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A comparison of the impact of current smoking on 2-year major clinical outcomes of first- and second-generation drug-eluting stents in acute myocardial infarction

Data from the Korea Acute Myocardial Infarction Registry

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Abstract

There are limited studies comparing the effect of current smoking on first-generation (1G)-drug-eluting stents (DES) and second-generation (2G)-DES in acute myocardial infarction (AMI) patients after successful percutaneous coronary intervention (PCI). We investigated the clinical impact of current smoking on 2-year clinical outcomes between the 1G-DES and the 2G-DES in AMI patients after PCI.

A total of 11,812 AMI patients with a history of current smoking who underwent successful PCI with 1G-DES (n = 4622) or 2G-DES (n = 7190) were enrolled. The primary endpoint was the occurrence of major adverse cardiac events (MACE) defined as all-cause death, recurrent AMI (re-MI) or any revascularization (target lesion revascularization [TLR], target vessel revascularization [TVR], and non-TVR). The secondary endpoint was the incidence of definite or probable stent thrombosis (ST).

Two propensity score-matched (PSM) groups (3900 pairs, n = 7800, C-statistic = .708) were generated. After PSM analysis, the 2-year cumulative incidence of MACE was significantly higher in the 1G-DES group compared with the 2G-DES (9.4% vs 7.4%, Log-rank $P = .002$; hazard ratio, 1.281; 95% confidence interval, 1.097–1.495; $P = .002$) and this increased incidence of MACE was associated with the increased incidence of any revascularization including TLR, TVR, and non-TVR. However, the incidences of ST, all-cause death, re-MI were not significantly different during 2-year follow-up period.

2G-DES was the preferred treatment strategy for AMI patients with a history of current smoking to reduce MACE especially, any revascularization rate rather than 1G-DES in this study.

Abbreviations: 1G = first generation, 2G = second generation, AMI = acute myocardial infarction, BMS = bare-metal stents, CABG = coronary artery bypass graft, CAG = coronary angiography, DES = drug-eluting stents, EES = everolimus-eluting stents, KAMIR = Korea Acute Myocardial Infarction Registry, NSTEMI = non-ST-segment elevation myocardial infarction, MACE = major adverse cardiac events, PCI = percutaneous coronary intervention, PES = paclitaxel-eluting stents, PSM = propensity score-matched analysis, SES = sirolimus-eluting stent, STEMI = ST-segment elevation myocardial infarction, TIMI = thrombolysis in myocardial infarction, TLR = target lesion revascularization, TVR = target vessel revascularization, ZES = zotarolimus-eluting stents.

Keywords: drug-eluting stent, myocardial infarction, smoking

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1. Introduction

Cigarette smoking is one of the important correctable risk factors of coronary artery disease and various other cardiovascular diseases.[1] In addition, smoking is a major causative factor of re-infarction, stent thrombosis, and death after percutaneous coronary intervention (PCI).[2,3] In general, even if the patients have stopped smoking during hospitalization, the complete cessation of cigarette smoking after PCI is a very difficult challenge and current smoking trigger severe adverse clinical events. Reported rates of successful smoking cessation after PCI are approximately 40% to 80%.[4,5] Inversely, about 20% to 60% of the patients who underwent PCI may continue to be smokers after discharge from the hospital. At present, second-generation (2G)-drug-eluting stents (DES) have nearly replaced first-generation (1G)-DES during PCI in routine daily clinical practice. However, not all operators of catheterization laboratories always use the 2G-DES worldwide, so 1G-DES are also inevitably available in some areas of the world for various reasons. DES have reduced target lesion revascularization (TLR) by inhibition of neointimal hyperplasia compared with bare-metal stents (BMS) but increased risk of fatal stent thrombosis (ST) is one a major concern.[6,7] Although the 2G-DES has a more advanced form of polymer (biocompatible polymer) than 1G-DES, the 2G-DES did not show superior clinical outcomes when compared with 1G-DES.[8,9] Furthermore, the comparison between 2 different types of 2G-DES also showed comparable results.[10]

The main contributable mechanisms of cigarette smoking on increased mortality and morbidity of cardiovascular disease are related to oxidative stress, increased thrombin generation, platelet aggregation, inflammation, and endothelial dysfunction.[11,12] Persistent long-term cigarette smoking may cause luminal narrowing of the coronary arteries, arterioles, and microvasculature.[13] Although the acute myocardial infarction (AMI) milieu tends to facilitate thrombotic conditions, DES implantation during primary PCI or staged PCI were commonly done from the 1G-DES era up to the 2G-DES era. Despite this, there are limited data comparing the effects of current smoking on 1G-DES and 2G-DES in patients with AMI.

The aim of this study was to investigate and compare the clinical impact of current cigarette smoking on 2-year clinical outcomes between the 1G-DES (sirolimus-eluting stent [SES, Cypher, Cordis Corp, Miami Lakes, Florida] and paclitaxel-eluting stent [PES, Taxus, Boston Scientific, Natick, Massachusetts]) and the 2G-DES (zotarolimus-eluting stent [ZES, Resolute Integrity stent; Medtronic, Inc, Minneapolis, MN] and everolimus-eluting stents [EES, Xience Prime stent, Abbott Vascular, Santa Clara, CA; or promus element stent, Boston Scientific, Natick, MA]) in AMI patients after successful PCI.

2. Methods

2.1. Study population

The Korea Acute Myocardial Infarction Registry (KAMIR) is a nationwide, prospective, observational on-line registry in South Korea established in November 2005 to evaluate current epidemiology and short-term and long-term clinical outcomes of patients with AMI. Fifty-three high-volume University and community hospitals with facilities for primary PCI and onsite cardiac surgery participated in this study. These data were collected by a trained study coordinator using a standardized web-based case report form at each site in South Korea. Details of the registry can be found at the KAMIR website (http://www.kamir.or.kr). This study was a nonrandomized, multicenter, observational, retrospective study. A total of 53,281 AMI patients between January 2005 and June 2015 in the KAMIR registry were evaluated. Patients with the following conditions were excluded:

(1) fibrinolysis was done (n=1982, 3.7%),
(2) failed PCI (n=548, 1.0%),
(3) suboptimal results (n=652, 1.2%),
(4) PCI was not done (n=1756, 3.3%),
(5) BMS deployment (n=2324, 4.4%),
(6) CABG was done (n=146, 0.3%),
(7) follow-up loss or did not participate (n=2822, 5.3%),
(8) incomplete laboratory results (n=2970, 5.6%),
(9) uncertainty of diagnosis (n=384, 0.7%),
(10) nonsmokers (n=18668, 35.0%),
(11) exsmokers (n=6746, 12.7%),
(12) other kinds of DES except for SES, PES, ZES, and EES (n=3375, 6.3%).

