflex artery	636 (53.5)	1,639 (27.5)	<0.0001
Right coronary artery	618 (54.6)	1,974 (32.7)	<0.0001
Type of DES implanted§			<0.0001
Early-generation DES	243 (14.9)	942 (12.1)	
New-generation DES	1,386 (85.1)	6,874 (87.9)	
Randomization			0.52
Longer DAPT	826 (49.2)	3,951 (50.0)	
Shorter DAPT	854 (50.8)	3,946 (50.0)	

Values are mean ± SD or n (%). *Includes unstable angina, non-ST-segment elevation myocardial infarction or ST-segment elevation myocardial infarction. †Includes non-ST-segment elevation myocardial infarction or ST-segment elevation myocardial infarction. ‡Variable included in the Complex PCI definition, reported for descriptive purposes. §Old-generation DES include sirolimus- and paclitaxel-eluting stents; new-generation DES include everolimus-, zotarolimus-, and biolimus-eluting stents.

ACS = acute coronary syndrome(s); CAD = coronary artery disease; DAPT = dual antiplatelet therapy; DES = drug-eluting stent(s); MI = myocardial infarction; PCI = percutaneous coronary intervention.

The treatment effect of long- versus short-term DAPT according to PCI complexity was estimated with a Cox regression model stratified by trial identifier. Due to observed imbalances in baseline characteristics, to minimize bias, this Cox regression analysis was also adjusted for a propensity score determined using a logistic regression model for treatment with long- versus short-term DAPT. The following variables were considered for the propensity score determination: age, sex, hypertension, dyslipidemia, smoking, diabetes, prior MI, prior revascularization (PCI or coronary artery bypass graft), high-risk ACS, and type of DES implanted. Goodness-of-fit of the propensity score model was evaluated with the Hosmer-Lemeshow test. The consistency of the treatment effect between the complex and noncomplex PCI groups was evaluated through the inclusion of randomized treatment-by-complex PCI interaction terms.

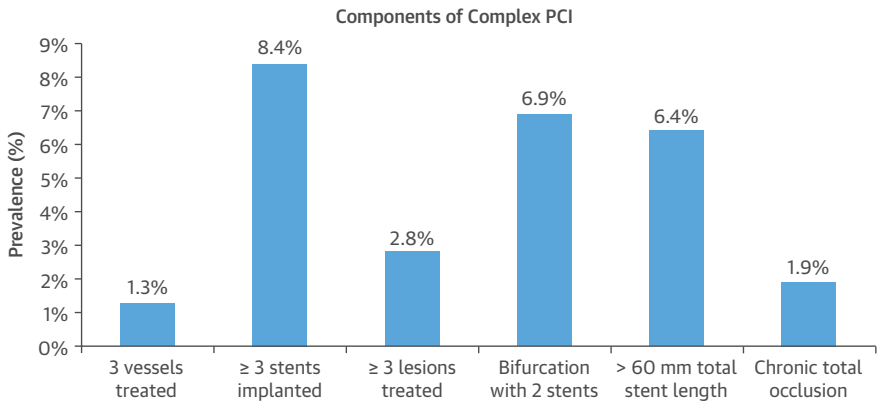
As in all of the included trials randomization was dissociated from actual treatment divergence (i.e., randomization after PCI and DAPT duration divergence at 6 months), implying that endpoint events occurring prior to treatment divergence could not be attributable to differences in DAPT duration, a landmark analysis at the time of treatment divergence in each trial was performed using a per-treatment cohort. To do so, all patients with endpoint events in the first 6 months (for the SECURITY, PRODIGY [Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study], ITALIC, and EXCELLENT [Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting] trials) and in the first 3 months (for the OPTIMIZE [Optimized Duration of Clopidogrel Therapy Following Treatment With the Zotarolimus-Eluting Stent in Real-World Clinical Practice] and RESET [REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation] trials) were excluded, as well as those randomized to short-term DAPT in whom DAPT was prolonged ≥1 month beyond the period scheduled for treatment cessation and those randomized to long-term DAPT who interrupted treatment more than 1 month before the temporal cutoff for treatment divergence versus short-term DAPT.

To evaluate treatment effect consistency within additional clinical subsets of patients, we evaluated the risk of MACE for long- versus short-term DAPT across the complex PCI components and in the following clinical subgroups of interest within the complex and noncomplex PCI subgroups: age >65 years, sex, diabetes, hypertension, high-risk ACS (including non-ST-segment elevation MI or ST-segment elevation MI), prior MI, prior revascularization, and stent type. For stent type, treatment effect consistency was also assessed for CTE, definite or probable ST, and MI.

Multiple intertrial heterogeneity assessments were performed by the Breslow-Day test, the I^2 statistic (with values <25%, 25% to 50%, and >50% representing mild, moderate, and severe heterogeneity, respectively), and by measuring the interaction term between trial identifier and randomized treatment within the Cox models for each outcome of interest. Bias assessment was performed according the Cochrane Collaboration tool (20).

Analyses were performed with IBM SPSS Statistics software, version 20.0 (SPSS, IBM, Armonk, New York)

FIGURE 1 Prevalence and Overlap of Complex PCI Components



Prevalence of complex PCI components in the overall population. PCI = percutaneous coronary intervention.

and Stata version 12.0 (Stata Corp., College Station, Texas). A 2-sided p value of ≤0.05 was considered statistically significant for all analyses.

RESULTS

EFFECT OF PROCEDURAL COMPLEXITY. Of 9,577 patients with available angiographic characteristics, 1,680 (17.5%) underwent complex PCI. Baseline clinical and procedural characteristics according to PCI complexity are reported in Table 1. Patients who underwent complex PCI more commonly had diabetes. Clinical presentation was similar between groups. Randomization assignment to shorter- or longer-term DAPT was well-balanced between the 2 groups. Overall, new-generation DES were used in approximately 86% of patients across all trials. The prevalence of the complex PCI components in the overall population is illustrated in Figure 1, and the overlap between complex PCI components in Online Table 4.

