

Comparison of Efficacy and Safety between First- and Second-Generation Drug-Eluting Stents in Patients with Acute Coronary Syndrome

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Abstract

Background: It remains undetermined whether second-generation drug-eluting stents (G2-DESs) outperform first-generation DESs (G1-DESs) in patients with acute coronary syndrome (ACS). We aimed to compare the efficacy and safety of G1-DES and G2-DES in ACS patients in a high-volume cardiovascular center.

Methods: In 2013, 10,724 consecutive patients underwent percutaneous coronary intervention in our institution. We included 4037 patients with ACS who underwent exclusively G1-DES or G2-DES implantation ($n = 364$ and $n = 3673$, respectively). We used propensity score matching to minimize the imbalance between the G1-DES and G2-DES groups and followed patients for 2 years. The efficacy endpoints were major adverse cardiac events (MACEs) and its components including target vessel-related myocardial infarction (TV-MI), target vessel revascularization/target lesion revascularization (TVR/TLR), and cardiac death. The safety endpoint was stent thrombosis. Continuous variables were compared by Mann-Whitney U -test, and categorical variables were compared using Pearson's Chi-square or Fisher's exact test. Kaplan-Meier curves were constructed to compare the event-free survival rates, and multivariate Cox proportional hazards regression analysis was used to assess whether stent type was an independent risk factor for the efficacy and safety endpoints.

Results: At the 2-year follow-up, the results for MACE and its components, as well as stent thrombosis, were similar for G1-DES and G2-DES (MACE, 5.2% vs. 4.3%, $\chi^2 = 0.514$, $P = 0.474$; TV-MI, 0.8% vs. 0.4%, $P = 0.407$; TVR, 4.9% vs. 3.7%, $\chi^2 = 0.939$, $P = 0.333$; TLR, 3.8% vs. 2.5%, $\chi^2 = 1.610$, $P = 0.205$; cardiac death, 0.3% vs. 0.5%, $P = 0.670$; and stent thrombosis, 0.5% vs. 0.4%, $P > 0.999$). Kaplan-Meier analysis indicated similar event-free survival rates between G1-DES and G2-DES after propensity score matching (all: log-rank $P > 0.05$). Multivariate analysis demonstrated that stent type was not an independent risk factor for the efficacy and safety endpoints (MACE, hazard ratio [HR] = 0.805, 95% confidence interval [CI]: 0.455–1.424, $P = 0.456$; TV-MI, HR = 0.500, 95% CI: 0.101–2.475, $P = 0.395$; TVR, HR = 0.732, 95% CI: 0.403–1.330, $P = 0.306$; TLR, HR = 0.629, 95% CI: 0.313–1.264, $P = 0.193$; cardiac death, HR = 1.991, 95% CI: 0.223–17.814, $P = 0.538$; and stent thrombosis, HR = 0.746, 95% CI: 0.125–4.467, $P = 0.749$).

Conclusion: G1-DES and G2-DES have similar efficacy and safety profiles in ACS patients at the 2-year follow-up.

Key words: Acute Coronary Syndrome; First-Generation Drug-Eluting Stent; Percutaneous Coronary Intervention; Second-Generation Drug-Eluting Stent; Stent Thrombosis

INTRODUCTION

Compared with bare metal stents, drug-eluting stents (DESs) have tremendously increased therapeutic benefits for percutaneous coronary intervention (PCI), predominantly represented by reduced incidence of target vessel revascularization/target lesion revascularization (TVR/TLR).^[1] The first-generation DESs (G1-DESs) adopted sirolimus or paclitaxel as the coated antiproliferative

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medications, which effectively eliminated coronary arterial neointimal hyperplasia and thus, in-stent restenosis, mitigating the risks of TVR/TLR events.^[2,3] However, safety concerns arose because of late- and very-late stent thrombosis associated with G1-DES,^[4,5] prompting the development of second-generation DESs (G2-DESs). Based on a novel platform design, more biocompatible polymers, and/or lipophilic antiproliferative medications, G2-DESs were demonstrated to have favorable efficacy and safety in patients undergoing PCI.^[6,7] However, G1-DESs are still used in certain countries because of various issues including economics. Controversy remains regarding the performance of G1-DES versus G2-DES.^[8-10] Based on our previous report, G1-DES had similar efficacy and safety profiles to those of G2-DES in patients with stable coronary artery disease.^[11] This impelled us to consider whether G2-DESs outperform G1-DESs in patients with acute coronary syndrome (ACS), a disorder with higher risks of adverse events after PCI.^[12] Therefore, we aimed to identify the efficacy and safety of G1-DES and G2-DES in patients with ACS in a high-volume PCI center.

METHODS

Ethical approval

This study met the guidelines of the *Helsinki Declaration* of 1975, as revised in 2000, and was approved by the ethics committee of our institution (No. 2013-449). Each patient provided written informed consent before PCI.