Finally, a total of 11,812 AMI patients who underwent successful PCI with 1G-DES (n=4622, 39.1%) or 2G-DES (n=7190, 60.9%) were enrolled (Fig. 1). The study protocol was approved by the ethics committee on research on humans at each participating center and was conducted according to the ethical guidelines of the 1975 Declaration of Helsinki. All patients provided written informed consent before enrollment. In this study, all 11,812 patients completed a 2-year clinical follow-up by face-to-face interviews, phone calls, or chart review.

2.2. PCI and medical treatments

A diagnostic coronary angiography and PCI were done through either the femoral or the radial artery after an administration of unfractionated heparin (50–100 IU/kg). Patients' activated clotting time was as maintained at >250 seconds during the procedure. All patients were given loading doses of 200 to 300 mg aspirin and 300 to 600 mg clopidogrel before PCI. Revascularization was considered clinically indicated when the patient had typical angina and/or signs of ischemia and ≥50% diameter restenosis or ≥70% diameter restenosis in a coronary artery by visual estimation. A successful PCI was defined as the achievement of angiographic residual stenosis was less than 30% and the final thrombolysis in myocardial infarction (TIMI) blood flow grade was 3. During the in-hospital stay and after discharge, all patients' medical treatments included aspirin, clopidogrel, beta-blockers (BB), angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), and lipid-lowering agents.

After discharge, the patients were recommended to stay on the same medications that they had received during hospitalization. Especially, the total duration of dual antiplatelet therapy (DAPT, the combination of aspirin [100 mg/d] and clopidogrel [75 mg/d]) was recommended for more than 12 months to patients who had undergone PCI. Triple antiplatelet therapy (TAT) (100 mg cilosatzol [Pletaa, Ostuska Pharmaceutical Co, Tokyo, Japan] twice a day) added on to DAPT was left to the discretion of the individual operators.

2.3. Study definitions and endpoints

AMI was defined as the presence of clinical symptoms, electrocardiographic changes, or abnormal imaging findings of MI, combined with an increase in the creatine kinase myocardial

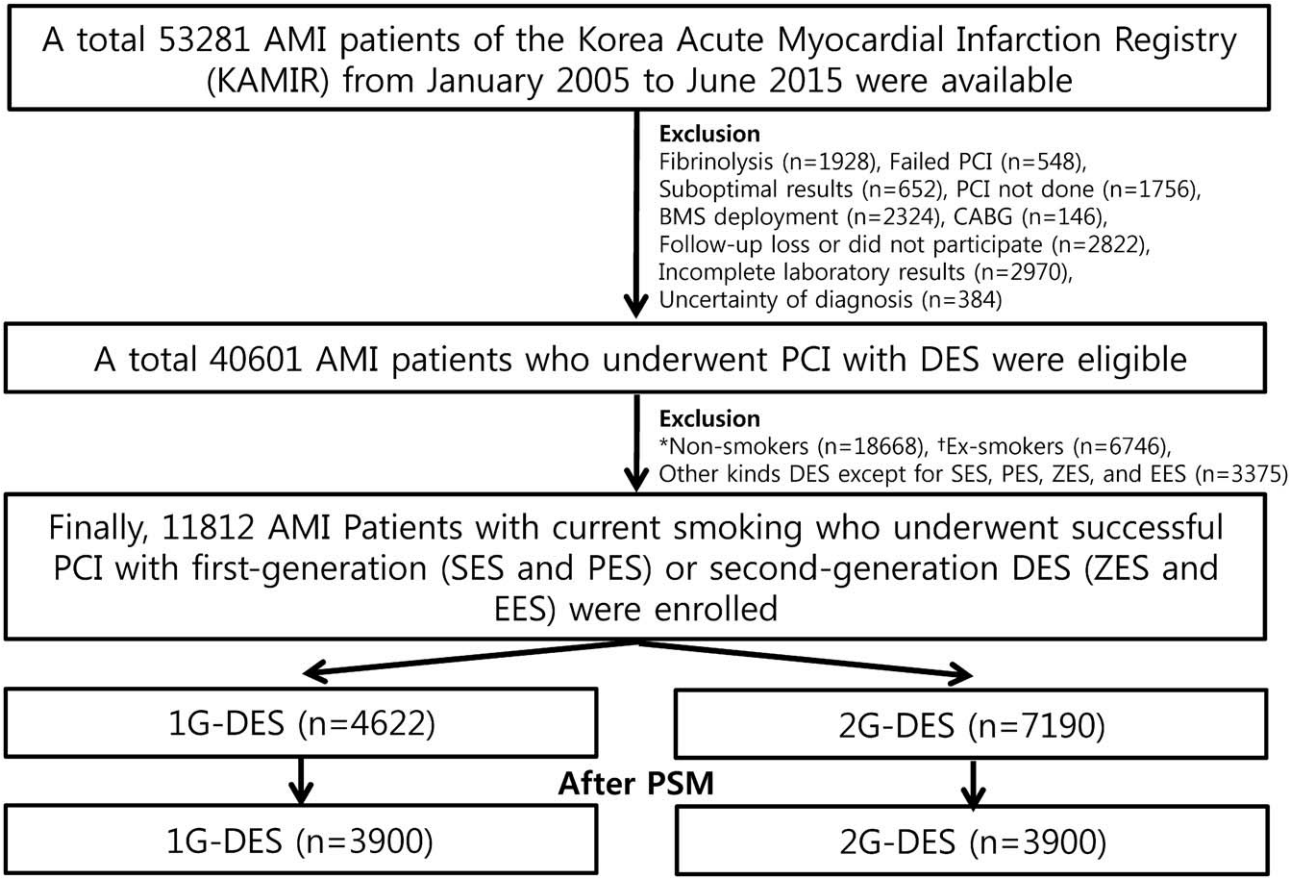

Figure 1. Flow chart. *Non-smoker was defined as who did not regularly smoke at any time. †Ex-smoker was defined as who had stopped smoking for more than 1 year before the index PCI. AMI = acute myocardial infarction, BES = biolimus-eluting stents, BMS = bare-metal stent, CABG = coronary artery bypass graft, DES = drug-eluting stents, EES = everolimus-eluting stents, KAMIR = Korea Acute Myocardial Infarction Registry, PCI = percutaneous coronary intervention, ZES = zotarolimus-eluting stents.

band fraction above the upper normal limits or an increase in troponin-T/troponin-I to greater than the 99th percentile of the upper normal limit.[14,15] The smoking status was assessed on the basis of information obtained from hospital medical records at the time of first medical examination and current smoking was defined as cigarette smoking within 1 year before the index PCI and currently smoking. The primary endpoint was the occurrence of major adverse cardiac events (MACE) defined as all-cause, recurrent myocardial infarction (re-MI), any coronary revascularization (TLR, target vessel revascularization [TVR], non-TVR) during the 2-year follow-up period. The secondary endpoint was the occurrence of definite or probable ST.