At a median follow-up time of 392 days (interquartile range: 366 to 710 days), patients who underwent complex PCI had higher crude rates of MACE (Table 2, Figure 2A) and CTE (Table 2, Figure 2B), MI, definite or probable ST, target vessel revascularization, and mortality (Table 2). By multivariable Cox regression modeling (Table 3), complex PCI remained strongly associated with increased risk of MACE, CTEs, definite or probable ST, and MI with a magnitude that was comparable to that of a history of prior MI or high-risk ACS presentation. Results were overall comparable following inclusion of left ventricular ejection fraction in the multivariable model (Online Table 5). Complex PCI was not associated with an increased risk of major bleeding at adjusted analyses (Figure 2C).

By including complex PCI as a continuous variable (per number of high-risk procedural features) within the same multivariable models, the risk of adverse events trended to be greater as the number of high-risk procedural characteristics increased (per number of complex PCI variables increase: for MACE, adjusted HR: 1.46; 95% CI: 1.27 to 1.69; $p_{trend} < 0.0001$; for CTE, adjusted HR: 1.37; 95% CI: 1.20 to 1.55; $p_{trend} < 0.0001$;

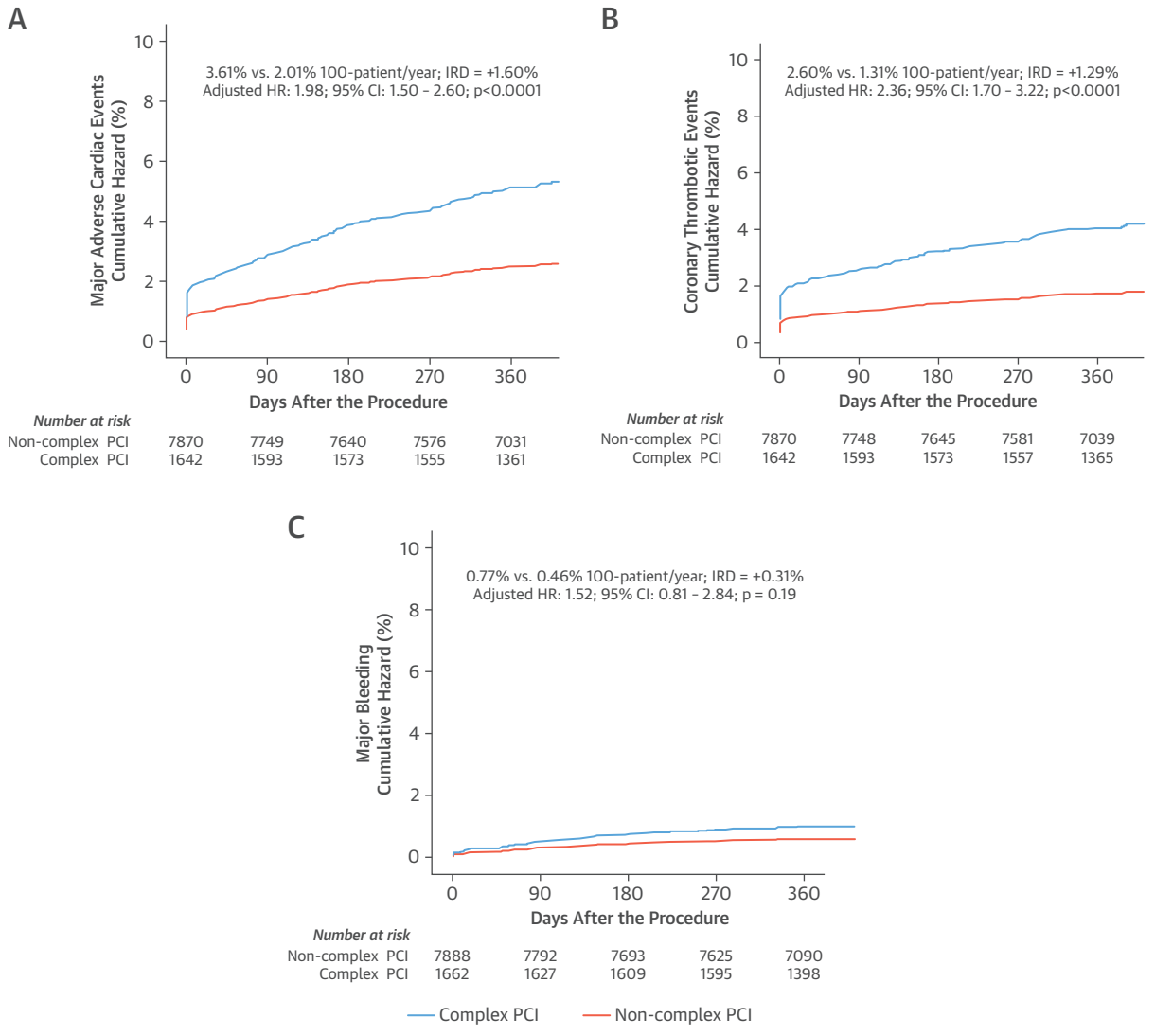
TABLE 2 Ischemic and Bleeding Outcomes in All Randomized Patients According to PCI Complexity

	Complex PCI (n = 1,680)	Noncomplex PCI (n = 7,897)	Univariate HR* (95% CI)	p Value†
MACE	91 (5.4)	230 (2.9)	2.05 (1.60–2.61)	<0.0001
Cardiac death	34 (2.0)	101 (1.3)	1.74 (1.18–2.57)	0.009
MI	65 (3.9)	143 (1.8)	2.32 (1.73–3.12)	<0.0001
Definite or probable ST	20 (1.2)	41 (0.5)	2.51 (1.47–4.3)	0.003
CTE‡	71 (4.2)	154 (2.0)	2.35 (1.77–3.19)	<0.0001
All-cause mortality	54 (3.2)	177 (2.2)	1.61 (1.18–2.18)	0.01
Noncardiac death	20 (1.2)	71 (0.9)	1.50 (0.91–2.46)	0.35
Stroke	10 (0.6)	49 (0.6)	1.05 (0.53–2.08)	0.74
Target vessel revascularization	111 (6.6)	285 (3.6)	2.00 (1.60–2.49)	<0.0001
Bleeding				
Major bleeding	17 (1.0)	50 (0.6)	1.70 (0.98–2.95)	0.06
Minor bleeding	18 (1.1)	79 (1.0)	1.14 (0.68–1.91)	0.62
Any bleeding	35 (2.1)	126 (1.6)	1.40 (0.96–2.03)	0.08

Values are number of events (%) unless otherwise indicated. *Generated with univariate Cox regression. †p value from univariate Cox regression. ‡Defined as the composite of definite or probable stent thrombosis or myocardial infarction.

