Comparison of Efficacy and Safety between First and Second Generation Drug-eluting Stents in Patients with Stable Coronary Artery Disease: A Single-center Retrospective Study

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Abstract

Background: Lots of trials demonstrate that second-generation drug-eluting stents (G2-DES), with their improved properties, offer significantly superior efficacy and safety profiles compared to first generation DES (G1-DES) for patients with coronary artery disease (CAD) receiving percutaneous coronary intervention (PCI). This study aimed to verify the advantage of G2-DES over G1-DES in Chinese patients with stable CAD (SCAD).

Methods: For this retrospective observational analysis, 2709 SCAD patients with either G1-DES (n = 863) or G2-DES (n = 1846) were enrolled consecutively throughout 2013. Propensity score matching (PSM) was applied to control differing baseline factors. Two-year outcomes, including major adverse coronary events as well as individual events, including target vessel-related myocardial infarction, target lesion revascularization (TLR), target vessel revascularization, and cardiogenic death were evaluated.

Results: The incidence of revascularization between G1- and G2-DES showed a trend of significant difference with a threshold P-value (8.6% vs. 6.7%, χ² = 2.995, P = 0.084). G2-DES significantly improved TLR-free survival compared to G1-DES (96.6% vs. 97.9%, P = 0.049) and revascularization-free survival curve showed a trend of improvement of G2-DES (92.0% vs. 93.8%, P = 0.082). These differences diminished after PSM. Multivariate Cox proportional hazard regression analysis showed a trend for G1-associated increase in revascularization (hazard ratio: 1.28, 95% confidence interval: 0.95–1.72, P = 0.099) while no significance was found after PSM. Other endpoints showed no significant differences after multivariate adjustment regardless of PSM.

Conclusions: G1-DES showed the same safety as G2-DES in this large Chinese cohort of real-world patients. However, G2-DES improved TLR-free survival of SCAD patients 2 years after PCI. The advantage was influenced by baseline clinical factors. G1-DES was associated with a trend of increase in revascularization risk and was not an independent predictor of worse medium-term prognosis compared with G2-DES.

Key words: Drug-eluting Stents; Percutaneous Coronary Intervention; Stable Coronary Artery Disease

Introduction

Ever since drug-eluting stents (DES) have become widely used in percutaneous coronary intervention (PCI), efficacy and safety of different types of DES have always been an area of clinical attention. Second-generation DES (G2-DES), represented by zotarolimus-eluting stents and cobalt-chromium everolimus-eluting stents, exhibit improved stability and lipotropism of eluting drugs compared with first-generation DES (G1-DES). Furthermore, improvements in the polymer biocompatibility coupled with a well-proportioned and slim frame help to reduce endothelial damage and proliferation. Many trials demonstrate that the improved properties of G2-DES result in therapeutic benefits for stable coronary artery disease (SCAD) patients. A recent network meta-analysis by Windecker...
et al. incorporating hundreds of trials showed that percutaneous transluminal coronary angioplasty (PTCA), bare-metal stent (BMS), and G1-DES all failed to significantly reduce mortality in SCAD patients undergoing PCI while G2-DES significantly reduced all-cause mortality, and decreased risks of revascularization, recurrent myocardial infarction (MI), and stent thrombosis (ST) compared to optimal drug therapy, affording benefits approaching that of the much more invasive coronary artery bypass graft (CABG). However, for economic reasons, G1-DES is still applied in local hospitals throughout our country. This study evaluated the efficacy and safety of G1-DES and G2-DES in patients with SCAD, by analyzing 2-year follow-up results of a large sample from a single PCI center in China.

**Methods**

**Ethical approval**

As a retrospective study and data analysis were performed anonymously, this study was exempt from the ethical approval and informed consent from patients.