All-cause deaths were classified as cardiac (CD) or non-CD. Re-MI was defined as the recurrence of AMI. Any coronary revascularization was defined as revascularization of the target vessel or nontarget vessels. TLR was defined as revascularization of the target lesion due to restenosis or reocclusion within the stent or within 5 mm of the distal or proximal segment. TVR was defined as revascularization of the target vessel or any segment of the coronary artery containing the target lesion. Non-TVR was defined as a revascularization of any segment of the nontarget coronary artery. ST classified as acute (0–24 hours), subacute (24 hours – 30 days), late (30 days – 1 year) and very late (>1 year) according to the onset time of ST.[16] In addition, the modified American College of Cardiology/American Heart Association (ACC/AHA) criteria was used to classify coronary lesion morphology.[17] The TIMI score was used to determine the degree of coronary flow before and after the procedure.[15]

2.4. Statistical analysis

All statistical analyses were performed using SPSS software, version 20 (IBM; Armonk, NY). For continuous variables, differences between the 2 groups were evaluated with the unpaired *t* test or Mann–Whitney rank test. Data expressed as mean ± standard deviations. For discrete variables, differences were expressed as counts and percentages and were analyzed with either the χ^2 or Fisher exact test, between the groups as appropriate. To adjust for any potential confounders, propensity score-matched (PSM) analysis was performed using the logistic regression model. We tested all available variables that could be of potential relevance: age, gender (men), left ventricular ejection fraction (LVEF), body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), ST-segment elevation MI (STEMI), non-ST-segment elevation MI (NSTEMI), primary PCI, hypertension, diabetes mellitus (DM), dyslipidemia, previous MI, previous PCI, creatine kinase myocardial band, high-sensitivity C-reactive protein, total cholesterol, triglyceride, high-density lipoprotein (HDL)-cholesterol, aspirin, clopidogrel, ticagrelor, prasugrel, cilostazole, CCB, BB, ACEI, ARB, lipid lowering agent, infarct-related artery (IRA, left anterior descending [LAD], left circumflex [LCx], right coronary artery [RCA], left main

[LM]), treated vessel (LAD, LCx, RCA, left main [LM]), American College of Cardiology/American Heart Association type B1, B2 and C lesions, 1-vessel disease, 2-vessel disease, 3-vessel disease, pre-PCI TIMI 0, post-PCI TIMI 2, post-PCI TIMI 3, stent diameter, stent length, and number of stents. The logistic model by which the propensity scores were estimated showed good predictive value (C-statistic = 0.708). Patients in the 1G-DES group were then one-to-one matched to those in the 2G-DES group, according to propensity scores with the nearest available pair matching method. Subjects were matched with a caliper width equal to 0.01. The procedure yielded 3900 well-matched pairs. Cox-proportional hazard models were used to assess the adjusted hazard ratio (HR) comparing the 2 groups in PSM population. For all analyses, a 2 sided $P < .05$ was considered statistically significant.

3. Results

3.1. Baseline clinical, angiographic, and procedural characteristics

Baseline clinical and laboratory characteristics of this study population are summarized in Table 1. In the entire patient population, the mean age of the participants was higher in the 1G-DES group compared with 2G-DES group (58.1 ± 11.8 years vs 57.4 ± 11.4 years, $P = .002$). In both groups, the proportion of men was above 90% and higher in the 2G-DES group (92.4% vs 93.6%, $P = .012$). The mean value of LVEF was similar between the 2 groups and nearly within the normal range (52.4 ± 11.0% vs 52.6 ± 10.6%, $P = .274$). Also, the numbers of hypertension and DM patients were similar between the 2 groups. The mean value of BMI, SBP, and DBP and the number of NSTEMI and dyslipidemia patients were significantly higher in the 2G-DES group. By contrast, the numbers of STEMI patients were higher in the 1G-DES group. The mean values of serum cholesterol and LDL cholesterol were as similar between the 2 groups; triglyceride was higher in the 2G-DES, and HDL was higher in the 1G-DES group. In the 2G-DES group, even though the prescription rate of clopidogrel (84.9%) was lower, ticagrelor and prasugrel were more frequently prescribed as discharge medications than the 1G-DES group. Regarding angiographic and procedural characteristics, LAD was more frequent IRA in the 1G-DES compared with 2G-DES group (49.1% vs 47.1%, $P = .031$). The ACC/AHA type B1 lesion, 2-vessel disease, and ≥3-vessel disease were more frequent in the 1G-DES group. ACC/AHA type B2 lesion and 1-vessel disease were more frequent in the 2G-DES group. The diameter (3.20 ± 0.44 mm vs 3.16 ± 0.38, $P < .001$) and length (26.5 ± 10.5 mm vs 25.9 ± 6.7 mm, $P < .001$) of deployed stents were larger and longer in the 2G-DES group compared with the 1G-DES group. However, the number of deployed stents (1.49 ± 0.81 vs 1.44 ± 0.75) was higher in the 1G-DES group. In addition, these different variables were well-balanced after PSM analysis.

3.2. Clinical outcomes

The cumulative incidences of major clinical outcomes at 2 years are listed in Table 2. In the entire patient population, the primary endpoint, the cumulative incidence of MACE was significantly higher in the 1G-DES group compared with the 2G-DES group (9.3% vs 7.5%, Log-rank $P < .001$; HR, 1.255; 95% confidence interval [CI]; 1.104–1.427; $P = .001$). The majority of this increased incidence in the 1G-DES group was associated with a significantly increased incidence of any revascularization rate including TLR, TVR, and non-TVR. Incidences of all-cause death, CD, and Re-MI were not significantly different between the 2 groups. The secondary endpoint, the incidence of ST was similar between the 2 groups (0.9% vs 0.7%, Log-rank $P = .169$; HR, 1.334; 95% CI, 0.884–2.015; $P = .170$). After PSM analysis, the incidence of MACE was also higher in the 1G-DES group (9.4% vs 7.4%, Log-rank $P = .002$; HR, 1.281; 95% CI, 1.097–1.495; $P = .002$, Fig. 2A) than the 2G-DES group. However, the incidence of ST was also similar between the 2 groups (1.0% vs 0.96%, Log-rank $P = .637$; HR, 1.118; 95% CI, 0.704–1.775; $P = .638$, Fig. 2B). In addition, the incidence of all-cause death, CD, and Re-MI was not significantly different (Fig. 3). Fig. 4 shows the results of subgroup analysis for MACE at 2 years. In cases of age <65 years, men, STMI, BMI ≥24 kg/m^2, primary PCI, LAD (treated vessel), ACC/AHA type B2/C lesion, 1-vessel disease, post-PCI TIMI 3 flow, short stent length (<28 mm), and large diameter (≥3.0 mm), 2G-DES was preferred treatment strategy for the AMI patient with current smoking to reduce MACE than 1G-DES in this study.