Study population

This was a prospective observational study. In 2013, 10,724 consecutive patients underwent PCI or percutaneous transluminal coronary angioplasty in our hospital. Among these patients, 6431 were diagnosed with ACS, including 4511 patients with unstable angina, 1445 patients with ST-segment elevation myocardial infarction (STEMI), and 475 patients with non-STEMI (NSTEMI). The exclusion criteria were: (1) patients undergoing percutaneous transluminal coronary angioplasty without stent implantation, (2) patients receiving neither G1-DES nor G2-DES, and (3) patients receiving multiple types of stents concurrently. In our center, G1-DES included sirolimus-eluting stents (Cypher, Cordis Corp., Milpitas, CA, USA; Firebird, MicroPort Medical, Shanghai, China; Partner, Lepu Medical Technology Co., Beijing, China) and paclitaxel-eluting stents (Taxus Express2 and Taxus Liberté, Boston Scientific Corporation, Natick, MA, USA), while G2-DES included everolimus-eluting stents (Promus Element, Boston Scientific; Xience V and Xience Prime, Abbott Vascular, Santa Clara, CA, USA), sirolimus-eluting stents (Firebird2, MicroPort Medical), and zotarolimus-eluting stents (Endeavor and Endeavor Resolute, Medtronic, Minneapolis, MN, USA). A final total of 4037 patients were enrolled in this study, including 2865 patients with unstable angina, 875 patients with STEMI, and 297 patients with NSTEMI. Among these, 364 patients underwent G1-DES implantation and

3673 patients underwent G2-DES implantation. In patients receiving staged PCI, data were combined from all phases of the procedure.

Procedure and medications

Selective or emergency PCI was performed in all enrolled patients. Before the procedure, patients received aspirin 100 mg/d and clopidogrel 75 mg/d for at least four continuous days. Otherwise, a loading dose of 300 mg aspirin and 300–600 mg clopidogrel were given before PCI. During the procedure, unfractionated heparin (100 U/kg body weight) was administered via the arterial sheath, and an additional 1000 U heparin was given when the procedure lasted for more than 1 h. The use of glycoprotein IIb/IIIa inhibitors was based on the operator's judgment, and the decision to implant a G1-DES or G2-DES was based on the agreement between patients and cardiologists, depending on patients' clinical conditions and economic factors including price and local insurance compensation. After PCI, patients were prescribed aspirin 100 mg/d indefinitely and clopidogrel 75 mg/d for at least 1 year.

Follow-up and endpoints

All patients were followed up at 30 days, 6 months, and then annually after PCI. Of the enrolled 4037 patients, 3955 (98.0%) completed the 2-year follow-up. In-hospital data were collected by reviewing patients' medical records, and follow-up data were collected through medical records, telephone calls, or clinical visits. An independent group of follow-up investigators oversaw data collection, and data accuracy was audited by professional cardiologists. Although not mandatory, patients were advised to return for coronary angiography if an ischemic episode occurred. Efficacy endpoints included major adverse cardiac events (MACEs) and related components, and the safety endpoint was stent thrombosis. MACE was the composite of target vessel-related myocardial infarction (TV-MI), TVR, TLR, and cardiac death. TV-MI was defined as newly occurring MI confirmed by coronary angiography and revealing the target vessel as the culprit lesion, or by electrocardiogram indicating new abnormal ST-T changes and/or left bundle branch block related to the target vessel. TVR was defined as revascularization for a new lesion on the target vessel either by PCI or by coronary artery bypass grafting (CABG), while TLR was defined as revascularization for a new lesion at or within 5 mm of the previously implanted stent either by PCI or by CABG. Cardiac death was defined as death resulting from MI, heart failure, or fatal arrhythmia, and death not attributable to noncardiac reasons. In our study, stent thrombosis included definite, probable, and possible stent thrombosis based on the Academic Research Consortium criteria.^[13]

Statistical analysis

To minimize the differences in sample size and baseline characteristics between the G1-DES and G2-DES groups, we used propensity score matching (PSM) with the nearest-neighbor algorithm and 1:2 matching to avoid

excessive reduction in sample size. The adjusted variables included age, gender, staged PCI, and B₂/C type lesion. Continuous variables were presented as median (25th and 75th percentile) because they were nonnormally distributed by Kolmogorov-Smirnov testing (all: $P < 0.05$). These data were compared using the Mann-Whitney U -test. Categorical variables were expressed as frequency (percentage) and were compared using Pearson's Chi-square or Fisher's exact test. We constructed cumulative survival curves for endpoint events using the Kaplan-Meier method and compared them using the log-rank test. We used a Cox proportional regression model to assess the independent predictors of endpoint events. Variables with $P < 0.10$ in univariate analysis were included in the multivariate Cox regression analysis based on the backward stepwise method. All P values were two sided, and $P < 0.05$ was considered statistically significant. PSM was performed using the MatchIt package in R (R Project for Statistical Computing Version 3.2.4, R Core Team, 2016, <https://www.r-project.org>), and other statistical calculations were performed using SPSS Statistics (Version 22.0, IBM Corp., Armonk, NY, USA).

RESULTS

We enrolled 4037 patients diagnosed with ACS and receiving G1-DES or G2-DES implantation, with 364 of the patients receiving G1-DES and 3673 patients receiving G2-DES implants [Table 1 and Table 2]. We implanted a total of 6697 coronary stents at 5342 lesion sites. There were obvious differences between the two groups concerning staged PCI, incidence of diabetes mellitus, number of target vessels and lesions, left circumflex artery involvement, number of bifurcation lesions, stent overlapping, stent number and average diameter, and the use of glycoprotein IIb/IIIa inhibitors and low-molecular weight heparin or fondaparinux. Therefore, we used a 1:2 PSM to minimize the imbalances between the two groups and described the adjusted covariates in the statistics section of the methods. All baseline data, and the majority of angiographic and procedural data, were well matched after PSM, except that the number of stents was higher and the average stent diameter was lower in the G2-DES group.