CI = confidence interval; CTE = coronary thrombotic event; HR = hazard ratio; MACE = major adverse cardiac events; ST = stent thrombosis; other abbreviations as in Table 1.

FIGURE 2 Effect of Procedural Complexity on Ischemic and Bleeding Outcomes



Cumulative hazard curves for major adverse cardiac events **(A)**, coronary thrombotic events **(B)**, and major bleeding **(C)**. Incidence rates are expressed as 100 patient-years of follow-up. CI = confidence interval; HR = hazard ratio; IRD = incidence rate difference; PCI = percutaneous coronary intervention.

for definite or probable ST, adjusted HR: 1.35; 95% CI: 1.00 to 1.82; $p_{trend} = 0.05$; and for MI, adjusted HR: 1.47; 95% CI: 1.25 to 1.73; $p_{trend} < 0.0001$). Adjusted risk for the cardiac ischemic endpoints according to the type of high-risk procedural feature is illustrated in **Figure 3**. Bifurcation with 2 stents implanted was the angiographic subset most consistently and strongly associated with increased ischemic risk. The effect of complex PCI on cardiac ischemic endpoints was uniform between early- and new-generation DES (Online Figure 2).

LONG- VERSUS SHORT-TERM DAPT IN PATIENTS WITH OR WITHOUT COMPLEX PCI. Baseline characteristics according to procedural complexity and randomized assignment to long- or short-term DAPT are illustrated in Online Table 6. The differential median exposure time to DAPT between the long- and short-term DAPT groups was 9 months. Results for long- versus short-term DAPT in the complex and noncomplex PCI groups are reported in **Table 4**. The effect of long-term DAPT was heterogeneous per PCI complexity, with a significant benefit in patients

who underwent complex PCI (Figure 4A) (adjusted HR: 0.56; 95% CI: 0.35 to 0.89) compared with those who had noncomplex PCI (adjusted HR: 1.01; 95% CI: 0.75 to 1.35; $p_{interaction} = 0.01$). Importantly, the benefit on MACE of long-term DAPT was greater as the number of high-risk procedural features increased (Central Illustration). Long-term DAPT was also associated with significantly greater benefit on the risk of CTEs in patients who underwent complex PCI (Figure 4B) (adjusted HR: 0.57; 95% CI: 0.33 to 0.97) compared with noncomplex PCI (adjusted HR: 0.87; 95% CI: 0.61 to 1.25; $p_{interaction} = 0.04$). Long-term DAPT was associated with an increased risk of major bleeding, which was uniform in magnitude and direction between patients with and without complex PCI (Figure 4C) ($p_{interaction} = 0.96$). Results were consistent at per-treatment landmark analysis (Figure 5, Online Figure 3). The effect of long-term DAPT on the composite and individual ischemic endpoints was uniform between early- and new-generation DES within the complex PCI group (Online Table 7). There was no evidence of intertrial heterogeneity for all of the investigated endpoints (Online Table 8). Bias assessment is reported in Online Table 9.

LONG- VERSUS SHORT-TERM DAPT IN PATIENTS WITH OR WITHOUT COMPLEX PCI ACROSS CLINICAL AND ANGIOGRAPHIC SUBGROUPS. The effect of long- versus short-term DAPT in patients who underwent complex and noncomplex PCI across clinical subsets is reported in Table 5. The effect of long- versus short-term DAPT was uniform across subsets within both the complex and noncomplex PCI groups (Table 5) and across the high-risk angiographic subsets included in the complex PCI definition (Online Figure 4).

TABLE 3 Predictors of MACE and CTEs in All Randomized Patients

	Adjusted HR* (95% CI)	Beta Coefficient	p Value
MACE			
High-risk ACS†	2.20 (1.67–2.90)	0.79	<0.0001
Complex PCI	1.98 (1.50–2.60)	0.68	<0.0001
Prior MI	1.77 (1.33–2.35)	0.57	<0.0001
Prior revascularization‡	1.73 (1.29–2.32)	0.71	<0.0001
Diabetes mellitus	1.41 (1.09–1.82)	0.35	0.008
Age/yr increase	1.04 (1.02–1.05)	0.04	<0.0001
CTE§			
Complex PCI	2.36 (1.70–3.22)	0.85	<0.0001
Prior revascularization‡	2.04 (1.45–2.89)	0.71	<0.0001
High-risk ACS†	1.86 (1.32–2.60)	0.62	<0.0001
Prior MI	1.85 (1.32–2.60)	0.62	<0.0001
Diabetes mellitus	1.36 (1.00–1.84)	0.31	0.05
Age/yr increase	1.02 (1.01–1.03)	0.02	0.01
Definite or probable ST			
Old-generation DES	2.76 (1.51–5.04)	1.02	0.001
Prior revascularization‡	2.66 (1.50–4.72)	0.98	0.001
High-risk ACS†	2.62 (1.49–4.60)	0.96	0.001
Complex PCI	2.25 (1.30–3.90)	0.81	0.004
Diabetes mellitus	1.88 (1.13–3.13)	0.63	0.02
Myocardial infarction			
Complex PCI	2.29 (1.64–3.20)	0.83	<0.0001
Prior revascularization‡	2.19 (1.48–3.03)	0.75	<0.0001
High-risk ACS†	1.92 (1.35–2.73)	0.65	<0.0001
Prior MI	1.92 (1.35–2.73)	0.65	<0.0001
Female sex	1.52 (1.10–2.11)	0.42	0.01
Diabetes mellitus	1.39 (1.01–1.91)	0.33	0.04
Age/yr increase	1.02 (1.00–1.03)	0.02	0.02

*The following covariates were included in the Cox regression multivariable model. for MACE, CTE, and MI: age, sex, prior revascularization, prior MI, hypertension, diabetes mellitus, high-risk ACS, current smoking, stent type, and complex PCI; and for definite or probable ST: high-risk ACS, diabetes mellitus, prior MI, DES generation, and prior revascularization. †Includes non-ST-segment elevation MI or ST-segment elevation MI. ‡Includes prior PCI or prior coronary artery bypass graft surgery. §Defined as the composite of definite or probable ST or MI.