**Study population**

For this retrospective, observational study, we identified a consecutive group of 10,724 patients with coronary artery disease (CAD) who had either received PCI or PTCA throughout 2013 in our specialized hospital, Beijing. We excluded patients without a SCAD diagnosis according to criteria based on the “2013 ESC guidelines on the management of SCAD.” Additional exclusion criteria include: (1) patients who received only PTCA without stents implantation; (2) patients who received neither G1-DES nor G2-DES, or received multiple types of stents concurrently; and (3) patients who were diagnosed with acute MI or unstable angina pectoris. Totally 2709 patients were enrolled, including 2152 patients with SCAD and 557 patients with asymptomatic myocardial ischemia. All patients received either G1-DES (n = 863) or G2-DES (n = 1846) [Figure 1]. If patients received PCI treatment in multiple stages due to multivessel disease, we combined the data from all phases of treatment. G1-DES included sirolimus-eluting stents (Partner, Lepu Medical, China; Firebird, MicroPort Medical, China), paclitaxel-eluting stents (Taxus and Taxus Liberté, Boston Scientific, USA). G2-DES included zotarolimus-eluting stents (Endeavor and Endeavor Resolute, Medtronic Vascular, USA), everolimus-eluting stents (Xience V and Xience Prime, Abbott Vascular, USA; Promus and Promus Element, Boston Scientific, USA), and domestic sirolimus-eluting stents (Firebird2, MicroPort Medical, China).

**Procedural details**

Patients all received elective PCI treatment after admission. Preoperative oral treatment included aspirin 100 mg/d and clopidogrel loading dose of 300 mg or cumulative dose of 300 mg followed by 75 mg/d. All patients were to take aspirin 100 mg/d indefinitely and clopidogrel 75 mg/d for at least 1 year after stent implantation. Before coronary angiography (CAG), 3000 U heparin sodium was administered through an arterial sheath or intravenously. Before PCI, 100 U/kg of heparin sodium was administered. The dose was lowered to 50–70 U/kg in patients over the age of seventy to reduce bleeding risk. If PCI proceeded for more than 1 h, an additional 1000 U of heparin sodium was administered. Results of CAG were read by experienced cardiologists. More than 50% stenosis of left main artery, left anterior descending artery (LAD), left circumflex artery (LCX), right coronary artery, and main branch of these vessels was defined as coronary artery stenosis. More than 70% stenosis of the vessels mentioned above was indicated for coronary stent implantation. Implantation of G1-DES or G2-DES was decided in consequence of an agreement between our cardiologists and patients, depending on economic factors, including price and insurance.

**Follow-up and definitions**

The average follow-up was 874.9 days. The patients were visited 30 days, 6 months after PCI and every 1 year thereafter. Totally 2682 patients (99.0%) have completed 2-year follow-up in this study. Information of in-hospital outcome was obtained through review of medical records, and the long-term clinical outcome was collected from survey completed by telephone follow-up, follow-up letter or visit. A group of independent clinical physicians was in charge of checking and confirming all adverse events carefully. Investigators training, blinded questionnaire filling, and telephone recording were performed to control the data quality. Primary efficacy endpoints were all major adverse coronary events (MACEs) as well as individual events, including target vessel-related MI (TV-MI), target lesion revascularization (TLR), target vessel revascularization (TVR), and cardiogenic death. TV-MI is clearly diagnosed as newly occurring MI, which is either confirmed by CAG that the lesion of target vessel exists, such as severe stenosis, total occlusion, or thrombosis, or showed by electrocardiogram that the new abnormal ST segment and/or T-wave changes related to the target vessel. TVR is defined as revascularization for a new lesion of the target vessel, including PCI or CABG. TLR is defined as revascularization for a new lesion at or within 5 mm from the location of the previously implanted stent. Cardiogenic death is identified as death caused by MI, heart failure, and/or
malignant arrhythmia definitely; or death which cannot be explained clearly by other reasons. Primary safety endpoint was defined as definite or probable ST based on the Academic Research Consortium criteria, excluding definite ST.

