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Short-Term Versus Long-Term Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation in Elderly Patients

A Meta-Analysis of Individual Participant Data From 6 Randomized Trials

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ABSTRACT

OBJECTIVES This study sought to evaluate the optimal duration of dual antiplatelet therapy (DAPT) after the implantation of a drug-eluting stent (DES) in elderly patients.

BACKGROUND Qualified studies to evaluate the optimal duration of DAPT in elderly patients have been very limited.

METHODS Using 6 randomized trials that compared short-term (≤6 months) and long-term (12 months) DAPT, individual participant data meta-analysis was performed in elderly patients (≥65 years of age). The primary study outcome was the 12-month risk of a composite of myocardial infarction, definite or probable stent thrombosis, or stroke. The major secondary outcome was the 12-month risk of major bleeding.

RESULTS The primary outcome risk did not significantly differ between patients receiving short-term and long-term DAPT (hazard ratio [HR]: 1.12; 95% confidence interval [CI]: 0.88 to 1.43; p = 0.3581) in the overall group of study participants. In subgroup analysis, a significant interaction between age and DAPT duration was observed for primary outcome risk (p for interaction = 0.0384). In the subset of younger patients (<65 years of age, n = 6,152), short-term DAPT was associated with higher risk of primary outcome (HR: 1.67; 95% CI: 1.14 to 2.44; p = 0.0082). In elderly patients (n = 5,319), however, the risk of primary outcome did not significantly differ between patients receiving short-term and long-term DAPT (HR: 0.84; 95% CI: 0.60 to 1.16; p = 0.2856). Short-term DAPT was associated with a significant reduction in major bleeding compared with long-term DAPT (HR: 0.50; 95% CI: 0.30 to 0.84; p = 0.0081) in the overall group, and particularly in elderly patients (HR: 0.46; 95% CI: 0.24-0.88; p = 0.0196).

CONCLUSIONS Short-term DAPT after new-generation DES implantation may be more beneficial in elderly patients than in younger patients. (J Am Coll Cardiol Intv 2018;11:435–43) © 2018 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CI = confidence interval

DAPT = dual antiplatelet therapy

DES = drug-eluting stent(s)

HR = hazard ratio

Several clinical and procedural factors have been reported to be associated with increased ischemic (e.g., stent thrombosis) and bleeding risk in patients with an implanted drug-eluting stent (DES) (1,2). Individual patients may have factors that increase both ischemic and bleeding risk (e.g., advanced age, diabetes mellitus, and chronic kidney disease), which renders it difficult to assess the benefit-risk ratio of prolonged dual antiplatelet therapy (DAPT) and make a clinical decision (1). Two large randomized trials, the DAPT (Dual AntiPlatelet Therapy) trial and PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis In Myocardial Infarction 54) trial, showed a significant reduction in cardiac and cerebrovascular events and an increase in bleeding episodes with prolonged DAPT (3,4). A recent meta-analysis confirmed that extending DAPT beyond 12 months conferred a trade-off between reduced ischemic events and increased bleeding (5). However, the application of such findings to elderly patients is challenging because of a higher risk of bleeding and ischemic events occurring in this subgroup compared with younger patients (6). In general, elderly individuals have been under-represented in randomized trials that investigated different durations of DAPT following DES implantation (6). Qualified studies (i.e., patient-level meta-analyses from randomized trials with larger number of patients) to evaluate the optimal duration of DAPT in these elderly patients have been very limited. Consequently, the optimal duration of DAPT among elderly patients remains controversial.

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The objective of the present study was to evaluate clinical outcomes between short-term (≤6 months) and long-term (12 months) DAPT after DES implantation in elderly patients.