Abbreviations as in Tables 1 and 2.

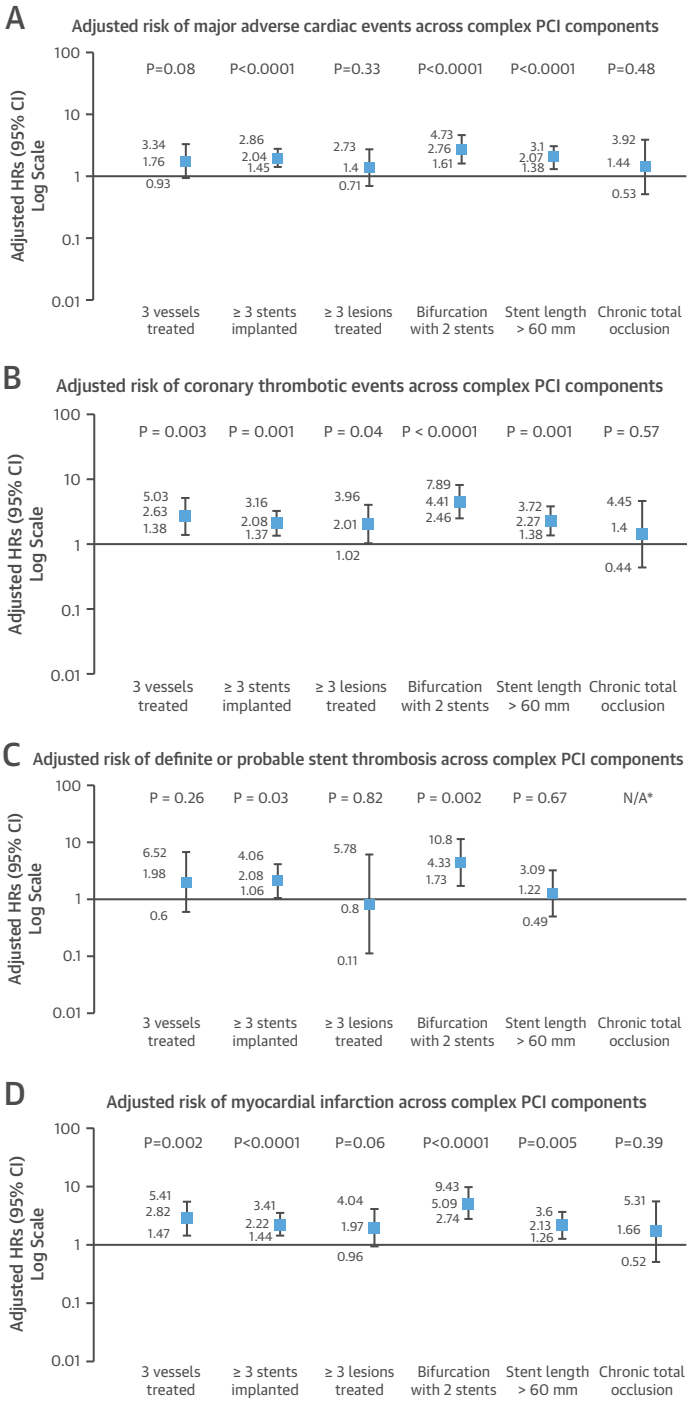
DISCUSSION

The present study of more than 9,000 patients randomized to different durations of DAPT after PCI with mostly new-generation DES introduces procedural complexity as an ischemic risk factor to take into account for clinical decision-making surrounding DAPT duration. The main findings of the present analysis can be summarized as follows:

1. Patients who underwent complex PCI had a higher risk of MACE and CTE at follow-up. This risk was similar in magnitude to that of other well-established clinical risk factors and tended to be greater for progressively higher degrees of procedural complexity. Additionally, the effect of procedural complexity was uniform between DES generations.
2. DAPT for ≥1 year was associated with a significant benefit on the risk of MACE and CTEs compared with 3 or 6 months of DAPT in patients who underwent complex PCI. Importantly, the anti-ischemic benefits of prolonged DAPT were progressively greater as the degree of procedural complexity increased.
3. The benefits of prolonged DAPT appeared to be uniform across complex PCI components, DES generations, and clinical presentation.
4. Long-term DAPT was associated with an increased risk of major bleeding, irrespective of procedural complexity.

Currently, clinical decision-making on *upfront* DAPT intensity and duration after coronary stenting is predominantly made on the basis of clinical ischemic and bleeding risk factors. However, it remains unclear whether the degree of procedural

FIGURE 3 Effect of High-Risk Procedural Subsets on Ischemic Outcomes



Adjusted risk of major adverse cardiac events **(A)**, coronary thrombotic events **(B)**, definite or probable stent thrombosis **(C)**, and myocardial infarction **(D)** across high-risk procedural subsets. *Not estimable because the number of events was too low. Incidence rates are expressed as 100 patient-years of follow-up. Abbreviations as in Figure 2.

TABLE 4 Ischemic and Bleeding Outcomes in All Randomized Patients According to PCI Complexity and DAPT Duration