At the 2-year follow-up, the occurrences of MACE and its individual components, as well as stent thrombosis, were similar between the G1-DES and G2-DES groups before PSM (respectively: MACE, 5.2% vs. 4.5%, $\chi^2 = 0.371$, $P = 0.542$; TV-MI, 0.8% vs. 0.7%, $P = 0.261$; TVR, 4.9% vs. 3.6%, $\chi^2 = 1.537$, $P = 0.215$; TLR, 3.8% vs. 2.4%, $P = 0.101$; cardiac death, 0.3% vs. 0.8%, $P = 0.521$; and stent thrombosis, 0.5% vs. 1.0%, $P = 0.575$; Table 3). The efficacy and safety endpoints were also not significantly different between G1-DES and G2-DES groups after PSM (respectively: MACE, 5.2% vs. 4.3%, $\chi^2 = 0.514$, $P = 0.474$; TV-MI, 0.8% vs. 0.4%, $P = 0.407$; TVR, 4.9% vs. 3.7%, $\chi^2 = 0.939$, $P = 0.333$; TLR, 3.8% vs. 2.5%, $\chi^2 = 1.610$, $P = 0.205$; cardiac death, 0.3% vs. 0.5%,

$P = 0.670$; and stent thrombosis, 0.5% vs. 0.4%, $P > 0.999$). Other prognostic events also occurred at similar rates between the two groups, including MI, revascularization, stroke (both ischemic and hemorrhagic), and all-cause death (all $P > 0.05$).

Based on Kaplan-Meier analysis, the event-free survival rates for both efficacy and safety endpoints were not statistically different between the G1-DES and G2-DES groups after PSM (MACE, $P = 0.455$; TV-MI, $P = 0.386$; TVR, $P = 0.304$; TLR, $P = 0.189$; cardiac death, $P = 0.530$; and stent thrombosis, $P = 0.748$; Figure 1). Multivariate Cox proportional hazard regression analysis demonstrated that the stent type was not an independent predictive factor for all endpoint events regardless of PSM (all $P > 0.05$; Figure 2).

DISCUSSION

This prospective observational study from a high-volume PCI center revealed the following: (1) the incidences of efficacy and safety endpoint events were similar between G1-DES and G2-DES, including MACE, TV-MI, TVR, TLR, cardiac death, and stent thrombosis, and (2) the stent type was not predictive of these prognostic events.

Compared with G1-DESs, G2-DESs are characterized by novel stent platforms, more lipophilic sirolimus analogues, and/or more biocompatible polymers. These advantages enabled a tremendous decrease in adverse events after PCI including reduced stent thrombosis and restenosis.^[14,15] However, evidence supports similar outcomes between G1-DES and G2-DES. In the SORT OUT IV Trial, a large-scale prospective randomized study comparing the performance of a first-generation sirolimus-eluting stent (Cypher Select Plus, Cordis) and second-generation everolimus-eluting stents (Promus, Boston Scientific and Xience V, Abbott Vascular), incidences and risks of TV-MI, TVR, TLR, and cardiac death were similar between the two groups at the 3-year follow-up.^[16] The SORT OUT IV trial also found that definite, probable, or possible stent thrombosis was not significantly different between the two groups at 3 years, despite the finding that patients were predisposed to definite- and very late-stent thrombosis following G1-DES implantation. Our previous study also found that G1-DES had similar efficacy and safety profiles to G2-DES in patients with stable coronary artery disease.^[11]

Despite these findings, controversy remains regarding whether G2-DESs outperform G1-DES in patients with ACS, and evidence is lacking, especially in certain ethnic groups. Patients with ACS have higher risks of adverse cardiac events after PCI;^[12,17] consequently, careful selection of the PCI strategy, including stent type, is necessary to improve therapeutic benefits. In the current study, we found no significant differences regarding MACE and its components, as well as stent thrombosis at the 2-year follow-up, similar to the findings in a substudy of the SORT OUT IV.^[18] In the substudy, second-generation everolimus-eluting stents were demonstrated to have similar incidences and