METHODS

STUDY DESIGN. The present study was an individual participant data meta-analysis from randomized trials that investigated the efficacy and safety of short-term DAPT in elderly patients undergoing DES implantation. Randomized trials comparing short-term DAPT (3 or 6 months) with long-term DAPT (12 or 24 months) were eligible for inclusion in this study. Randomized trials comparing 12-month DAPT with ≥12-month DAPT or enrolling patients not treated with DES were excluded. Methodological details of this meta-analysis have previously been described (7–11). Briefly, in August 2015, relevant randomized trials were identified through searches in Medline, Embase, the Cochrane database, and prominent international websites and meetings. The following keywords were used: *randomized clinical trial*, *DES*, *DAPT*, *clopidogrel*, *aspirin*, and *thienopyridines*. Two investigators (T.P. and Diego Della Riva) independently reviewed the titles, abstracts, and studies to determine whether they met the inclusion criteria (8). The internal validity of each randomized trial was assessed by evaluating concealment of allocation, blind adjudication of events, and the inclusion of all randomized patients in the analysis (7,8). Risk of bias was assessed using the Cochrane method. Patient-level data were obtained from the principal investigators of the trials that met the eligibility criteria, and were combined in a single pooled database (7,8). The study flow diagram is shown in Online Figure 1. Seven trials met the inclusion criteria, and patient-level data were obtained for 6 of these trials and included in the final meta-analysis. These included RESET (REal Safety and Efficacy of a 3-month dual antiplatelet Therapy following E-ZES implantation) (12), EXCELLENT (Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting) (13), PRODIGY (Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study) (14), OPTIMIZE (Optimized Duration of Clopidogrel Therapy Following Treatment With the Zotarolimus-Eluting Stent in Real-World Clinical Practice) (15), SECURITY (Second Generation Drug-Eluting Stent Implantation Followed by Six- Versus Twelve-Month Dual Antiplatelet Therapy) (16), and ITALIC (Is There A LIfe for DES After Discontinuation of Clopidogrel) (17) trials. The major characteristics, inclusion and exclusion criteria, and assessments of internal validity are shown in Online Tables 1 and 2. The risk of bias was generally low, as shown

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in Online Table 3 and Online Figure 2, and no relevant issues that could undermine data integrity were identified. The present meta-analysis was performed in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) individual participant data statements (18).

ENDPOINTS AND DEFINITIONS. The primary study outcome was the 12-month rate of a composite of myocardial infarction, definite or probable stent thrombosis, or stroke. The major secondary outcome was the 12-month rate of major bleeding. The definitions of the endpoints are provided in Online Table 4. The endpoint definitions applied in each trial have been incorporated. In each trial, a blinded clinical event committee adjudicated events.

STATISTICAL ANALYSIS. Individual participant data meta-analysis was performed using a 1-stage approach. The intention-to-treat population was used for analysis, and events beyond 12 months (360 days) were censored to preserve analysis homogeneity. Continuous variables were reported in terms of mean and SD, and compared using 2-way analysis of variance stratified by trial. Categorical variables were reported as number and percentage, and compared using logistic regression analysis stratified by trial. Endpoints were reported in terms of hazard ratio (HR) and 95% confidence interval (CI), and compared using a Cox regression model stratified by trial, using trial identifiers as random effects. Cumulative event curves were constructed using the Kaplan-Meier method.

The risk of primary outcome with short-term and long-term DAPT was also analyzed in pre-specified subgroups based on age (<65 and ≥65 years of age), sex, diabetes mellitus, clinical presentation (stable ischemic heart disease and acute coronary syndrome), presence of multivessel disease, and location of stented coronary artery (left anterior descending artery and others) (7). Cox regression was used for formal interaction testing to evaluate the consistency of treatment effects between subgroups. In subgroups of patients with <65 (younger patients) and ≥65 (elderly patients) years of age, the risk of outcome was adjusted, considering overfitting, statistical difference across groups, and clinical significance, with the following variables: sex, diabetes mellitus, clinical presentation of acute coronary syndrome, numbers of diseased vessels per patient, and types of DES (19).

An additional analysis was also performed using a 2-stage approach. HR and 95% CI by each trial were available from individual participant data, and the estimates of effectiveness were calculated using standard meta-analysis methods. The publication bias of included trials was assessed by visual inspection of the funnel plot. Heterogeneity was assessed using the I^2 statistic, and categorized as mild (<25%), moderate (25% to 75%), and severe (>75%). In sensitivity analyses, the risk of primary efficacy endpoint was evaluated in younger patients before and after time points of 90 and 180 days (20), and was analyzed according to patients' age of 75 years of age.