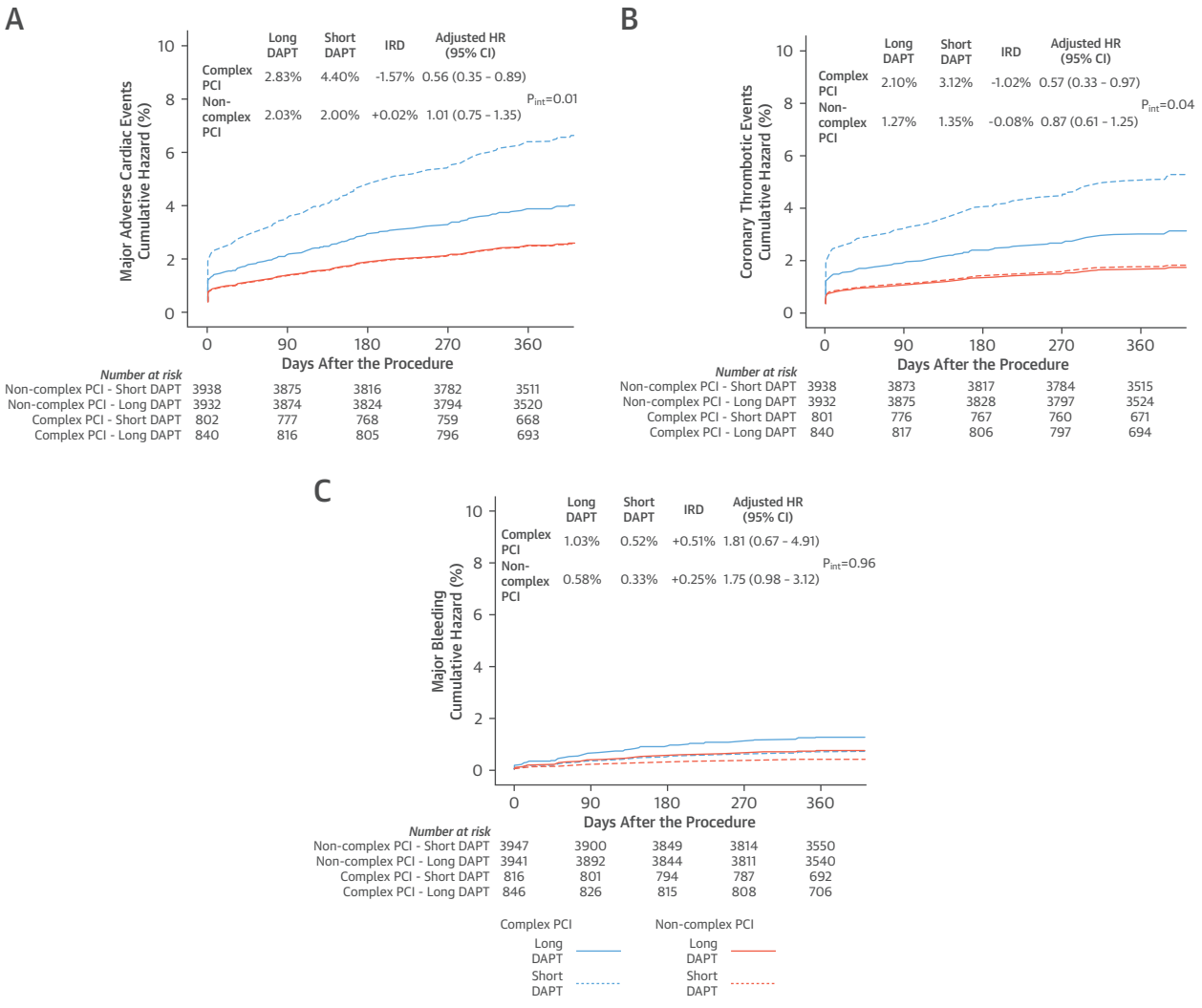
	Complex PCI (n = 1,680)			Noncomplex PCI (n = 7,897)			
	Longer DAPT (n = 854)	Shorter DAPT (n = 826)	Adjusted HR (95% CI)	Longer DAPT (n = 3,946)	Shorter DAPT (n = 3,951)	Adjusted HR (95% CI)	p Value for Interaction
MACE	35 (4.1)	56 (6.8)	0.56 (0.35–0.89)	116 (2.9)	114 (2.9)	1.01 (0.75–1.35)	0.01
Cardiac death	15 (1.8)	19 (2.3)	0.65 (0.30–1.41)	56 (1.4)	45 (1.1)	1.34 (0.86–2.09)	0.33
Myocardial infarction	25 (2.9)	40 (4.8)	0.60 (0.35–1.06)	71 (1.8)	72 (1.8)	0.90 (0.62–1.30)	0.08
Definite or probable stent thrombosis	7 (0.8)	13 (1.6)	0.37 (0.12–1.16)	20 (0.5)	21 (0.5)	0.95 (0.51–1.75)	0.08
CTE*	27 (3.2)	44 (5.3)	0.57 (0.33–0.97)	75 (1.9)	79 (2.0)	0.87 (0.61–1.25)	0.04
All-cause mortality	27 (3.2)	27 (3.3)	1.11 (0.60–2.04)	94 (2.4)	83 (2.1)	1.20 (0.87–1.67)	0.81
Noncardiac death	12 (1.4)	8 (1.0)	2.87 (0.91–9.03)	35 (0.9)	36 (0.9)	1.03 (0.62–1.70)	0.07
Target vessel revascularization	55 (6.4)	56 (6.8)	1.01 (0.68–1.49)	129 (3.3)	156 (3.9)	0.81 (0.64–1.02)	0.39
Stroke	7 (0.8)	3 (0.4)	2.67 (0.69–10.42)	25 (0.6)	24 (0.6)	1.04 (0.58–1.86)	0.32
Bleeding							
Major bleeding	11 (1.3)	6 (0.7)	1.81 (0.67–4.91)	32 (0.8)	18 (0.5)	1.75 (0.98–3.12)	0.96
Minor bleeding	11 (1.3)	7 (0.8)	1.51 (0.59–3.90)	44 (1.1)	35 (0.9)	1.25 (0.80–1.94)	0.68
Any bleeding	22 (2.6)	13 (1.6)	1.64 (0.83–3.26)	75 (1.9)	51 (1.3)	1.45 (1.02–2.07)	0.72

Values are number of events (%) unless otherwise indicated. *Defined as the composite of definite or probable ST or MI.
Abbreviations as in Tables 1 and 2.

complexity substantially influences future ischemic risk and identifies patients who may benefit from longer or more intense antithrombotic therapies. In the present study, PCI complexity not only exerted an effect on ischemic risk proportional to the number of high-risk procedural features (degree of procedural complexity), but also had an overall association with MACE that was similar in magnitude to that of other well-established clinical risk factors. The association between procedural complexity and thrombotic risk is multifactorial, and can be both correlative and causative in nature: first, patients who undergo more complex revascularization procedures may have more advanced CAD and a greater prevalence of comorbidities, implying a status of higher risk for atherothrombosis due to the natural progression of atherosclerotic CAD; second, a greater number of stents implanted and stenting of more complex lesions may act as true mediators of the stent-related thrombotic risk, as these factors directly influence the propensity to platelet activation and intracoronary thrombosis (7,21); and third, PCI in the presence of complex CAD may be associated with a greater likelihood of incomplete myocardial revascularization, with subsequent higher risk of recurrent cardiac ischemic events, ventricular dysfunction, and mortality (5).