4. Discussion

In this study, we investigated the impact of current smoking on 2-year clinical outcomes between 1G-DES and 2G-DES in AMI patients after successful PCI. The main findings of this study are as follows:

(1) The cumulative incidence of MACE was significantly higher in the 1G-DES group compared with the 2G-DES group during the 2-year follow-up period. The main cause of this increased incidence of MACE was associated with the increased incidence of any revascularization including TLR, TVR, and non-TVR which were higher in the 1G-DES compared with the 2G-DES.
(2) The cumulative incidence of ST was not significantly different between the 2 groups, and
(3) The cumulative incidence of all-cause death, CD, and re-MI was similar between the 2 groups.

The relationship between smoking and MI is well known.[18,19] Even though the AMI milieu is prone to be thrombotic compared to stable coronary artery disease; previous studies showed that 1G-DES was associated with a reduced incidence of repeat intervention and MACE compared with BMS.[20,21] Regarding safety and efficacy, there is some debate on the relative superiority between 1G-DES and 2G-DES.[9,22] Hofma et al[23] demonstrated EES had superiority for MACE over SES (4.0% vs 7.7%, $P = .048$) in AMI patients during a 1- year follow-up period in the XAMI (XienceV Stent vs Cypher Stent in Primary PCI for AMI) randomized controlled trial (RCT). However, the cumulative incidences of 1-year CD (1.5% vs 2.7%, $P = .36$) and definite and/or probable ST (1.2% vs 2.7%, $P = .21$) were similar between the 2 groups. Lee et al[24] reported similar efficacy and safety of ZES, SES, PES in patients with AMI during the 1-year follow-up period in the ZEST-AMI (the comparison of the efficacy and safety of ZES vs SES vs PES for AMI patients) RCT trial. Kufner et al[25] reported that the incidence of TLR (12.3% vs 15.9%, $P = .10$) was not statistically significant but numerically higher in the SES group as compared to EES during the 5-year follow-up period.

Even though, there is some debate, Huang et al[26] demonstrated that persistent smoking increased the size of the neointimal hyperplasia area (1.04 ± 0.72 mm^2 vs 0.96 ± 0.68 mm^2; $P = .04$) and malapposed struts (3.2% vs 1.6%; $P = .004$)

Table 1

Baseline clinical, laboratory, angiographic, and procedural characteristics.