The p value for interaction was corrected using the following formula: $1-(1\text{-resulting p})^6$, (21). A p value <0.05 was considered statistically significant for all analyses. Statistical analysis was performed using SAS version 9.2 (SAS Institute, Cary, North Carolina), SPSS version 18.0.0 (SPSS, Chicago, Illinois), or Reviewer Manager version 5.3 (Nordic Cochrane Center, Copenhagen, Denmark).

RESULTS

Among 11,473 randomized patients, 6,152 (53.6%) were younger (<65 years of age) and 5,319 (46.4%) were elderly (≥65 years of age). Information was missing for 2 patients. New-generation DES was used in 89.6% (10,156 of 11,341) of the analyzed patients. Baseline characteristics of the study participants are presented in Online Table 5.

ASSOCIATIONS BETWEEN AGE AND DAPT DURATION FOR CARDIAC AND CEREBROVASCULAR EVENTS. In the overall study population, the risk of primary outcome was not significantly different between short-term and long-term DAPT (unadjusted HR: 1.12; 95% CI: 0.88 to 1.43; p = 0.3581) (Online Figure 3). However, a significant interaction between age and DAPT duration was identified (p for interaction = 0.0384) (Online Figure 4). Baseline characteristics according to age and DAPT duration are shown in **Table 1**. In younger patients, a new-generation DES was more frequently used in patients with short-term DAPT compared with those with long-term DAPT. After adjustments, the risk of primary outcome was higher in patients with short-term DAPT (adjusted HR: 1.67; 95% CI: 1.14 to 2.44; p = 0.0082) (**Table 2, Figure 1**). The difference was driven by a higher risk of myocardial infarction in patients with short-term DAPT (adjusted HR: 1.56; 95% CI: 1.03 to 2.36; p = 0.0355). In elderly patients, male patients were more common in patients with short-term DAPT, and a new-generation DES was more frequently used in patient with short-term DAPT. The risk of primary outcome did not differ between short-term and long-term DAPT even after adjustments (adjusted HR: 0.84; 95% CI: 0.60 to 1.16; p = 0.2856) (**Table 3, Figure 1**). The results of individual studies are represented on a forest plot (**Figure 2**). In sensitivity analyses, the increased risk of primary outcome in younger patients with short-term DAPT

TABLE 1 Baseline Characteristics According to Duration of DAPT After Implantation of Drug-Eluting Stent in Randomized Trials, Grouped by Patient Age (<65 or ≥65 Years of Age)