Statistical analysis

Independent t-tests were used to compare continuous variables fitting normal distribution while Chi-square tests were applied to compare categorical variables between the two groups. Propensity score matching (PSM) using closest match with a 1:1 ratio was applied using SPSS 22.0 (IBM Corp., Armonk, New York, USA) to control for baseline differences. T-test, Chi-square test, Kaplan–Meier analysis, and multivariate Cox proportional hazard regression analysis were applied using SPSS 22.0 (IBM Corp., Armonk, New York, USA). Covariates for Cox regression were those variables with significant differences in baseline or important clinical meaning. All P values were two-sided with a significance level of 0.05. Tendency of significant difference was judged when 0.05 < P < 0.1.

Results

Of 2709 total patients enrolled, 863 received G1-DES and 1846 received G2-DES. There were significant differences in the baseline levels of hypertension, old MI, lesions involving LAD or LCX, number of lesions treated, number of stents, number of target vessel, thrombolysis in MI flow before PCI, B2, or C lesions, chronic total occlusion lesions, and bifarction lesions between the two groups [Tables 1 and 2]. PSM was applied to control these differences. The two groups were effectively equalized after PSM with 833 patients selected from each group [Tables 1 and 2].

Before PSM, the occurrence of MACE between G1-DES and G2-DES showed no significant difference (4.9% vs. 3.6%, P = 0.127), and neither were differences observed in the incidence of TV-MI (0.3% vs. 0.5%, P = 0.496), TVR (4.1% vs. 3.1%, P = 0.224), TLR (3.4% vs. 2.3%, P = 0.120), cardiogenic death (0.7% vs. 0.3%, P = 0.176), and bleeding events (6.7% vs. 7.5%, P = 0.480). The incidence of revascularization between G1-DES and G2-DES showed a trend of significant difference with a threshold P-value (8.6% vs. 6.7%, P = 0.084). The incidence of ST showed no difference (0.3% vs. 0.3%, P = 0.924). After PSM, the occurrence of MACE (4.8% vs. 4.0%, P = 0.399), TV-MI (0.2% vs. 0.7%, P = 0.156), TVR (4.1% vs. 3.1%, P = 0.293), TLR (3.5% vs. 2.5%, P = 0.251), cardiogenic death (0.6% vs. 0.5%, P = 0.738), ST (0.4% vs. 0.6%, P = 0.478), and bleeding events (6.2% vs. 8.3%, P = 0.109) between two groups did not significantly differ [Table 3].

Table 1: Clinical baseline data before and after propensity score matching

| Characteristics | Before PSM | After PSM | Statistics | P |
|-----------------|------------|-----------|------------|---|
| Age (years)     |            |           |            |   |
| Sex (male)      |            |           |            |   |
| BMI (kg/m²)     |            |           |            |   |
| LVEF (%)        |            |           |            |   |
| Hypertension    |            |           |            |   |
| Hyperlipidemia  |            |           |            |   |
| DM              |            |           |            |   |
| Smoking         |            |           |            |   |
| Family history  |            |           |            |   |
| CVD             |            |           |            |   |
| PAD             |            |           |            |   |
| COPD            |            |           |            |   |
| OMI             |            |           |            |   |
| Previous PCI    |            |           |            |   |
| Previous CABG   |            |           |            |   |
| eGFR before PCI (ml/min/1.73m²) | | | | |
| Medication (cases) | | | | |
| Aspirin         | 857 (99.3) | 828 (99.4) | 0.698† | 0.404 |
| Clopidogrel     | 856 (99.2) | 826 (99.2) | 1.331† | 0.249 |
| Statin          | 836 (96.9) | 806 (96.8) | 1.356† | 0.248 |
| β-blocker       | 790 (91.5) | 764 (91.7) | 0.008† | 0.929 |
| Calcium antagonist | 402 (46.6) | 388 (46.6) | 0.060† | 0.806 |
| Nitrate         | 843 (97.7) | 813 (97.6) | 0.998† | 0.755 |