Variables	Entire patients			Propensity score-matched patients		
	1G-DES (n = 4622)	2G-DES (n = 7190)	*P*-value	1G-DES (n = 3900)	2G-DES (n = 3900)	*P*-value
Age, yr	58.1 ± 11.8	57.4 ± 11.4	.002	57.9 ± 11.7	57.9 ± 11.7	.823
Men, n (%)	4273 (92.4)	6733 (93.6)	.012	3609 (92.5)	3612 (92.6)	.897
LVEF (%)	52.4 ± 11.0	52.6 ± 10.6	.274	52.5 ± 10.9	52.5 ± 10.8	.898
Height, m	167.2 ± 6.9	168.0 ± 6.9	<.001	167.3 ± 6.8	167.7 ± 7.0	.748
Weight, kg	67.6 ± 10.8	68.9 ± 11.3	<.001	67.9 ± 10.8	68.2 ± 11.3	.329
BMI, kg/m^2	24.1 ± 3.0	24.3 ± 3.1	<.001	24.2 ± 3.0	24.2 ± 3.1	.914
SBP, mm Hg	128.5 ± 26.9	130.4 ± 27.5	<.001	129.2 ± 27.2	129.6 ± 27.4	.536
DBP, mm Hg	79.3 ± 16.3	80.2 ± 16.8	<.001	79.6 ± 16.4	79.8 ± 16.6	.676
STEMI, n (%)	3036 (65.7)	4454 (61.9)	<0.001	2494 (63.9)	2484 (63.7)	.814
NSTEMI, n (%)	1586 (40.2)	2736 (49.3)	<.001	1406 (36.1)	1416 (36.3)	.814
Primary PCI, n (%)	2719 (58.8)	4319 (60.1)	.179	2356 (60.4)	2358 (60.5)	.963
Hypertension, n (%)	1754 (37.9)	2735 (38.0)	.922	1489 (38.2)	1471 (37.7)	.674
Diabetes mellitus, n (%)	1057 (22.9)	1619 (22.5)	.656	911 (23.4)	902 (23.1)	.809
Dyslipidemia, n (%)	481 (10.4)	849 (11.8)	.019	426 (10.9)	443 (11.4)	.541
Previous MI, n (%)	137 (3.0)	219 (3.0)	.800	114 (2.9)	115 (2.9)	.947
Previous PCI, n (%)	164 (3.5)	335 (4.7)	.004	151 (3.9)	161 (4.1)	.563
Previous CABG, n (%)	13 (0.3)	17 (0.2)	.637	12 (0.3)	10 (0.3)	.669
Previous CVA, n (%)	196 (4.2)	279 (3.9)	.331	163 (4.3)	152 (3.9)	.527
Previous HF, n (%)	42 (0.9)	38 (0.5)	.014	28 (0.7)	32 (0.8)	.604
CK-MB, mg/dL	164.9 ± 283.1	149.2 ± 258.5	.002	159.7 ± 229.4	160.8 ± 313.5	.849
Troponin-I, ng/mL	49.8 ± 83.9	54.0 ± 334.2	.407	49.3 ± 83.7	48.0 ± 74.7	.463
NT-ProBNP, pg/mL	1354.2 ± 2887.0	1195.6 ± 2688.9	.002	1335.7 ± 1874.6	1262.6 ± 2810.5	.256
hs-CRP, mg/dL	10.9 ± 52.7	8.7 ± 38.6	.007	10.8 ± 45.5	10.4 ± 48.6	.726
Serum creatinine, mg/L	1.1 ± 1.4	1.1 ± 1.2	.035	1.1 ± 1.0	1.1 ± 1.5	.868
Total cholesterol, mg/dL	186.8 ± 42.5	188.4 ± 43.5	.057	187.8 ± 42.2	188.3 ± 42.9	.660
Triglyceride, mg/L	141.4 ± 112.5	154.5 ± 129.4	<.001	144.1 ± 115.6	145.3 ± 115.0	.664
HDL cholesterol, mg/L	44.3 ± 24.0	42.3 ± 13.3	<.001	43.1 ± 12.4	43.3 ± 14.3	.477
LDL cholesterol, mg/L	120.1 ± 39.4	119.4 ± 36.4	.434	120.2 ± 36.3	120.2 ± 36.6	.997
Discharge medications						
Aspirin, n (%)	4391 (95.0)	6813 (94.8)	.556	3679 (94.3)	3687 (94.5)	.693
Clopidogrel, n (%)	4523 (97.9)	6105 (84.9)	<.001	3811 (97.7)	3803 (97.5)	.553
Ticagrelor, n (%)	10 (0.2)	540 (7.5)	<.001	10 (0.3)	8 (0.2)	.637
Prasugrel, n (%)	10 (0.2)	352 (4.9)	<.001	10 (0.3)	12 (0.3)	.669
Cilostazole, n (%)	1612 (34.9)	1353 (18.8)	<.001	1160 (29.7)	1192 (30.6)	.430
CCB, n (%)	347 (7.5)	358 (5.0)	<.001	250 (6.4)	254 (6.5)	.854
BB, n (%)	3416 (73.9)	5835 (81.2)	<.001	2966 (76.1)	2986 (76.7)	.594
ACEI, n (%)	3025 (65.4)	4165 (57.9)	<.001	2494 (63.9)	2461 (63.1)	.438
ARB, n (%)	699 (15.1)	1606 (22.3)	<.001	636 (16.3)	642 (16.5)	.854
Lipid lowering agents	3412 (73.8)	5972 (83.1)	<.001	2958 (75.8)	2988 (76.6)	.425
Angiographic and procedural characteristics						
Infarct-related artery						
Left anterior descending, n (%)	2271 (49.1)	3387 (47.1)	.031	1901 (48.7)	1880 (48.2)	.634
Left circumflex, n (%)	778 (16.8)	1215 (16.9)	.926	639 (16.4)	674 (17.3)	.290
Right coronary artery, n (%)	1499 (32.4)	2441 (33.9)	.088	1301 (33.4)	1280 (32.8)	.613
Left main, n (%)	66 (1.4)	137 (1.9)	.051	54 (1.4)	57 (1.5)	.774
Treated vessel						
Left anterior descending, n (%)	2590 (56.0)	3974 (55.3)	.414	2174 (55.7)	2149 (55.1)	.569
Left circumflex, n (%)	1155 (25.0)	1753 (24.4)	.454	950 (24.4)	999 (25.4)	.307
Right coronary artery, n (%)	1787 (38.7)	2866 (39.3)	.193	1533 (39.3)	1517 (38.9)	.710
Left main, n (%)	98 (2.1)	186 (2.6)	.106	82 (2.1)	91 (2.3)	.489
ACC/AHA lesion type						
Type B1, n (%)	758 (16.4)	1032 (14.4)	.002	638 (16.4)	628 (16.1)	.759
Type B2, n (%)	1168 (25.3)	2185 (30.5)	<.001	1023 (26.2)	1005 (25.8)	.642
Type C, n (%)	2067 (44.7)	3240 (45.1)	.716	1719 (44.1)	1725 (44.2)	.891
Extent of coronary artery disease						
1-vessel, n (%)	2098 (45.4)	3693 (51.4)	<.001	1829 (46.9)	1804 (46.3)	.570
2-vessel, n (%)	1491 (32.3)	2147 (29.9)	.006	1248 (32.0)	1262 (32.4)	.734
≥3-vessel, n (%)	977 (21.1)	1310 (18.2)	<.001	791 (20.3)	798 (20.5)	.844
Pre-PCI TIMI 0, n (%)	2156 (46.6)	3623 (50.4)	<.001	1871 (48.0)	1868 (47.9)	.946
Post-PCI TIMI 2, n (%)	154 (3.3)	220 (3.1)	.410	135 (3.5)	140 (3.6)	.759
Post-PCI TIMI 3, n (%)	4210 (91.9)	6573 (91.4)	.532	3532 (90.6)	3503 (89.8)	.270
IVUS	322 (7.0)	1492 (20.8)	<.001	273 (7.0)	275 (7.1)	.824
Stent diameter, mm	3.16 ± 0.38	3.20 ± 0.44	<.001	3.17 ± 0.38	3.17 ± 0.43	.752
Stent length, mm	25.9 ± 6.7	26.5 ± 10.5	<.001	25.8 ± 6.8	25.8 ± 9.5	.646
Number of stent	1.49 ± 0.81	1.44 ± 0.75	<.001	1.47 ± 0.80	1.47 ± 0.78	.693

Values are mean ± SD or n (%). The *P* values for continuous data were obtained from the analysis of the unpaired *t* test. The *P* values for categorical data were obtained from the chi-square test.
1G = first-generation, 2G = second generation, ACC/AHA = American College of Cardiology/American Heart Association, BMI = body mass index, CABG = coronary artery bypass graft, CCB = calcium channel blockers, CK-MB = creatine kinase myocardial band, CVA = cerebrovascular accidents, DBP = diastolic blood pressure, DES = drug-eluting stents, HDL = high-density lipoprotein, HF = heart failure, hs-CRP = high sensitivity-C-reactive protein, IVUS = intravascular ultrasound, LDL = low-density lipoprotein, LVEF = left ventricular ejection fraction, MI = myocardial infarction, NSTEMI = non-ST-segment elevation myocardial infarction, NT-ProBNP = N-terminal pro-brain natriuretic peptide, PCI = percutaneous coronary intervention, SBP = systolic blood pressure, STEMI = ST-segment elevation myocardial infarction, TIMI = thrombolysis in myocardial infarction.

Table 2

Clinical outcomes by Kaplan–Meier analysis and Cox-proportional hazard ratio analysis at 2-yr.