	<65 Years of Age (n = 6,152)			≥65 Years of Age (n = 5,319)		
	≤6-Month DAPT (n = 3,093)	12-Month DAPT (n = 3,059)	p Value	≤6-Month DAPT (n = 2,635)	12-Month DAPT (n = 2,684)	p Value
Age, yrs	55.1 ± 6.7	55.0 ± 6.9	0.4458	72.4 ± 5.4	72.5 ± 5.4	0.3338
Weight, kg	73.6 ± 14.3	74.3 ± 14.4	0.1856	70.1 ± 13.6	69.5 ± 13.5	0.2192
Male	75.6 (2,339/3,093)	76.6 (2,343/3,059)	0.3717	64.1 (1,688/2,635)	61.4 (1,647/2,684)	0.0420
Medically treated hypertension	74.8 (2,312/3,091)	76.3 (2,328/3,053)	0.1847	81.9 (2,152/2,629)	81.3 (2,179/2,679)	0.6251
Medically treated diabetes	30.7 (942/3,068)	30.9 (939/3,035)	0.8424	32.2 (842/2,618)	32.6 (870/2,666)	0.7144
Medically treated dyslipidemia	64.6 (1,958/3,031)	65.4 (1,961/2,998)	0.5091	63.1 (1,639/2,599)	63.4 (1,673/2,639)	0.8029
Current smoker	30.0 (803/2,674)	29.8 (793/2,663)	0.8410	13.8 (314/2,270)	12.3 (280/2,276)	0.1258
Prior myocardial infarction	23.8 (650/2,737)	23.3 (623/2,670)	0.7190	19.7 (478/2,428)	20.0 (498/2,487)	0.7671
Prior percutaneous coronary intervention	18.0 (493/2,746)	16.6 (445/2,674)	0.2019	18.7 (455/2,440)	17.4 (434/2,498)	0.2442
Prior coronary bypass surgery	5.1 (140/2,745)	5.1 (137/2,672)	0.9639	7.0 (171/2,442)	7.5 (188/2,495)	0.4712
Left ventricular ejection fraction <40%	7.1 (186/2,610)	7.1 (183/2,592)	0.9258	9.3 (210/2,250)	8.4 (192/2,278)	0.2844
Hemoglobin, g/dl	14.0 ± 1.5	14.1 ± 1.5	0.5798	13.2 ± 1.6	13.2 ± 1.5	0.4069
Clinical diagnosis			0.9823			0.6707
Stable ischemic heart disease	59.3 (1,833/3,093)	59.2 (1,812/3,059)		57.4 (1,512/2,635)	58.0 (1,555/2,683)	
Acute coronary syndrome	40.7 (1,260/3,093)	40.8 (1,247/3,059)		42.6 (1,123/2,635)	42.0 (1,128/2,683)	
Unstable angina	872	844		732	738	
Non-ST-segment elevation myocardial infarction	235	246		224	239	
ST-segment elevation myocardial infarction	153	157		167	151	
Clopidogrel at discharge	99.5 (2,226/2,237)	99.7 (2,169/2,176)	0.3756	99.7 (1,740/1,745)	99.8 (1,828/1,832)	0.7482
Diseased vessels	1.4 ± 0.8	1.4 ± 0.8	0.8081	1.6 ± 0.8	1.6 ± 0.8	0.3700
Stented vessels	1.2 ± 0.4	1.2 ± 0.4	0.4948	1.2 ± 0.5	1.2 ± 0.5	0.2617
Stented coronary artery						
Left main	1.5 (27/1,834)	1.5 (27/1,784)	0.9185	3.4 (52/1,540)	3.2 (50/1,583)	0.7318
Left anterior descending artery	62.9 (1,308/2,079)	63.6 (1,282/2,017)	0.6687	63.7 (1,111/1,745)	61.8 (1,101/1,783)	0.2389
Left circumflex artery	30.1 (580/1,927)	31.1 (588/1,890)	0.4973	32.9 (536/1,630)	33.7 (571/1,694)	0.6144
Right coronary artery	35.6 (696/1,953)	35.8 (680/1,899)	0.9119	36.8 (606/1,646)	36.4 (610/1,676)	0.8015
Stented lesions	1.3 ± 0.5	1.3 ± 0.5	0.9822	1.3 ± 0.6	1.3 ± 0.6	0.7295
Implanted stents	1.5 ± 0.8	1.5 ± 0.8	0.6126	1.6 ± 0.9	1.6 ± 0.9	0.8369
Type of drug-eluting stent			<0.0001			<0.0001
First generation	5.5 (169/3,052)	12.1 (366/3,034)		9.7 (254/2,608)	15.0 (396/2,645)	
Sirolimus-eluting stent	78	264		86	241	
Paclitaxel-eluting stent	91	102		168	155	
Next generation	94.5 (2,883/3,052)	87.9 (2,668/3,034)		90.3 (2,354/2,608)	85.0 (2,249/2,645)	
Zotarolimus-eluting stent	1,789	1,433		1,366	1,137	
Everolimus-eluting stent	989	1,145		863	973	
Biolimus-eluting stent	105	90		125	139	
Smallest device diameter >3.0 mm	37.1 (458/1,236)	39.1 (483/1,237)	0.3079	30.3 (390/1,286)	27.7 (356/1,287)	0.1363
Total stent length, mm	34.1 ± 24.1	35.1 ± 23.6	0.2912	36.7 ± 24.4	36.6 ± 24.3	0.9148

Values are mean ± SD, % (n/N), or n.
DAPT = dual antiplatelet therapy.

remained regardless of the specified time points (Online Appendix). The risk of primary outcome with short-term DAPT decreased with age, showing that age of 65 years of age was around a trade-off point among changes of the risk (Online Figure 5). The risk of primary outcome according to cutoff of 75 years of age was provided in Online Table 6.