Data are shown as mean ± SD or n (%). †Values; ‡P-values. PSM: Propensity score matching; BMI: Body mass index; LVEF: Left ventricular ejection fraction; DM: Diabetes mellitus; CVD: Cerebral vascular disease; PAD: Peripheral artery disease; COPD: Chronic obstructive pulmonary disease; OMI: Old myocardial infarction; eGFR: Estimated glomerular filtration rate; G1-DES: First-generation drug-eluting stent; G2-DES: Second-generation drug-eluting stent; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass graft; SD: Standard deviation.
| Characteristics                        | Before PSM | Statistics | P   | After PSM | Statistics | P   |
|---------------------------------------|------------|------------|-----|-----------|------------|-----|
|                                       | G1-DES     | G2-DES     |     | G1-DES    | G2-DES     |     |
|                                       | (n = 863)  | (n = 1846) |     | (n = 833) | (n = 833)  |     |
| Lesions involving LM                  | 25 (2.9)   | 42 (2.3)   | 0.942* | 24 (2.9)  | 26 (3.1)   | 0.082* |
| Lesions involving LAD                 | 761 (88.2) | 1709 (92.6) | 14.139* | 733 (88.0) | 743 (89.2) | 0.594* |
| Lesions involving LCX                 | 170 (19.7) | 236 (12.8) | 22.066* | 164 (19.7) | 156 (18.7) | 0.248* |
| Number of lesions treated             | 1.4 ± 0.6  | 1.3 ± 0.6  | 3.967* | 1.4 ± 0.6 | 1.4 ± 0.7  | 0.453* |
| Number of stents                      | 2.0 ± 1.1  | 1.7 ± 0.9  | 7.097* | 2.0 ± 1.1 | 1.9 ± 1.1  | 0.791* |
| Number of target vessel               |            |            |       |           |            |     |
| Single vessel                         | 639 (74.0) | 1513 (82.0) | 24.490* | 619 (74.3) | 627 (75.3) | 2.098* |
| Double vessel                         | 186 (21.6) | 274 (14.8) |       | 178 (21.4) | 165 (19.8) |     |
| Triple vessel                         | 13 (1.5)   | 16 (0.9)   |       | 12 (1.4)  | 14 (1.7)   |     |
| LM + single vessel                    | 4 (0.5)    | 10 (0.5)   |       | 4 (0.5)   | 4 (0.5)    |     |
| LM + double vessel                    | 17 (2.0)   | 26 (1.4)   |       | 16 (1.9)  | 16 (1.9)   |     |
| LM + triple vessel                    | 4 (0.5)    | 6 (0.3)    |       | 4 (0.5)   | 6 (0.7)    |     |
| SVG + single vessel                   | 0          | 1 (0.1)    |       | 0         | 1 (0.1)    |     |
| Normal origin of coronary artery      | 833 (96.5) | 1757 (95.2) | 2.533* | 805 (96.6) | 793 (95.2) | 2.208* |
| Right distribution of coronary artery | 767 (88.9) | 1614 (87.4) | 1.152* | 741 (89.0) | 728 (87.4) | 0.973* |
| Transradial approach                  | 761 (88.2) | 1645 (89.1) | 0.513* | 736 (88.4) | 729 (87.5) | 0.277* |
| Pulling out sheath directly           | 750 (86.9) | 1641 (88.9) | 2.245* | 723 (86.8) | 723 (86.8) | >0.999 |
| IVUS application                      | 46 (5.3)   | 124 (6.7)  | 1.923* | 44 (5.3)  | 63 (7.6)   | 3.605* |
| IABP application                      | 6 (0.7)    | 19 (1.0)   | 0.718* | 6 (0.7)   | 12 (1.4)   | 2.022* |
| TIMI flow before PCI                  |            |            |       |           |            |     |
| 0                                     | 146 (16.9) | 228 (12.4) | 16.115* | 148 (17.8) | 127 (15.2) | 2.209* |
| 1                                     | 30 (3.5)   | 41 (2.2)   |       | 27 (3.2)  | 28 (3.4)   | 0.530 |
| 2                                     | 105 (12.2) | 212 (11.5) |       | 103 (12.4) | 99 (11.9)  |     |
| 3                                     | 582 (67.4) | 1365 (73.9) |       | 555 (66.6) | 579 (69.5) |     |
| TIMI flow after PCI                   |            |            |       |           |            |     |
| 1                                     | 1 (0.1)    | 2 (0.1)    | 0.688* | 1 (0.1)   | 1 (0.1)    | 0.336* |
| 2                                     | 7 (0.8)    | 10 (0.5)   |       | 7 (0.8)   | 5 (0.6)    | 0.845 |
| 3                                     | 855 (99.1) | 1834 (99.3) |       | 825 (99.0) | 827 (99.3) |     |
| B2 or C lesions                       | 656 (76.0) | 1336 (72.4) | 4.006* | 635 (76.2) | 623 (74.8) | 0.467* |
| Moderate or severe calcification      | 158 (18.3) | 289 (15.7) | 3.004* | 148 (17.8) | 148 (17.8) | >0.999 |
| CTO lesions                           | 157 (18.2) | 235 (12.7) | 14.176* | 153 (18.4) | 132 (15.8) | 1.867* |
| Ostial lesions                        | 123 (14.3) | 281 (15.2) | 0.436* | 118 (14.2) | 136 (16.3) | 1.505* |
| Bifurcation lesions                   | 147 (17.0) | 382 (20.7) | 5.012* | 140 (16.8) | 167 (20.0) | 2.911* |
| Thrombosis lesions                    | 19 (2.2)   | 32 (1.7)   | 0.698* | 18 (2.2)  | 17 (2.0)   | 0.029* |