DAPT has been established as a standard-of-care treatment to prevent stent- and nonstent-related ischemic events after PCI with DES (1-3). The antithrombotic benefits of DAPT extend beyond the stented vascular segment to the whole coronary circulation and possibly the systemic arterial vasculature. However, because of the systemic effect of pharmacological platelet inhibition, this antithrombotic protection is achieved at the expense of an increased risk of bleeding (1-3). The anti-ischemic and prohemorrhagic effects of DAPT are proportional to the potency and duration of platelet inhibition and are both influenced by the underlying individual ischemic and bleeding risk factors (22,23). In the present study, we clarified the comparative effectiveness of 1 year or more versus 3 or 6 months of DAPT after complex percutaneous revascularization. Prolonged DAPT was associated with a greater anti-ischemic benefit in patients who underwent complex PCI, with an increased magnitude of benefit with greater procedural complexity (**Central Illustration**). The greater benefits with prolonged DAPT in patients with more complex angiographic features can be explained by the following: 1) more and longer stents implanted imply the presence of additional potential sites of delayed metallic platform endothelialization, which may act as a trigger for platelet activation and arterial thrombosis (7,21); 2) stenting of complex lesions (i.e., bifurcations, longer lesions, or chronic total occlusions) may enhance the risk of stent malapposition, incomplete lesion coverage, and delayed endothelialization, which, in turn, all interplay in enhancing the thrombotic propensity within the target vascular segment (6); and 3) as patients who are undergoing more complex revascularization procedures have more advanced CAD and comorbidities, they are more prone to native plaque progression and acute changes with subsequent atherothrombosis. In the Gene Polymorphism, Platelet Reactivity, and SYNTAX (Synergy

FIGURE 4 Intention-to-Treat Analysis for Long- Versus Short-Term DAPT in Patients With or Without Complex PCI

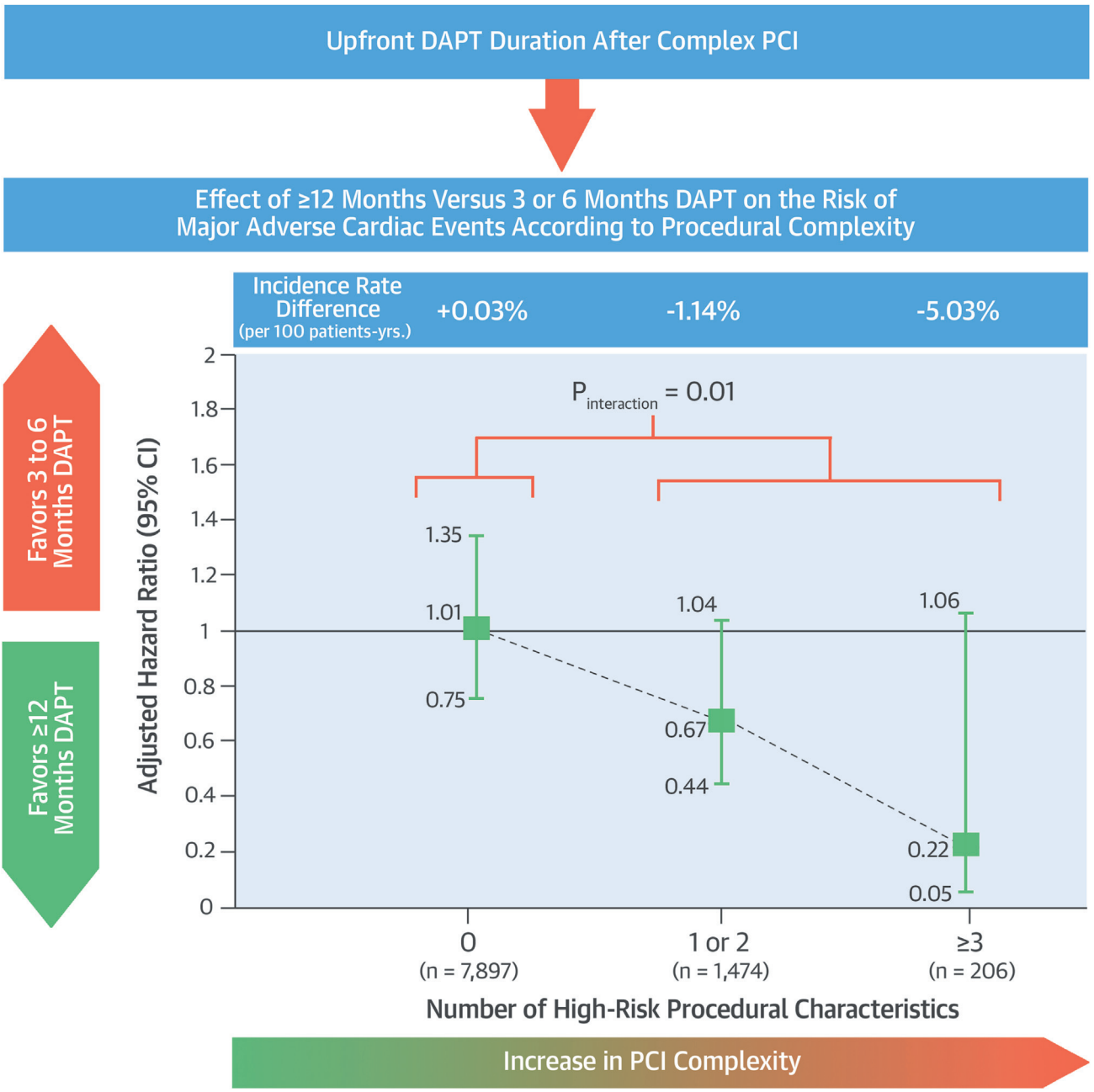


Cumulative hazard curves for long-term DAPT versus short-term DAPT for major adverse cardiac events **(A)**, coronary thrombotic events **(B)**, and major bleeding **(C)** in patients with or without complex PCI. Incidence rates are expressed as 100 patient-years of follow-up. DAPT = dual antiplatelet therapy; other abbreviations as in Figure 2.