ASSOCIATIONS BETWEEN AGE AND DAPT DURATION FOR MAJOR BLEEDING. In the entire study population, short-term DAPT was associated with reduced risk of major bleeding, compared with long-term DAPT (unadjusted HR: 0.50; 95% CI: 0.30 to 0.84; p = 0.0081) (Online Figure 3). There was no apparent heterogeneity in the efficacy of short-term DAPT with respect to the risk of major bleeding across the age subgroups (p for interaction = 0.9980). In younger patients, the risk of major bleeding was not significantly different in patients with short-term DAPT (unadjusted HR: 0.59; 95% CI: 0.26 to 1.34; p = 0.2073) (**Table 2**). However, in elderly patients, it

TABLE 2 Clinical Outcomes at 12 Months According to Duration of DAPT in Patients' Age <65 Years of Age

	≤6-Month DAPT (n = 3,093)	12-Month DAPT (n = 3,059)	Unadjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value
All-cause death	21 (0.7)	41 (1.3)	0.50 (0.30–0.85)	0.0097	0.51 (0.30–0.88)	0.0154
Cardiac	13 (0.4)	25 (0.8)	0.51 (0.26–1.00)	0.0500	–	–
Noncardiac	8 (0.3)	16 (0.5)	0.49 (0.21–1.14)	0.0989	–	–
Myocardial infarction	60 (1.9)	37 (1.2)	1.59 (1.05–2.39)	0.0275	1.56 (1.03–2.36)	0.0355
Definite or probable stent thrombosis	14 (0.5)	10 (0.3)	1.37 (0.61–3.09)	0.4447	–	–
Stroke*	9 (0.3)	6 (0.2)	–	–	–	–
Bleeding	29 (0.9)	37 (1.2)	0.76 (0.47–1.24)	0.2724	0.74 (0.45–1.22)	0.2437
Major	9 (0.3)	15 (0.5)	0.59 (0.26–1.34)	0.2073	–	–
Minor	21 (0.7)	22 (0.7)	0.93 (0.51–1.69)	0.8029	–	–
Myocardial infarction or definite/probable stent thrombosis	65 (2.1)	40 (1.3)	1.59 (1.07–2.35)	0.0214	1.57 (1.06–2.33)	0.0262
Myocardial infarction, definite/probable stent thrombosis, or stroke	74 (2.4)	44 (1.4)	1.65 (1.13–2.39)	0.0089	1.67 (1.14–2.44)	0.0082