Data were shown as mean ± SD or n (%). * χ² values; † t values. CAG: Coronary angiography; LAD: Left anterior descending artery; LCX: Left circumflex artery; LM: Left main artery; SVG: Saphenous vein graft; IVUS: Intravascular ultrasound; IABP: Intra-aortic balloon pump; TIMI: Thrombolysis in myocardial infarction; CTO: Chronic total occlusion; PCI: Percutaneous coronary intervention; SD: Standard deviation; G1-DES: First-generation drug-eluting stent; G2-DES: Second-generation drug-eluting stent; PSM: Propensity score matching.

Application of Kaplan–Meier survival analysis showed that G2-DES significantly improved TLR-free survival compared to G1-DES (96.6% vs. 97.9%, P = 0.049), and also a trend for G2-associated decrease in revascularization (92.0% vs. 93.8%, P = 0.082). There is a separative trend in MACE-free survival and TVR-free survival. Although no significant differences were found in all endpoints including bleeding events after PSM, we can still see a separative trend in MACE-free survival, revascularization-free survival, TVR-free survival, and TLR-free survival curves [Figures 2 and 3]. After multivariate adjustment, there was only a trend for G1-associated increase in revascularization (hazard ratio: 1.28, 95% confidence interval: 0.95–1.72, P = 0.099), and no significance was found after PSM. Other endpoints, including bleeding events showed no significant differences after multivariate adjustment regardless of PSM between two groups [Table 4].

**DISCUSSION**

Several clinical trials reached the conclusion that G2-DES reduced ST, MI, and TLR risks compared to G1-DES. The SCAAR registry showed, in a 2-year follow-up of 94384 consecutively enrolled CAD patients, that G2-DES reduced the incidence of in-stent restenosis (ISR) by 38%, definite ST by 43%, and mortality by 23% compared to G1-DES. The Endeavor trial and the SPIRIT trials I–IV collectively concluded that (1) G2-DES were superior to BMS in...
Table 3: Two-year outcomes before and after propensity score matching, n (%)