Outcomes	Cumulative events at 2 yr (%)			Hazard ratio (95% CI)	*P*-value
	1G-DES	2G-DES	Log-rank		
Entire patients					
Primary endpoint					
MACE	430 (9.3)	514 (7.5)	<.001	1.255 (1.104–1.427)	.001
All-cause death	150 (3.2)	255 (3.6)	.288	0.897 (0.733–1.097)	.289
Cardiac death	129 (3.8)	210 (3.0)	.606	0.944 (0.758–1.175)	.607
Re-MI	62 (1.4)	91 (1.4)	.984	1.003 (0.726–1.386)	.984
Any revascularization	233 (5.2)	200 (3.1)	<.001	1.717 (1.421–2.074)	<.001
TLR	74 (1.7)	47 (0.7)	<.001	2.315 (1.606–3.337)	<.001
TVR	110 (2.5)	101 (1.6)	.001	1.587 (1.211–2.079)	.001
Non-TVR	125 (2.8)	101 (1.6)	<.001	1.818 (1.399–2.364)	<.001
Secondary endpoint					
Stent thrombosis (probable or definite)	42 (0.9)	49 (0.7)	.169	1.334 (0.884–2.015)	.170
Acute	3 (0.1)	6 (0.1)	.722	0.778 (0.195–3.110)	.722
Subacute	13 (0.3)	16 (0.2)	.529	1.264 (0.608–2.628)	.530
Late	18 (0.4)	22 (0.3)	.445	1.274 (0.683–2.375)	.446
Very late	8 (0.2)	5 (0.1)	.097	2.494 (0.816–7.625)	.109
Propensity score matched patients					
Primary endpoint					
MACE	367 (9.4)	284 (7.4)	.002	1.281 (1.097–1.495)	.002
All-cause death	134 (3.4)	147 (3.8)	.404	0.905 (0.716–1.144)	.405
Cardiac death	114 (2.9)	124 (3.2)	.498	0.916 (0.710–1.181)	.499
Re-MI	56 (1.5)	45 (1.2)	.322	1.219 (0.823–1.805)	.323
Any revascularization	189 (5.0)	107 (2.9)	<.001	1.740 (1.373–2.205)	<.001
TLR	61 (1.6)	23 (0.6)	<.001	2.602 (1.610–4.203)	<.001
TVR	94 (2.5)	52 (1.4)	.001	1.768 (1.260–2.480)	.001
Non-TVR	97 (2.6)	55 (1.5)	.001	1.762 (1.240–2.403)	.001
Secondary endpoint					
Stent thrombosis (probable or definite)	38 (1.0)	34 (0.9)	.637	1.118 (0.704–1.775)	.638
Acute	3 (0.1)	6 (0.2)	.317	0.500 (0.125–1.999)	.327
Subacute	12 (0.3)	10 (0.3)	.671	1.199 (0.518–2.776)	.671
Late	17 (0.4)	15 (0.4)	.724	1.133 (0.566–2.269)	.724
Very late	6 (0.2)	3 (0.1)	.316	2.002 (0.501–8.006)	.326

1G = first-generation, 2G = second-generation, CI = confidence interval, DES = drug-eluting stents, MACE = major adverse cardiac events, Non-TVR = non-target vessel revascularization, Re-MI = recurrent myocardial infarction, TLR = target lesion revascularization, TVR = target vessel revascularization.

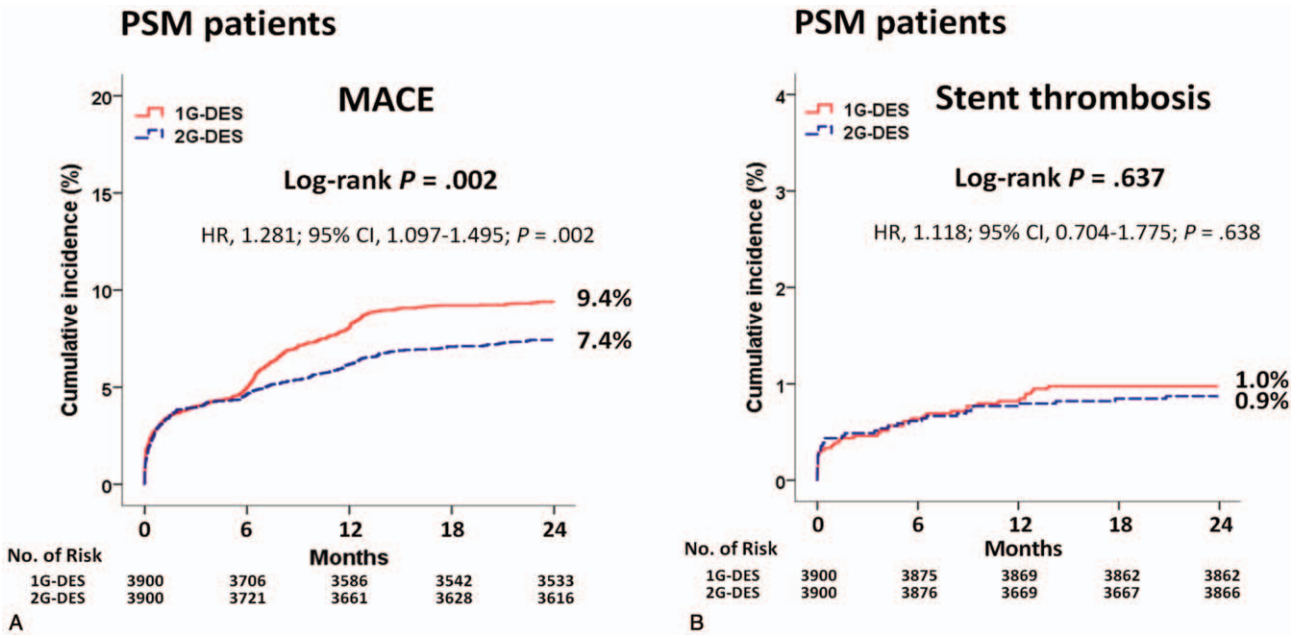

Figure 2. Kaplan–Meier curved analysis for MACE (A) and stent thrombosis (B) at 2-year. 1G = first-generation, 2G = second-generation, CI = confidence interval, DES = drug-eluting stents, HR = hazard ratio, MACE = major adverse cardiac event, PSM = propensity score-matched analysis.