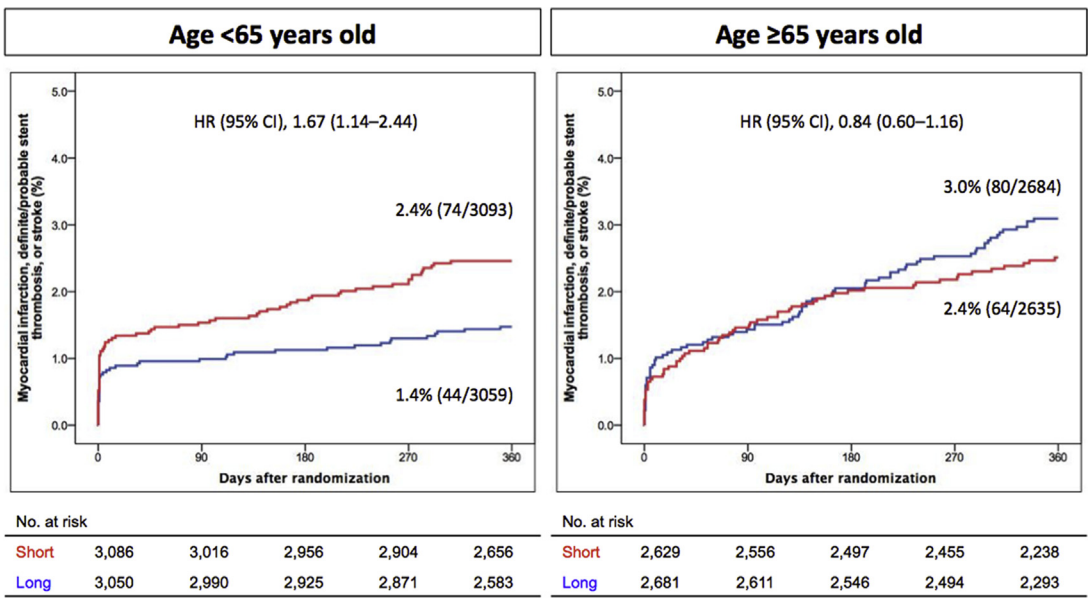
Values are n (%) unless otherwise indicated. *Convergence was not attained.
CI = confidence interval; DAPT = dual antiplatelet therapy; HR = hazard ratio.

was significantly lower in patients with short-term DAPT (unadjusted HR: 0.46; 95% CI: 0.24 to 0.88; p = 0.0196) (Table 3).

DISCUSSION

In this individual participant data meta-analysis of 6 randomized trials, the risk of a composite of myocardial infarction, definite or probable stent thrombosis, or stroke did not differ between short-term and long-term DAPT in patients treated with next-generation DES. However, treatment effects were observed to be heterogeneous between elderly and younger patients. Short-term DAPT was associated with increased risk of ischemic events in younger patients, but not in elderly patients.

FIGURE 1 Events of Myocardial Infarction, Definite or Probable Stent Thrombosis, or Stroke at 12 Months Stratified Based on Short- and Long-Term DAPT, and Grouped by Patient Age (Either <65 or ≥65 Years of Age)



The hazard ratio (HR) with 95% confidence interval (CI) is for short-term dual antiplatelet therapy (DAPT) **(red)** relative to long-term DAPT **(blue)**. Note that 16 and 9 observations were not included due either to missing or invalid values, respectively, for the time.

TABLE 3 Clinical Outcomes at 12 Months According to Duration of DAPT in Patients ≥65 Years of Age