| Items            | Before PSM | After PSM | z² | P   | z² | P   |
|------------------|------------|-----------|----|-----|----|-----|
|                  | G1-DES     | G2-DES    |    |     |    |     |
|                  | (n = 863)  | (n = 1846)|    |     |    |     |
|                  | G1-DES     | G2-DES    |    |     |    |     |
|                  | (n = 833)  | (n = 833) |    |     |    |     |
| MACE             | 42 (4.9)   | 67 (3.6)  | 2.331 | 0.127 | 40 (4.8) | 33 (4.0) | 0.702 | 0.402 |
| MI               | 16 (1.9)   | 31 (1.7)  | 0.105 | 0.746 | 15 (1.8) | 15 (1.8) | 0     | >0.999 |
| TV-MI            | 3 (0.3)    | 10 (0.5)  | 0.464 | 0.496 | 2 (0.2)  | 6 (0.7)  | 2.010 | 0.156 |
| Revascularization| 74 (8.6)   | 124 (6.7) | 2.995 | 0.084 | 71 (8.5) | 65 (7.8) | 0.288 | 0.591 |
| TVR              | 35 (4.1)   | 58 (3.1)  | 1.481 | 0.224 | 34 (4.1) | 26 (3.1) | 1.107 | 0.293 |
| TLR              | 29 (3.4)   | 43 (2.3)  | 2.416 | 0.120 | 29 (3.5) | 21 (2.5) | 1.320 | 0.251 |
| All-cause death  | 9 (1.0)    | 16 (0.9)  | 0.200 | 0.655 | 8 (1.0)  | 8 (1.0)  | 0     | >0.999 |
| Cardiogenic death| 6 (0.7)    | 6 (0.3)   | 1.828 | 0.176 | 5 (0.6)  | 4 (0.5)  | 0.112 | 0.738 |
| ST               | 3 (0.3)    | 6 (0.3)   | 0.099 | 0.924 | 3 (0.4)  | 4 (0.5)  | 0.143 | 0.705 |
| Acute ST         | 0          | 1 (0.1)   | 0    | >0.999 | 0      | 0       | 0     | >0.999 |
| Subacute ST      | 1 (0.1)    | 0         | 0    | >0.999 | 1 (0.1) | 0       | 0     | >0.999 |
| Very late ST     | 1 (0.1)    | 5 (0.3)   | 0.639 | 0.424 | 1 (0.1) | 4 (0.5)  | 1.805 | 0.179 |
| Bleeding         | 58 (6.7)   | 138 (7.5) | 0.499 | 0.480 | 52 (6.2) | 69 (8.3) | 2.575 | 0.109 |
| Bleeding of BARC 2 and 3 | 18 (2.1) | 58 (3.1)  | 2.406 | 0.121 | 17 (2.0) | 25 (3.0) | 1.563 | 0.211 |

MACE: Major adverse cardiovascular event; MI: Myocardial infarction; TV-MI: Target vessel-related myocardial infarction; TVR: Target vessel revascularization; TLR: Target lesion revascularization; ST: Stent thrombosis; BARC: Bleeding academic research consortium; PSM: Propensity score matching; G1-DES: First generation drug-eluting stent; G2-DES: Second generation drug-eluting stent.