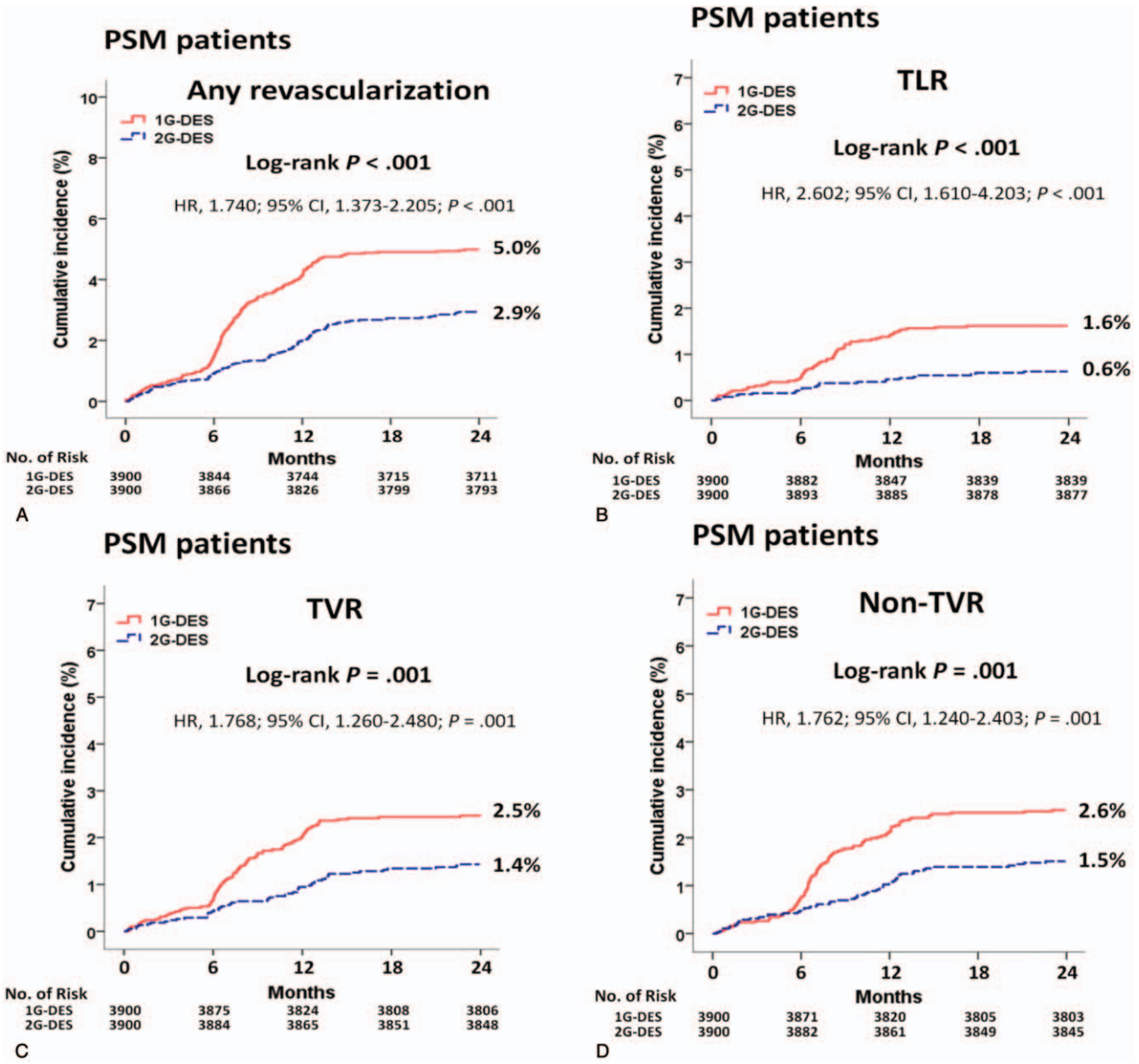

Figure 3. Kaplan–Meier curved analysis for any revascularization (A), TLR (B), TVR (C), and non-TVR (D) at 2-year. 1G = first-generation, 2G = second-generation, CI = confidence interval, DES = drug-eluting stents, HR = hazard ratio, PSM = propensity score-matched analysis, TLR = target lesion revascularization, TVR = target vessel revascularization.

compared with nonsmokers. In addition, persistent smoking for more than 1-year leads to a high incidence of uncovered struts. However, these results were obtained from the patients who underwent PCI and a 1G-DES (SES) was deployed. Although the majority of 2G-DES showed noninferior clinical outcomes compared with 1G-DES, these durable-polymer based stents have been associated with persistent local inflammatory and toxic reactions, delayed healing, hypersensitivity reactions, endothelial dysfunction, and neoatherosclerosis.[27,28] In this study, 2G-DES showed a decreased incidence of MACE compared to 1G-DES after PSM analysis (9.4% vs 7.4%, Log-rank $P = .002$; HR, 1.281; 95% CI, 1.097–1.495; $P = .002$). Furthermore, this result was related with a decreased incidence of any revascularization rate including TLR, TVR, and non-TVR. The increased incidence of non-TVR after PSM analysis (2.6% vs 1.5%, Log-rank $P = .001$; HR, 1.762; 95% CI, 1.240–2.403; $P = .001$) in this study can be explained by Hong et al's report.[29] In their 3-vessel intravascular imaging study of 235 patients, Hong showed that secondary remote plaque ruptures and multiple plaque ruptures and culprit lesion plaque rupture were all more common in patients with MI than in those with stable ischemic heart disease. Stone et al[30] also demonstrated MACE occurring during follow-up were equally attributable to recurrence at the site of culprit lesions and to nonculprit lesions in patients with acute coronary syndrome who underwent PCI. Compared with 1G-DES, ZES (Resolute Integrity Stent) that utilize the BioLinx-polymer and antiproliferative agent, zotarolimus is equivalent to sirolimus in terms of antiproliferative power but is more lipophilic than sirolimus.[31,32] This BioLinx-polymer was able to exhibit delayed zotarolimus release (50% and 85% released at 7 and