Table 1: Baseline patient's characteristics before and after PSM

Characteristics	Before PSM		Statistics	P
	G1-DES (n = 364)	G2-DES (n = 3673)		
Age (years)	59 (51, 64)	58 (50, 66)	0.036*	0.971
Male gender	284 (78.0)	2846 (77.5)	0.055†	0.815
BMI (kg/m ²)	25.5 (23.4, 27.7)	25.9 (23.9, 27.8)	1.897*	0.058
Hospital stay (days)	5 (4, 7)	5 (4, 7)	0.375*	0.707
Staged PCI	18 (4.9)	292 (7.9)	4.218†	0.040
EF (%)	63.0 (58.9, 67.0)	63.0 (60.0, 67.0)	1.088*	0.277
LDL-C (mmol/L)	2.4 (1.9, 3.0)	2.4 (1.9, 3.0)	-0.461*	0.645
eGFR (ml·min ⁻¹ ·1.73 m ⁻²)	94.0 (82.0, 100.7)	94.4 (83.9, 102.2)	1.021*	0.307
Previous MI	44 (12.1)	440 (12.0)	0.004†	0.951
Previous PCI	66 (18.1)	786 (21.4)	2.124†	0.145
Previous CABG	10 (2.7)	140 (3.8)	1.049†	0.306
Clinical presentation				
UA	249 (68.4)	2616 (71.2)	1.275†	0.259
STEMI	90 (24.7)	785 (21.4)	2.193†	0.139
NSTEMI	25 (6.9)	272 (7.4)	0.140†	0.708
Relevant histories				
Hypertension	236 (64.8)	2295 (62.5)	0.783†	0.376
Hyperlipidemia	228 (62.6)	2429 (66.1)	1.797†	0.180
DM	86 (23.6)	1067 (29.0)	4.774†	0.029
Smoker	232 (63.7)	2167 (59.0)	3.084†	0.079
Family history of CAD	80 (22.0)	932 (25.4)	2.050†	0.152
CVD	33 (9.1)	364 (9.9)	0.266†	0.606
PVD	7 (1.9)	78 (2.1)	0.065†	0.799
COPD	6 (1.6)	87 (2.4)	0.763†	0.382
Characteristics	After PSM		Statistics	P
	G2-DES (n = 364)	G2-DES (n = 728)		
Age (years)	59 (51, 64)	59 (51, 64)	0.002*	0.999
Male gender	284 (78.0)	568 (78.0)	<0.001†	>0.999
BMI (kg/m ²)	25.5 (23.4, 27.7)	25.7 (23.7, 27.7)	0.812*	0.417
Hospital stay (days)	5 (4, 7)	5 (4, 7)	0.314*	0.753
Staged PCI	18 (4.9)	36 (4.9)	<0.001†	>0.999
EF (%)	63.0 (58.9, 67.0)	63.0 (59.6, 67.5)	0.824*	0.410
LDL-C (mmol/L)	2.4 (1.9, 3.0)	2.4 (1.8, 3.0)	-0.961*	0.336
eGFR (ml·min ⁻¹ ·1.73 m ⁻²)	94.0 (82.0, 100.7)	95.6 (85.6, 102.4)	1.704*	0.088
Previous MI	44 (12.1)	96 (13.2)	0.262†	0.609
Previous PCI	66 (18.1)	157 (21.6)	1.761†	0.785
Previous CABG	10 (2.7)	32 (4.4)	1.783†	0.182
Clinical presentation				
UA	249 (68.4)	516 (70.9)	0.707†	0.400
STEMI	90 (24.7)	155 (21.3)	1.644†	0.200
NSTEMI	25 (6.9)	57 (7.8)	0.323†	0.570
Relevant histories				
Hypertension	236 (64.8)	434 (59.6)	2.789†	0.095
Hyperlipidemia	228 (62.6)	485 (66.6)	1.699†	0.192
DM	86 (23.6)	205 (28.2)	2.551†	0.110
Smoker	232 (63.7)	424 (58.2)	3.054†	0.081
Family history of CAD	80 (22.0)	179 (24.6)	0.936†	0.333
CVD	33 (9.1)	70 (9.6)	0.086†	0.770
PVD	7 (1.9)	14 (1.9)	<0.001†	>0.999
COPD	6 (1.6)	17 (2.3)	0.555†	0.456

Data were presented as n (%) for categorical variables, and median (P₂₅, P₇₅) for continuous variables. *Z value; †χ² value. BMI: Body mass index; CABG: Coronary artery bypass grafting; CAD: Coronary artery disease; COPD: Chronic obstructive pulmonary disease; CVD: Cerebrovascular disease; DM: Diabetes mellitus; EF: Ejection fraction; eGFR: Estimated glomerular filtration rate; G1-DES: First-generation drug-eluting stent; G2-DES: Second-generation drug-eluting stent; LDL-C: Low-density lipoprotein-cholesterol; MI: Myocardial infarction; NSTEMI: Non-ST-segment elevation myocardial infarction; PCI: Percutaneous coronary intervention; PVD: Peripheral vascular disease; STEMI: ST-segment elevation myocardial infarction; UA: Unstable angina; PSM: Propensity score matching.

Table 2: Patient's angiographic and procedural characteristics before and after PSM