Between PCI With Taxus and Cardiac Surgery) score studies, high on-clopidogrel platelet reactivity on a background of high SYNTAX score was associated with a 5-fold higher risk of MACE compared with patients with high on-clopidogrel platelet reactivity but a low SYNTAX score (24). In line with these proposed pathobiological mechanisms, prolonged and/or more intensified platelet inhibition may protect from all of the previously mentioned factors. Of paramount importance, the effect of long-term DAPT on the primary efficacy endpoint persisted in the per-treatment landmark analysis in which endpoint events were analyzed after treatment divergence. Considering that 1 of the main limitations of the included trials was that patients were randomized before the scheduled period of DAPT cessation, this observation is reassuring regarding the robustness of the main findings.

The increased risk of major bleeding with prolonged DAPT is consistent with previous published reports and was uniform between PCI complexity groups (1). Given the greater anti-ischemic benefits of prolonged DAPT, alongside a similar bleeding hazard, the current findings support the hypothesis that patients who undergo complex coronary revascularization will benefit from upfront longer (>1 year) DAPT duration. These findings may provide useful

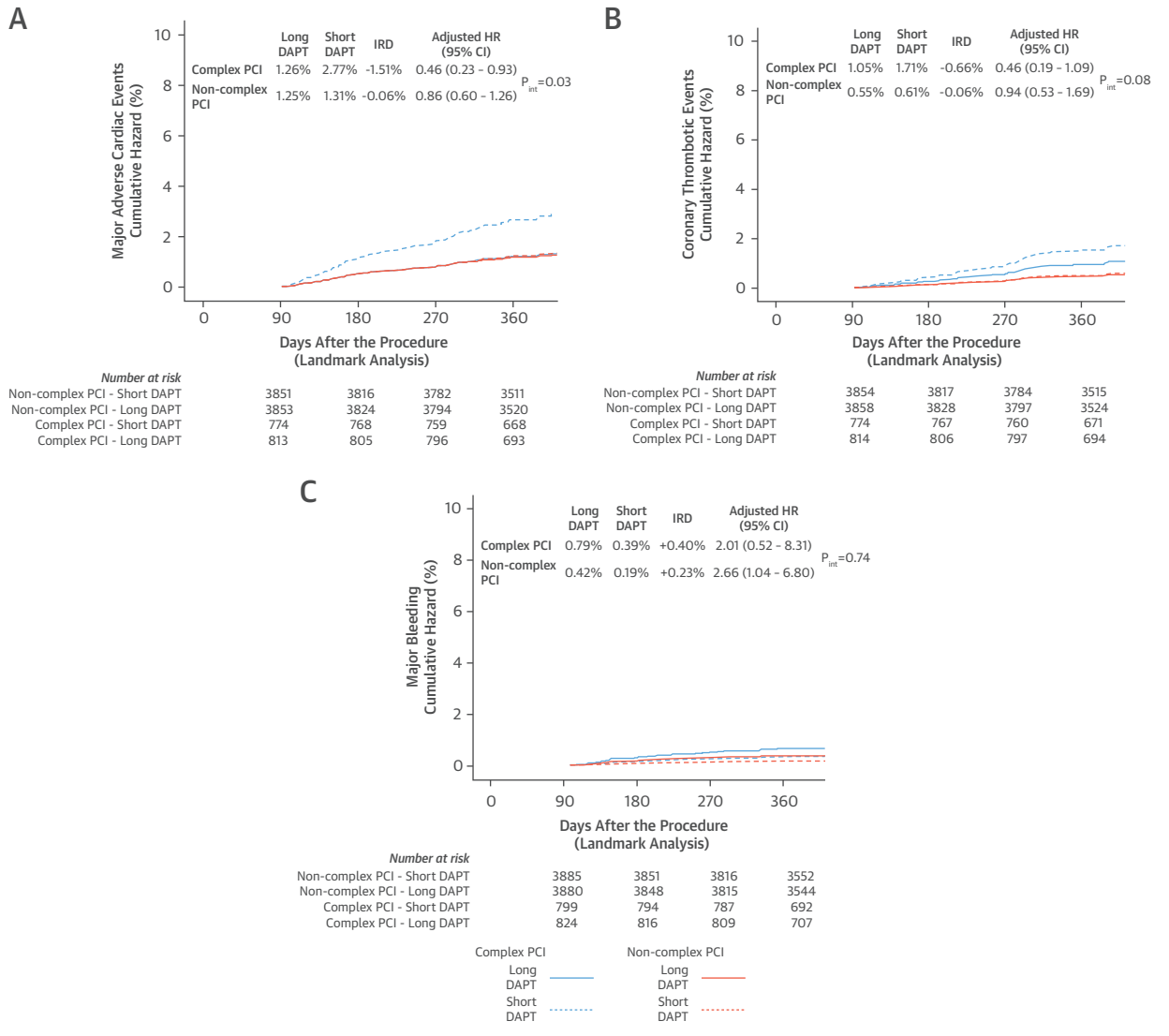
CENTRAL ILLUSTRATION **Ischemic Benefit of Long-Term DAPT According to the Degree of PCI Complexity**



Giustino, G. et al. J Am Coll Cardiol. 2016;68(17):1851–64.

DAPT for ≥1 year significantly reduced the risk of major adverse cardiac events after complex PCI compared with 3 or 6 months of DAPT. Complex PCI was defined as the composite of 3 vessels treated, ≥3 stents implanted, ≥3 lesions treated, bifurcation with 2 stents implanted, total stent length >60 mm, or chronic total occlusion. The y-axis displays the adjusted hazard ratios for long-term DAPT on risk of major adverse cardiac events. The x-axis displays the number of high-risk procedural features. Incidence rate differences per 100 patient-years of follow-up per number of high-risk procedural features are displayed above the plot. Complex PCI is associated with increased risk of major adverse cardiac events with a magnitude comparable to that of traditional clinical risk factors (i.e., prior myocardial infarction or acute coronary syndrome presentation). The magnitude of the anti-ischemic effect of long-term DAPT trended to be greater for increase in PCI complexity.
CI = confidence interval; DAPT = dual antiplatelet therapy; IRD = incidence rate differences; PCI = percutaneous coronary intervention.