Table 4: Multivariate Cox proportional hazard regression analysis

| Items            | Before PSM | After PSM | HR (95% CI) | P   | HR (95% CI) | P   |
|------------------|------------|-----------|-------------|-----|-------------|-----|
|                  |            |           |             |     |             |     |
| MACE             | 1.26 (0.85–1.87) | 0.247 | 1.19 (0.75–1.89) | 0.462 |
| MI               | 1.00 (0.54–1.85) | 0.997 | 0.97 (0.48–2.00) | 0.940 |
| TV-MI            | 0.62 (0.17–2.33) | 0.478 | 0.31 (0.06–1.54) | 0.151 |
| Revascularization| 1.28 (0.95–1.72) | 0.099 | 1.08 (0.77–1.51) | 0.660 |
| TLR              | 1.42 (0.88–2.29) | 0.153 | 1.33 (0.76–2.33) | 0.327 |
| TVR              | 1.27 (0.83–1.94) | 0.277 | 1.28 (0.76–2.13) | 0.352 |
| All-cause death  | 1.12 (0.49–2.58) | 0.786 | 1.03 (0.38–2.78) | 0.951 |
| Cardiogenic death| 1.68 (0.53–5.38) | 0.381 | 1.08 (0.29–4.13) | 0.906 |
| ST               | 0.99 (0.24–4.05) | 0.990 | 0.69 (0.15–3.10) | 0.625 |
| Bleeding         | 0.90 (0.66–1.22) | 0.486 | 0.75 (0.52–1.08) | 0.117 |
| Bleeding of BARC II and III | 0.62 (0.36–1.07) | 0.085 | 0.66 (0.35–1.22) | 0.180 |

A trend for G1-associated increase in revascularization was found, while other endpoints showed no significantly differences. TV-MI: Target vessel-related myocardial infarction; TVR: Target vessel revascularization; ST: Stent thrombosis; BARC: Bleeding academic research consortium; PSM: Propensity score matching; G1: First generation; G2: Second generation drug-eluting stent.

Reducing ISR and revascularization risk, and (2) G2-DES were superior to G1-DES in reducing risks of ISR, ST, TV-MI, and cardiogenic death. A 2012 meta-analysis showed that, compared to G1-DES, G2-DES lowered the rate of definite ST during both 1- and 2-year follow-ups. Some evidence supporting the superiority of G2-DES came from a recent large meta-analysis showing significantly better efficacy and safety of G2-DES compared to G1-DES. In light of these results, we hypothesized that G2-DES would show significantly improved efficacy and safety profiles in Chinese SCAD patients during a 2-year follow-up.

In this retrospective analysis, we draw several points: (1) Though all the event rates showed no significant differences, G2-DES improved TLR-free survival compared to G1-DES, and revascularization-free survival curve showed a trend of G2-associated improvement. The advantage was diminished by removing effects of baseline factors. (2) G1-DES was only associated with a trend of increase in revascularization risk and was not an independent predictor of worse medium-term prognosis compared with G2-DES. (3) G1-DESs were as safety as G2-DESs in this large Chinese cohort of real-world patients. Although the conclusion does not go against the findings from the above-mentioned trials, the differences are not as significant as we expected. One possible reason may due to the low rates of coronary adverse events in SCAD patients compared to all-comer study. The all-cause mortality in this study was about 1% while in SOUT OUT IV trial the
Pathophysiology of SCAD involves stable plaques, which have thicker fibrous caps, smaller lipid cores, more collagen and smooth muscle cells, and fewer macrophages. As such, stable plaques seldom rupture and lead to the acute coronary thrombus. In addition, this is a study performed in a single center with advanced PCI technology and standard secondary prevention medication, both leading to rates of adverse coronary events lower than those reported elsewhere. Therefore, the benefits of G2-DES would be too difficult to detect without enormous sample sizes, probably covering more years or multicenter patients. It may be for this reason that we only see a trend of separating-curves with critical P values. Meanwhile, follow-up of our study may too short to find the difference. The Kaplan–Meier curves of MACE, revascularization, TVR, TLR may significantly separate during subsequent follow-up. This study may simply be underpowered for detection of advantage in the efficacy of G2-DES. In light of these considerations, it is arguable whether the differences we found are underestimated.

Furthermore, G1-DESs were found the same safety as G2-DESs in definite/probable ST. In SORT OUT IV trial, the definite/probable ST showed no difference while definite ST showed significant increase in sirolimus-eluting stent group at 18 months. One possible reason may be that long-term follow-up should be conducted. Ten-year outcomes of SORT OUT II trial showed a steady annual rate of 1.3% in definite, probable and possible ST after the 1st year. Patients received G1-DES need for continuous surveillance for ST.