Characteristics	Before PSM		Statistics	P
	G1-DES (n = 364)	G2-DES (n = 3673)		
Normal origin of CA	348 (99.1)	3515 (99.0)	0.057 [†]	0.811
Right distribution of CA	324 (91.0)	3255 (90.4)	0.122 [†]	0.727
Radial approach PCI	336 (92.3)	3377 (91.9)	0.060 [†]	0.806
Number of TVs	1 (1, 1)	1 (1, 1)	2.421*	0.015
Number of TLs	1 (1, 1)	1 (1, 2)	3.478*	0.001
LM involved	5 (1.4)	74 (2.0)	0.709 [†]	0.400
LAD involved	343 (94.2)	3406 (92.7)	1.125 [†]	0.289
LCX involved	39 (10.7)	534 (14.5)	3.977 [†]	0.046
RCA involved	38 (10.4)	496 (13.5)	2.709 [†]	0.100
Graft involved	0 (0.0)	5 (0.1)	-	>0.999 [‡]
<i>De novo</i> lesion	352 (96.7)	3507 (95.5)	1.175 [†]	0.278
B ₂ /C type lesion	252 (69.2)	2709 (73.8)	3.467 [†]	0.063
CTO	16 (4.4)	217 (5.9)	1.393 [†]	0.238
Ostial lesion	51 (14.0)	590 (16.1)	1.044 [†]	0.307
Bifurcation lesion	49 (13.5)	659 (17.9)	4.597 [†]	0.032
Heavy calcification	57 (15.7)	560 (15.2)	0.044 [†]	0.835
Thrombus extraction	12 (3.3)	146 (4.0)	0.405 [†]	0.524
Predilation	348 (95.6)	3480 (94.7)	0.498 [†]	0.480
Postdilation	247 (67.9)	2489 (67.8)	0.001 [†]	0.971
Stent overlapping	109 (29.9)	1309 (35.6)	4.711 [†]	0.030
Number of stents	1 (1, 2)	1 (1, 2)	3.779*	<0.001
Average stent diameter (mm)	3.2 (2.8, 3.5)	3.0 (2.8, 3.5)	-5.396*	<0.001
Average stent length (mm)	21.0 (18.0, 21.9)	23.0 (18.0, 23.3)	1.683*	0.092
IVUS application	16 (4.4)	173 (4.7)	0.073 [†]	0.786
IABP application	5 (1.4)	44 (1.3)	-	0.800 [‡]
Medication at discharge				
Aspirin	360 (98.9)	3623 (98.6)	0.173 [†]	0.678
Clopidogrel	356 (97.8)	3614 (98.4)	0.710 [†]	0.399
Glycoprotein IIb/IIIa inhibitor	57 (15.7)	439 (12.0)	4.224 [†]	0.040
LMWH/fondaparinux	306 (84.1)	3225 (87.8)	4.219 [†]	0.040
Statin	347 (95.3)	3519 (95.8)	0.186 [†]	0.666
β-blocker	313 (86.0)	3269 (89.0)	3.004 [†]	0.083
Nitrates	356 (97.8)	3588 (97.7)	0.020 [†]	0.888
CCB	179 (49.2)	1833 (49.9)	0.070 [†]	0.791
Duration of DAPT				
1 year	347 (95.3)	3523 (95.9)	0.387 [†]	0.592
2 years	97 (26.6)	1073 (29.2)	1.058 [†]	0.304
Characteristics	After PSM		Statistics	P
	G2-DES (n = 364)	G2-DES (n = 728)		
Normal origin of CA	348 (99.1)	695 (98.0)	1.866 [†]	0.172
Right distribution of CA	324 (91.0)	654 (91.5)	0.063 [†]	0.802
Radial approach PCI	336 (92.3)	661 (90.8)	0.698 [†]	0.404
Number of TVs	1 (1, 1)	1 (1, 1)	0.566*	0.571
Number of TLs	1 (1, 1)	1 (1, 1)	1.179*	0.238
LM involved	5 (1.4)	10 (1.4)	<0.001 [†]	>0.999
LAD involved	343 (94.2)	683 (93.8)	0.073 [†]	0.788
LCX involved	39 (10.7)	87 (12.0)	0.363 [†]	0.547
RCA involved	38 (10.4)	77 (10.6)	0.005 [†]	0.944
Graft involved	0 (0.0)	0 (0.0)	-	-
<i>De novo</i> lesion	352 (96.7)	690 (94.8)	2.054 [†]	0.152
B ₂ /C type lesion	252 (69.2)	504 (69.2)	<0.001 [†]	>0.999
CTO	16 (4.4)	33 (4.5)	0.011 [†]	0.918
Ostial lesion	51 (14.0)	116 (15.9)	0.693 [†]	0.405

Contd...

Table 2: Contd...

Characteristics	After PSM		Statistics	P
	G2-DES (n = 364)	G2-DES (n = 728)		
Bifurcation lesion	49 (13.5)	108 (14.8)	0.372 [†]	0.542
Heavy calcification	57 (15.7)	119 (16.3)	0.085 [†]	0.771
Thrombus extraction	12 (3.3)	31 (4.3)	0.593 [†]	0.441
Predilation	348 (95.6)	686 (94.2)	0.910 [†]	0.340
Postdilation	247 (67.9)	503 (69.1)	0.172 [†]	0.678
Stent overlapping	109 (29.9)	241 (33.1)	1.112 [†]	0.292
Number of stents	1 (1, 2)	1 (1, 2)	2.011*	0.044
Average stent diameter (mm)	3.2 (2.8, 3.5)	3.0 (2.8, 3.5)	-4.003*	<0.001
Average stent length (mm)	21.0 (18.0, 21.9)	22.0 (18.0, 26.0)	0.490*	0.624
IVUS application	16 (4.4)	32 (4.4)	<0.001 [†]	>0.999
IABP application	5 (1.4)	7 (1.0)	-	0.547 [‡]
Medication at discharge				
Aspirin	360 (98.9)	717 (98.5)	0.304 [†]	0.581
Clopidogrel	356 (97.8)	708 (97.3)	0.293 [†]	0.588
Glycoprotein IIb/IIIa inhibitor	57 (15.7)	104 (14.3)	0.364 [†]	0.546
LMWH/fondaparinux	306 (84.1)	635 (87.2)	2.033 [†]	0.154
Statin	347 (95.3)	696 (95.6)	0.043 [†]	0.836
β-blocker	313 (86.0)	644 (88.5)	1.369 [†]	0.242
Nitrates	356 (97.8)	706 (97.0)	0.617 [†]	0.432
CCB	179 (49.2)	369 (50.7)	0.222 [†]	0.638
Duration of DAPT				
1 year	347 (95.3)	693 (95.2)	0.010 [†]	0.920
2 years	97 (26.6)	189 (26.0)	0.059 [†]	0.808

Data were presented as n (%) for categorical variables, and median (P₂₅, P₇₅) for continuous variables. *Z value; [†]χ² value; [‡]Fisher's exact P value; "-": Not available. CA: Coronary artery; CCB: Calcium channel blocker; CTO: Chronic total occlusion; DAPT: Dual antiplatelet therapy; G1-DES: First-generation drug-eluting stent; G2-DES: Second-generation drug-eluting stent; IABP: Intra-aortic balloon pumping; IVUS: Intravenous ultrasound; LAD: Left anterior descending artery; LCX: Left circumflex artery; LM: Left main artery; LMWH: Low-molecular weight heparin; PCI: Percutaneous coronary intervention; RCA: Right coronary artery; TIs: Target lesions; TVIs: Target vessels; PSM: Propensity score matching.