FIGURE 5 Per-Treatment Analysis for Long- Versus Short-Term DAPT in Patients With or Without Complex PCI



Cumulative hazard curves for long-term versus short-term DAPT for major adverse cardiac events **(A)**, coronary thrombotic events **(B)**, and major bleeding **(C)** in patients with or without complex PCI. Incidence rates are expressed as 100 patient-years of follow-up. Abbreviations as in Figures 2 and 4.

information for practicing cardiologists when decisions regarding the optimal upfront duration of "mandatory DAPT" need to be made. Our results must be put into perspective with the recently developed DAPT risk score and Patterns of Non-Adherence to Dual Anti-Platelet Regimen In Stented Patients (PARIS) risk scores from the DAPT trial and PARIS registry, respectively (22,23). Our findings complement these scores by introducing the concept that in the presence of a low or moderate bleeding risk, angiographic risk factors, in addition to other, well-established ischemic risk factors, must be taken into account when decisions surrounding DAPT duration have to be made. Finally, the prevalence of "complex PCI" in our study was 18.0%. This is most likely an underestimate because of the exclusion criteria of the individual RCTs included in this pooled analysis; it is plausible that the number of patients receiving complex procedures in a real-world practice is substantially higher.

STUDY LIMITATIONS. Although our findings rely on individual patient-level data from prospective

TABLE 5 Effect of Long- Versus Short-Term DAPT on Risk of MACE Across Clinical Subsets Within the Complex and Noncomplex PCI Groups

	Adjusted HR (95% CI)	p Value for Interaction
Complex PCI		
Age, yrs		
>65	0.76 (0.44–1.30)	0.78
≤65	0.42 (0.21–0.86)	
Sex		
Male	0.57 (0.34–0.97)	0.51
Female	0.67 (0.33–1.37)	
Diabetes		
Yes	0.55 (0.29–1.04)	0.86
No	0.68 (0.39–1.19)	
High-risk ACS*		
Yes	0.37 (0.16–0.83)	0.18
No	0.75 (0.45–1.23)	
Smoking		
Yes	0.60 (0.18–2.06)	0.93
No	0.55 (0.33–0.91)	
Prior MI		
Yes	0.44 (0.20–0.95)	0.60
No	0.72 (0.43–1.20)	
Prior revascularization		
Yes	0.58 (0.26–1.28)	0.97
No	0.65 (0.40–1.08)	
DES generation		
Early generation†	0.35 (0.07–1.68)	0.15
New generation	0.79 (0.50–1.25)	
Noncomplex PCI		
Age, yrs		
>65	0.97 (0.70–1.36)	0.11
≤65	1.03 (0.68–1.55)	
Sex		
Male	0.90 (0.65–1.26)	0.18
Female	1.20 (0.78–1.83)	
Diabetes		
Yes	1.07 (0.71–1.61)	0.37
No	0.96 (0.69–1.34)	
High-risk ACS*		
Yes	1.02 (0.62–1.66)	0.47
No	0.98 (0.73–1.34)	
Smoking		
Yes	0.74 (0.42–1.31)	0.75
No	1.11 (0.79–1.57)	
Prior MI		
Yes	1.05 (0.70–1.58)	0.94
No	0.97 (0.69–1.35)	
Prior revascularization		
Yes	1.28 (0.80–2.06)	0.17
No	0.91 (0.67–1.24)	
DES generation†		
Early generation	1.02 (0.51–2.06)	0.96
New generation	0.98 (0.73–1.30)	

*Includes non-ST-segment elevation MI or ST-segment elevation MI. †Old-generation DES include sirolimus- and paclitaxel-eluting stents; new-generation DES include everolimus-, zotarolimus-, and biolimus-eluting stents.

Abbreviations as in Tables 1 and 2.

randomized trials with data monitoring and event adjudication by clinical event committees, several limitations need to be disclosed. First, our results have to be considered hypothesis-generating, as this is a non-pre-specified, post hoc analysis from RCTs that were not designed to test the benefit of long-term DAPT according to procedural complexity. Second, the included trials had significant design limitations, including lack of statistical power to detect differences in hard endpoints, slow enrollment, premature interruption, lower than expected event rates, open-label design, exclusion of high-risk patients (with low prevalence of high-risk ACS presentations), and treatment crossover. Third, procedural complexity definitions included variables available in the pooled dataset; therefore, other markers of anatomic and/or procedural complexity, such as calcified lesions, graft lesions, rotablator use, Medina class, SYNTAX score, and vessel size, were not available. Fourth, although patient-level pooled analyses overcome some of the limitations of study-level meta-analyses, even the present study is subject to the intrinsic limitations of the included trials, such as relatively limited external validity (due to the inclusion/exclusion criteria of each trial), and the heterogeneous study designs. Fifth, the lack of significant differences according to DAPT duration in the noncomplex PCI cohort does not imply the lack of difference or the lack of benefit of prolonged DAPT in this subset of patients (due to the limited power and follow-up of the included studies).

CONCLUSIONS

Patients who undergo complex percutaneous coronary revascularization procedures are at a substantially higher risk of ischemic events, in a graded fashion, with increased procedural complexity. In patients who underwent complex PCI, compared with a short period of DAPT (3 or 6 months), long-term DAPT (≥1 year) significantly reduced the risk of cardiac ischemic events with a magnitude that was greater for higher procedural complexity. The results of the present study suggest that, along with other well-established clinical ischemic risk factors, complexity of coronary artery stenting is an important parameter to take into account in tailoring upfront duration of DAPT, and possibly potency, for cardiac ischemic protection.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Patients undergoing complex PCI are at higher risk of cardiac ischemic events, in a graded fashion with increase in procedural complexity. In patients who undergo complex PCI, compared with a short period of DAPT (3 or 6 months), longer DAPT (≥1 year) significantly reduced the risk of ischemic events. The magnitude of the benefit of prolonged DAPT seems to be greater as the degree of PCI complexity is higher.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Patients who undergo complex PCI might benefit from upfront longer (>6 months) DAPT duration to prevent MACE, irrespective of clinical presentation.

TRANSLATIONAL OUTLOOK: Ad hoc pharmacological strategies to optimize outcomes after complex PCI may warrant prospective randomized investigation.

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KEY WORDS bleeding, drug-eluting stents, myocardial infarction, stent thrombosis

APPENDIX For an expanded Methods section as well as supplemental figures and tables, please see the online version of this article.