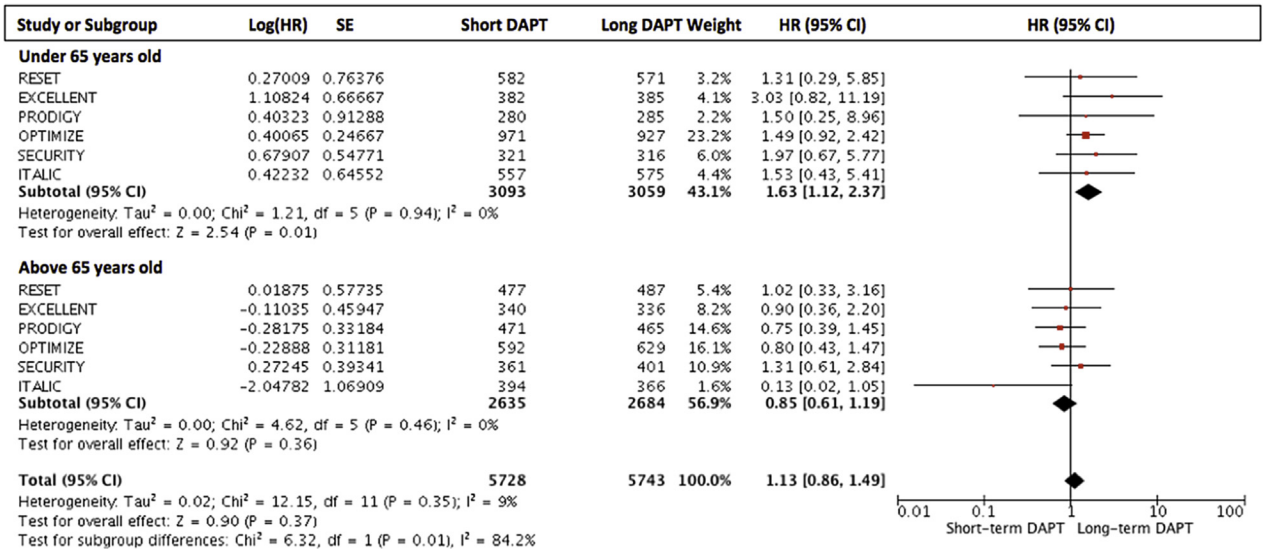
	≤6-Month DAPT (n = 2,635)	12-Month DAPT (n = 2,684)	Unadjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value
All-cause death	76 (2.9)	66 (2.5)	1.18 (0.85–1.64)	0.3231	1.15 (0.83–1.60)	0.4110
Cardiac	45 (1.7)	42 (1.6)	1.11 (0.73–1.68)	0.6417	–	–
Noncardiac	31 (1.2)	24 (0.9)	1.31 (0.77–2.24)	0.3147	–	–
Myocardial infarction	41 (1.6)	55 (2.1)	0.77 (0.52–1.16)	0.2085	0.80 (0.53–1.20)	0.2751
Definite or probable stent thrombosis	14 (0.5)	14 (0.5)	1.04 (0.49–2.17)	0.9271	–	–
Stroke	17 (0.7)	22 (0.8)	0.79 (0.42–1.48)	0.4607	–	–
Bleeding	39 (1.5)	63 (2.4)	0.63 (0.42–0.94)	0.0248	0.64 (0.43–0.95)	0.0276
Major	13 (0.5)	29 (1.1)	0.46 (0.24–0.88)	0.0196	–	–
Minor	27 (1.0)	35 (1.3)	0.79 (0.48–1.31)	0.3585	–	–
Myocardial infarction or definite/probable stent thrombosis	47 (1.8)	58 (2.2)	0.84 (0.57–1.23)	0.3703	0.86 (0.58–1.27)	0.4430
Myocardial infarction, definite/probable stent thrombosis, or stroke	64 (2.4)	80 (3.0)	0.82 (0.59–1.15)	0.2487	0.84 (0.60–1.16)	0.2856

Values are n (%) unless otherwise indicated.
Abbreviations as in Table 2.

Short-term DAPT was associated with a reduced risk of major bleeding compared with long-term DAPT, demonstrating no apparent heterogeneity in different age subgroups.

The possible heterogeneity of treatment-by-age effects on the primary outcome has been observed in previous studies: PEGASUS-TIMI 54 (p for interaction = 0.09), ISAR-SAFE (Intracoronary Stenting and Antithrombotic Regimen: Safety And EFficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting, p for interaction = 0.03), and IVUS-XPL (Impact of Intravascular Ultrasound Guidance on Outcomes of XIENCE PRIME Stents in Long Lesions, p for interaction = 0.051) (4,22,23) trials.

FIGURE 2 Forest Plots of Events of Myocardial Infarction, Definite or Probable Stent Thrombosis, or Stroke: Results of Individual Studies



Note that the random-effects model was applied to evaluate the HR with 95% CI. EXCELLENT = Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting; ITALIC = Is There A LIfe for DES After Discontinuation of Clopidogrel; 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; other abbreviations as in Figure 1.