Table 3: Patient's 2-year follow-up data before and after PSM

Characteristics	Before PSM		Statistics	P	After PSM		Statistics	P
	G1-DES (n = 364)	G2-DES (n = 3673)			G2-DES (n = 364)	G2-DES (n = 728)		
MACE	19 (5.2)	166 (4.5)	0.371*	0.542	19 (5.2)	31 (4.3)	0.514*	0.474
MI	6 (1.6)	65 (1.8)	0.028*	0.867	6 (1.6)	12 (1.6)	<0.001*	>0.999
TV-MI	3 (0.8)	26 (0.7)	-	0.261 [†]	3 (0.8)	3 (0.4)	-	0.407 [†]
Revascularization	34 (9.3)	262 (7.1)	2.375*	0.123	34 (9.3)	49 (6.7)	2.354*	0.125
TVR	18 (4.9)	134 (3.6)	1.537*	0.215	18 (4.9)	27 (3.7)	0.939*	0.333
TLR	14 (3.8)	89 (2.4)	2.697*	0.101	14 (3.8)	18 (2.5)	1.610*	0.205
Stroke	5 (1.4)	49 (1.3)	-	0.814 [†]	5 (1.4)	8 (1.1)	-	0.769 [†]
Ischemic stroke	3 (0.8)	42 (1.1)	-	0.794 [†]	3 (0.8)	7 (1.0)	-	>0.999 [†]
Hemorrhagic stroke	2 (0.5)	7 (0.2)	-	0.192 [†]	2 (0.5)	1 (0.1)	-	0.259 [†]
All-cause death	6 (1.6)	44 (1.2)	-	0.452 [†]	6 (1.6)	6 (0.8)	-	0.230 [†]
Cardiac death	1 (0.3)	30 (0.8)	-	0.521 [†]	1 (0.3)	4 (0.5)	-	0.670 [†]
Stent thrombosis	2 (0.5)	36 (1.0)	-	0.575 [†]	2 (0.5)	3 (0.4)	-	>0.999 [†]
Acute thrombosis	0 (0.0)	9 (0.2)	-	>0.999 [†]	0 (0.0)	0 (0.0)	-	-
Subacute thrombosis	0 (0.0)	1 (0.0)	-	>0.999 [†]	0 (0.0)	0 (0.0)	-	-
Late thrombosis	1 (0.3)	7 (0.2)	-	0.531 [†]	1 (0.3)	1 (0.1)	-	>0.999 [†]
Very late thrombosis	1 (0.3)	19 (0.5)	-	>0.999 [†]	1 (0.3)	2 (0.3)	-	>0.999 [†]

Data were presented as n (%) for categorical variables, and median (P₂₅, P₇₅) for continuous variables. *χ² value; [†]Fisher's exact P value. "-": Not available. G1-DES: First-generation drug-eluting stent; G2-DES: Second-generation drug-eluting stent; MACEs: Major adverse cardiac events; MI: Myocardial infarction; PSM: Propensity score matching; TLR: Target lesion revascularization; TV-MI: Target vessel-related MI; TVR: Target vessel revascularization.

risks of MI, TLR, cardiac death, and stent thrombosis compared with first-generation sirolimus-eluting stents at

the 18-month follow-up. Furthermore, a SORT OUT III substudy including 1052 patients with ACS revealed that