Admittedly, there are several limitations in this study. (1) DES within the same generation is not directly compared to each other, the heterogeneity of efficacy and safety for different DESs within each generation may confound study.

**Figure 2:** Kaplan–Meier curve analysis before propensity score matching for 2-year follow-up of all-cause death (a), MI (b), revascularization (c), MACE (d), TV-MI (e), TVR (f), TLR (g), cardiogenic death (h), and ST (i). G2-DES significantly improved TLR-free survival compared to G1-DES, and also a trend for G1-associated increase in revascularization. There is a separate trend in MACE-free survival and TVR-free survival. G2-DES: Second-generation drug-eluting stents; G1-DES: First-generation drug-eluting stents; PSM: Propensity score matching; MI: Myocardial infarction; MACE: Major adverse cardiovascular event; TV-MI: Target vessel-related myocardial infarction; TVR: Target vessel revascularization; TLR: Target lesion revascularization; ST: Stent thrombosis.

all-cause mortality was around 4%. Pathophysiology of SCAD involves stable plaques, which have thicker fibrous caps, smaller lipid cores, more collagen and smooth muscle cells, and fewer macrophages. As such, stable plaques seldom rupture and lead to the acute coronary thrombus. In addition, this is a study performed in a single center with advanced PCI technology and standard secondary prevention medication, both leading to rates of adverse coronary events lower than those reported elsewhere. Therefore, the benefits of G2-DES would be too difficult to detect without enormous sample sizes, probably covering more years or multicenter patients. It may be for this reason that we only see a trend of separating-curves with critical P values. Meanwhile, follow-up of our study may too short to find the difference. The Kaplan–Meier curves of MACE, revascularization, TVR, TLR may significantly separate during subsequent follow-up. This study may simply be underpowered for detection of advantage in the efficacy of G2-DES. In light of these considerations, it is arguable whether the differences we found are underestimated.

Furthermore, G1-DESs were found the same safety as G2-DESs in definite/probable ST. In SORT OUT IV trial, the definite/probable ST showed no difference while definite ST showed significant increase in sirolimus-eluting stent group at 18 months. One possible reason may be that long-term follow-up should be conducted. Ten-year outcomes of SORT OUT II trial showed a steady annual rate of 1.3% in definite, probable and possible ST after the 1st year. Patients received G1-DES need for continuous surveillance for ST.

Admittedly, there are several limitations in this study. (1) DES within the same generation is not directly compared to each other, the heterogeneity of efficacy and safety for different DESs within each generation may confound study.
outcomes to a certain extent. (2) The nature of nonrandomized comparisons cannot be overlooked. Although PSM was applied to remove effects of differing baseline factors, the results were still influenced by other characteristics not including in the study, such as SNYTX scores. (3) All secondary prevention drugs in baseline data referred to medication at discharge definitely. Medication compliance of every patient during follow-up may bring about bias. Nevertheless, these results will help to guide clinical decision making by providing evidence that, as far as abroad groups concerned, the performance of first- and second-generation stents differs in their efficacy profiles. In our single-center study, G2-DES is more than 2-fold more prevalent than G1-DES for SCAD patients undergoing PCI during 2013. Although application of G1-DES declines rapidly in Third Grade Class A Hospital, it is still holding part of the market of local hospitals throughout our country. The results were driven from the tertiary hospital with high PCI volumes and skilled operators. Although it cannot be extrapolated to local hospitals with low PCI volumes and unskilled operators, it still provides some confidence that G1-DESs are not so bad. Cost performance may be taken into consideration by poor patients. Other indications also are objective, such as limited choices of DES types in basic hospital or on insurance list. Prognosis is decided by many factors, not only the stent type. At least, G1-DES application is not an independent predictor of worse medium-term outcomes compared with G2-DES. Overall, a better grasp of therapeutic benefits of these G2-DES would have deep economic effects on SCAD patients who undergo PCI, especially in developing countries like China.\textsuperscript{[24,25]}

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Conflicts of interest
There are no conflicts of interest.

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