Divergent findings between previous studies and the current analysis with respect to age may be explained as follows. Primary outcome was different among studies, and a composite of ischemic and bleeding events might not enable to assess the benefit-risk ratio associated with DAPT because ischemic events are counterbalanced by bleeding. In the present study, notably, all-cause or cardiac death was not a component of the primary outcome, because cardiac death not preceded by myocardial infarction or stent thrombosis accounted for an unexpectedly high rate of 76.3% (29 of 38) in younger patients. This might explain why such deaths might not be directly modified by DAPT. In addition, antiplatelet therapy is not theoretically effective for preventing type 2 myocardial infarction because of a supply-demand mismatch that is not the result of acute atherothrombosis (24). This may explain why short-term DAPT might be not associated with the risk of ischemic events in elderly patients. Type 2 myocardial infarction is often accompanied by anemia, sepsis, and other medical conditions that are more frequent in elderly patients compared with younger patients (24). Conversely, the present finding may be associated with impaired response to clopidogrel in elderly patients. According to a previous study investigating patients chronically treated with aspirin and thienopyridine, elderly patients had a higher rate of high platelet reactivity than did younger patients even after adjustment for potential confounders (25). Thus, paradoxically, clopidogrel on top of aspirin may be not enough to prevent ischemic events in elderly patients.

The DAPT study and PEGASUS-TIMI 54 trial showed that prolonged DAPT increased the risk of bleeding, and that treatment effects were consistent across age subgroups (3,4). According to the prospective ADAPT-DES (Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents) study, bleeding had a strong relationship with subsequent all-cause mortality, greater than that associated with myocardial infarction after discharge in patients treated with DES (26). Furthermore, prolonged DAPT after DES implantation was associated with increased mortality because of increased risk of noncardiovascular mortality that was not offset by a reduction in cardiac mortality (27). Recent DAPT guidelines, U.S. Food and Drug Administration drug safety communications, and analysis of the DAPT study have consistently concluded that long-term clopidogrel treatment did not increase the risk of all-cause death or cancer-related death (1,2,28,29); however, long-term DAPT should be administered with caution in elderly patients, because increasing age has been found to a significant predictor of bleeding (30). In the present study, reduced bleeding was observed with short-term DAPT, and the benefits of short-term DAPT for bleeding were consistent in the entire study population, particularly in elderly patients. These findings in the present study were consistent with those in previous studies (3,4,31).

STUDY LIMITATIONS. This study does not include individual participant data from randomized trials that were published after the present dataset was constructed, nor does it include a previous randomized trial (ISAR-SAFE trial). Two randomized trials included in the present study (SECURITY and ITALIC trials) were prematurely interrupted, thus not reaching the pre-defined number of patients to enroll. The main characteristics, inclusion and exclusion criteria, and definitions of outcomes differed among the included trials, potentially introducing bias. Because most patients were treated with clopidogrel as an adjunctive therapy to aspirin, the effects of more potent antiplatelet agents such as prasugrel and ticagrelor were beyond our observations. With caution, a significant interaction was observed between age and DAPT duration for all-cause death. However, the reduction in mortality with short-term DAPT in younger patients was driven by a lower rate of cardiac death, assuming chance finding. Further analyses related to this finding could not be performed because of the lack of available details. The impact of DAPT adherence on age and clinical outcomes could not be evaluated for the same reason. Finally, the present finding should be considered as hypothesis generating, and further studies are required to confirm the present results.

CONCLUSIONS

Short-term DAPT after next-generation DES implantation, compared with long-term DAPT, may be more beneficial in elderly patients than in younger patients. New-generation DES requiring a duration of DAPT that is shorter than 3 months (e.g., 1 month) might be considered as an alternative option in the treatment of elderly patients (32).

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PERSPECTIVES

WHAT IS KNOWN? Qualified studies (i.e., patient-level meta-analyses from randomized trials with larger number of patients) to evaluate the optimal duration of DAPT in DES-treated elderly patients have been very limited. Consequently, the optimal duration of DAPT among elderly patients remains controversial.

WHAT IS NEW? Short-term DAPT after next-generation DES implantation, compared with long-term DAPT, may be more beneficial in elderly patients than in younger patients.

WHAT IS NEXT? Further randomized studies to evaluate optimal duration of DAPT in elderly patients receiving new-generation DES are required.

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KEY WORDS coronary artery disease, drug-eluting stent(s), dual antiplatelet therapy

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