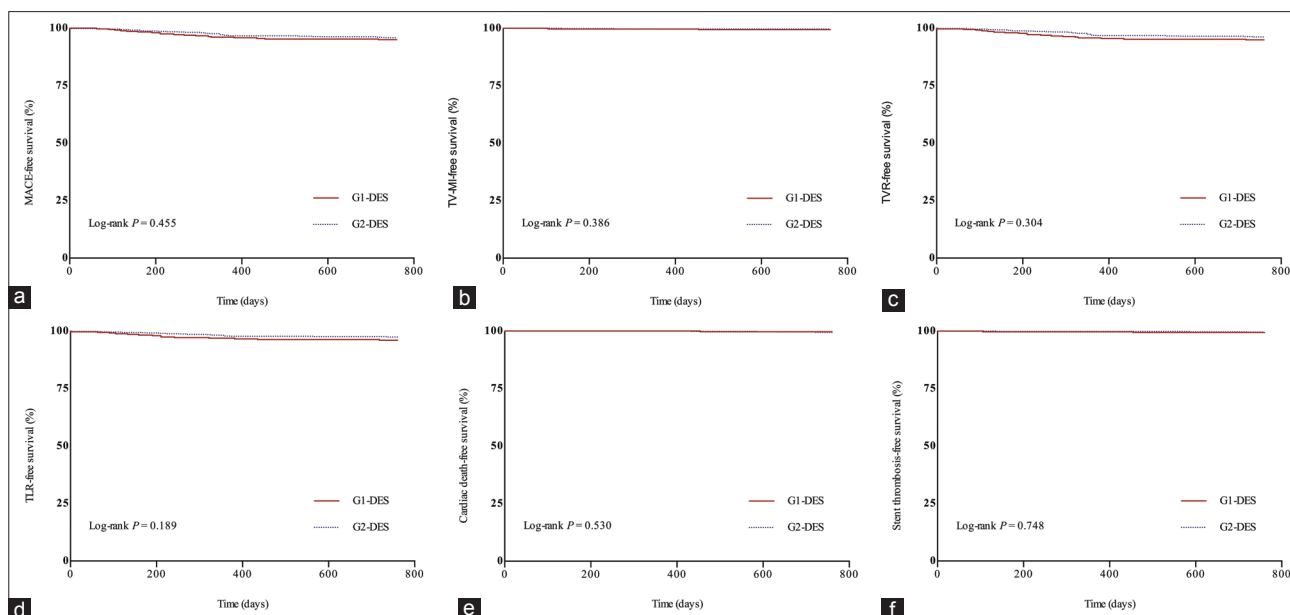


Figure 1: Kaplan-Meier analysis for endpoint event-free survivals after PSM (G1-DES, $n = 364$; G2-DES, $n = 728$). Kaplan-Meier analysis of 2-year event-free survival data for (a) MACE, (b) TV-MI, (c) TVR, (d) TLR, (e) cardiac death, and (f) stent thrombosis. G1-DES: First-generation drug-eluting stent; G2-DES: Second-generation drug-eluting stent; MACEs: Major adverse cardiac events; MI: Myocardial infarction; TLR: Target lesion revascularization; TV-MI: Target vessel-related myocardial infarction; TVR: Target vessel revascularization; PSM: Propensity score matching.

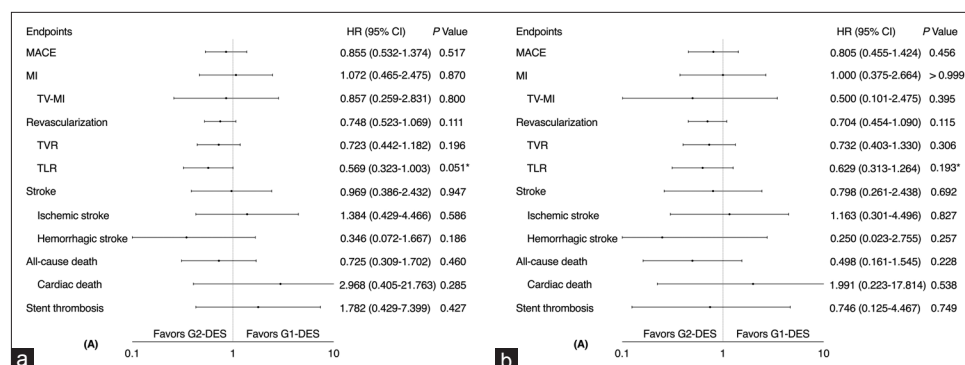


Figure 2: Multivariate Cox proportional regression analysis for efficacy, safety, and other prognostic endpoints. HRs before (a) and after PSM (b). *Adjusted for hospital stay, staged PCI, previous CABG, hypertension, number of TVs, LAD/LCX/RCA involvement, *de novo*/B₂/C type/CTO lesion, stent overlapping, IABP application, average stent length, and use of β -blockers and DAPT for 2 years. CABG: Coronary artery bypass grafting; CI: Confidence interval; CTO: Chronic total occlusion; DAPT: Dual antiplatelet therapy; G1-DES: First-generation drug-eluting stent; G2-DES: Second-generation drug-eluting stent; HRs: Hazard ratios; IABP: Intra-aortic balloon pumping; LAD: Left anterior descending artery; LCX: Left circumflex artery; MACEs: Major adverse cardiac events; MI: Myocardial infarction; PCI: Percutaneous coronary intervention; PSM: Propensity score matching; RCA: Right coronary artery; TLR: Target lesion revascularization; TV: Target vessel; TV-MI: Target vessel-related myocardial infarction; TVR: Target vessel revascularization.

a first-generation sirolimus-eluting stent (Cypher Select and Cypher Select Plus, Cordis) had similar incidences and risks of MI, cardiac death, and definite stent thrombosis compared with second-generation zotarolimus-eluting stents (Endeavor, Medtronic), despite the finding that the second-generation zotarolimus-eluting stent had higher associated risks of MACE and TVR.^[8] Compared with these trials, the study pooled the data for stent type, enabling comparisons between not only G1- and G2-DES but also different stents within the same generation.