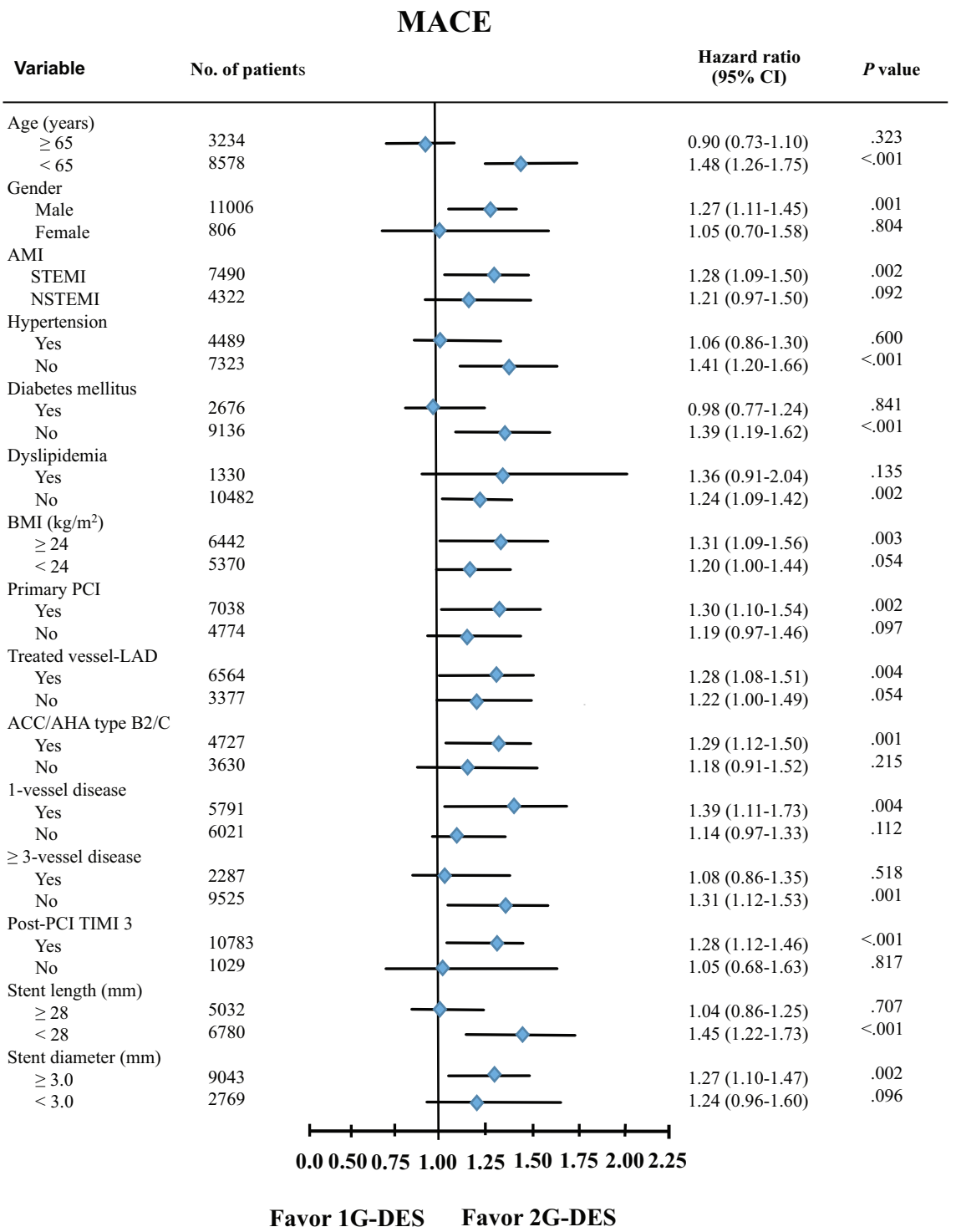

Figure 4. Subgroup analyses for MACE. 1G = first-generation, 2G = second-generation, ACC/AHA = American College of Cardiology/American Heart Association, AMI = acute myocardial infarction, BMI = bodymass index, DES = drug eluting stents, LAD = left anterior descending coronary artery, LVEF = left ventricular ejection fraction, MACE = major adverse cardiac events, NSTEMI = non-ST-segment elevation myocardial infarction, PCI = percutaneous coronary intervention, STEMI = ST-segment elevation myocardial infarction, TIMI = thrombolysis in myocardial infarction.

60 days), indeed for over approximately 180 days after PCI.[33] In this study, we could not precisely explain the reason for the differences of any revascularization rate between 1G-DES and 2G-DES, the possible mechanisms may be due to the different type of polymer between the 2 stent groups. Although nicotine may play an important role in atherogenesis and be involved in enhanced endothelial cell proliferation and migration, and accelerate intimal hyperplasia in vitro and animal study,[34,35] the operative mechanisms at the level of endothelium are not clearly understood.[34] Current smoking also increases inflam-

mation and oxidative damage to the vascular endothelium and impairs coronary circulatory function.[36] The relationship between stent strut thickness and platform design and long-term safety and efficacy of DES was not well defined. In this study, the occurrence of ST was not different between 1G-DES and 2G-DES (1.0% vs 0.96%, Log-rank $P = .637$; HR, 1.118; 95% CI, 0.704–1.775; $P = .638$). According to this study, regarding ST, we cautiously suggest that the presence or absence of a biocompatible polymer in AMI patients were not associated with current smoking.

Smoking cessation decreased by about a 36% crude relative risk (RR) of mortality for patients with coronary heart disease compared with continued smoking (RR, 0.64; 95% CI, 0.58–0.71)[37] and this beneficial effect of smoking cessation may be achieved by vascular healing after stent deployment through a decrease in the progression of neointimal hyperplasia and decrease the incidence of stent malapposition.[18] As mentioned, the successful smoking cessation rate after PCI was approximately 40% to80%. Taken together, we can assume that about 20% to 60% of enrolled patients of this study may continue to be current smokers after the index PCI during the 2-year follow-up period at that time. Therefore, in this study, even though the smoking status of the study population was assessed at the time of PCI, the results of this study may provide a meaningful message to the interventional cardiologist during PCI to help select the appropriate DES, especially in AMI patients with a history of current smoking.

The current study has some important limitations. First, the study was nonrandomized study and there may be some underreporting and/or missed data. Second, the smoking status of the study population was assessed at the time of the index PCI and we did not know the precise history of the smoking status during the follow-up period after discharge. This weak point can affect the results of this study. Third, because this registry data did not include the detailed full data concerning the prescription doses, long-term adherence, discontinuation, and drug-related adverse events, we evaluated all clinical outcomes based on discharge medications and this factor may act as an important bias in this study. Fourth, although we did multivariable Cox-proportional regression analysis to overcome the limitations of this retrospective study, the characteristics of this retrospective registry might have influenced the results of this study. Fifth, because the choice of 1G-DES or 2G-DES was dependent on the discretion of the physician, this may be another important bias in this study. Sixth, in this study AMI patients were consisted of STEMI and NSTEMI, therefore this heterogeneity can affect each other and may act as a bias. Seventh, although PSM analysis and subgroup analysis were done, the proportions of each type of stents in both groups were not evenly distributed. Eighth, the strategy of antiplatelet therapy (eg, DAPT or TAPT) was left to the physician's discretion, which may have influenced the major clinical outcomes.

In conclusion, the cumulative incidence of MACE and any revascularization was significantly higher in the 1G-DES group compared with the 2G-DES group during the 2-year follow-up period. However, the incidences of ST, all-cause death, CD, re-MI were not significantly different between the 2 groups. Therefore, 2G-DES may be the preferred treatment strategy for the AMI patient with a history of current smoking to reduce MACE rather than 1G-DES according to the results in this study. However, this result may be more precisely defined by other well-designed, prospective, randomized studies in the future.

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