For various reasons, including economic concerns and medical insurance, G1-DESs are still being used in some

countries, especially in local hospitals. The present study added evidence to their efficacy and safety for clinical application in patients with ACS. Although MACE had a higher incidence in the G1-DES group compared with the G2-DES group (before PSM: 5.2% vs. 4.5%, respectively, $\chi^2 = 0.371$, $P = 0.542$; after PSM: 5.2% vs. 4.3%, respectively, $\chi^2 = 0.514$, $P = 0.474$), the difference was not statistically significant, and the stent type was not predictive of MACE and its individual components. Similarly, the incidence and the risk of stent thrombosis were not significantly different between G1-DES and G2-DES. In a pathological study including 204 human autopsy

lesion samples, the frequency of neoatherosclerosis was similar among second-generation everolimus-eluting stents (Promus, Boston Scientific and Xience V, Abbott Vascular), a first-generation sirolimus-eluting stent (Cypher, Cordis), and a first-generation paclitaxel-eluting stent (Taxus Express or Taxus Liberté, Boston Scientific).^[19] This finding might in part explain the study finding that the efficacy endpoints were similar between G1-DES and G2-DES. The pathological study also revealed that definite-late or very-late stent thrombosis rates were lower for G2-DES compared with G1-DES, agreeing with the widespread idea that G2-DES reduces the risk of stent thrombosis.^[20] In contrast, this study included definite, probable, and possible stent thrombosis data during follow-up, and we found that cumulative thrombosis was not different between G1-DES and G2-DES (respectively: before PSM: 0.5% vs. 1.0%, Fisher's exact $P = 0.575$; after PSM: 0.5% vs. 0.4%, Fisher's exact $P > 0.999$). The overall stent thrombosis rate was actually low in our 2-year follow-up study, and the relatively small sample size and short follow-up might mean that the study was underpowered to detect statistical differences in stent thrombosis between G1-DES and G2-DES. In this study, ACS was primarily related to unstable angina (66.51%), which has a lower risk of stent thrombosis compared with STEMI and NSTEMI.^[21] Furthermore, up to 95.4% of patients received dual antiplatelet therapy for 1 year, and 28.7% patients were still receiving dual antiplatelet therapy at the 2-year follow-up, which might also have played an important role in preventing stent thrombosis in our patients.

Despite the encouraging findings, this study has several limitations. First, as in any nonrandomized study, the study is limited by the imbalance of patient and procedure selection between the two groups; however, we performed PSM to minimize dissymmetry between the groups. Second, the relatively small sample size of our single-center study hampered the power of the study, and the follow-up period may be insufficient to illuminate long-term outcomes after PCI compared with existing studies assessing 5-year follow-up data. Because of these longer studies, we are performing longer follow-up in our study patients. Third, G1-DES use will eventually decrease in our country; however, currently in most cases, G1-DES selection is associated with higher insurance compensation. It is difficult to say whether factors other than stent type affect outcomes in patients receiving G1-DES, for example, adequate use of necessary medications including statins and regular examinations after PCI. We are considering these factors in our future work.

In conclusion, in this prospective observational study in patients with ACS, we find that G1-DES have similar efficacy and safety compared with G2-DES at the 2-year follow-up. Stent type is not an independent risk factor for adverse outcomes, including stent thrombosis.

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Conflicts of interest

There are no conflicts of interest.

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第一代药物洗脱支架与第二代药物洗脱支架在急性冠脉综合征中的有效性与安全性比较研究

摘要

背景：在急性冠脉综合征（ACS）患者中，第一代药物洗脱支架（G1-DES）与第二代药物洗脱支架（G2-DES）的优劣比较尚无统一结论。本研究拟在ACS患者中比较G1-DES和G2-DES的有效性与安全性。

方法：在2013年，共有10,724名连续患者于阜外医院接受了冠状动脉介入治疗（PCI）。本研究纳入了4,037名置入G1-DES（ $n = 364$ ）或G2-DES（ $n = 3,673$ ）的ACS患者。采用倾向性评分匹配法（PSM）平衡两组间的基线差异。随访时间为2年。有效性终点为主要不良心脏事件（MACE）及其组成事件，包括靶血管相关心肌梗死（TV-MI）、靶血管/靶病变血运重建（TVR/TLR）、以及心脏性死亡。安全性终点为支架血栓。采用Mann-Whitney U 检验法比较连续变量，采用 χ^2 检验或Fisher确切概率法比较分类变量。通过Kaplan-Meier曲线比较两组间无事件生存率，并应用多因素Cox比例风险回归分析评估支架类型是否为终点事件的独立危险因素。

结果：经过2年随访发现，G1-DES组与G2-DES组之间MACE及其组成事件、以及支架血栓发生率无显著性差异（MACE, 5.2% vs. 4.3%, $\chi^2 = 0.514$, $P = 0.474$; TV-MI, 0.8% vs. 0.4%, Fisher确切概率 $P = 0.407$; TVR, 4.9% vs. 3.7%, $\chi^2 = 0.939$, $P = 0.333$; TLR, 3.8% vs. 2.5%, $\chi^2 = 1.610$, $P = 0.205$; 心脏性死亡, 0.3% vs. 0.5%, Fisher确切概率 $P = 0.670$; 支架血栓, 0.5% vs. 0.4%, Fisher确切概率 $P > 0.999$ ）。与此相似，G1-DES组与G2-DES组之间上述事件的生存曲线无显著性差异（所有log-rank P 值 > 0.05 ）。多因素分析表明支架类型不是上述研究终点的危险因素（MACE, 危险比[HR]=0.805, 95%可信区间[CI]0.455-1.424, $P = 0.456$; TV-MI, HR=0.500, 95% CI 0.101-2.475, $P = 0.395$; TVR, HR=0.732, 95% CI 0.403-1.330, $P = 0.306$; TLR, HR=0.629, 95% CI 0.313-1.264, $P = 0.193$; 心脏性死亡, HR=1.991, 95% CI 0.223-17.814, $P = 0.538$; 支架血栓, HR=0.746, 95% CI 0.125-4.467, $P = 0.749$ ）。

结论：经过2年随访研究发现，在ACS患者中G1-DES与G2-DES具有相似的有效性及安全性。