# In-Stent Restenosis in Saphenous Vein Grafts (from the DIVA Trial)

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**Saphenous vein grafts (SVGs) have high rates of in-stent restenosis (ISR). We compared the baseline clinical and angiographic characteristics of patients and lesions that did develop ISR with those who did not develop ISR during a median follow-up of 2.7 years in the DIVA study (NCT01121224). We also examined the ISR types using the Mehran classification. ISR developed in 119 out of the 575 DIVA patients (21%), with similar incidence among patients with drug-eluting stents and bare-metal stents (BMS) (21% vs 21%, p = 0.957). Patients in the ISR group were younger (67 ± 7 vs 69 ± 8 years, p = 0.04) and less likely to have heart failure (27% vs 38%, p = 0.03) and SVG lesions with Thrombolysis In Myocardial Infarction 3 flow before the intervention (77% vs 83%, p <0.01), but had a higher number of target SVG lesions (1.33 ± 0.64 vs 1.16 ± 0.42, p <0.01), more stents implanted in the target SVG lesions (1.52 ± 0.80 vs 1.31 ± 0.66, p <0.01), and longer total stent length (31.37 ± 22.11 vs 25.64 ± 17.42 mm, p = 0.01). The incidence of diffuse ISR was similar in patients who received drug-eluting-stents and BMS (57% vs 54%, p = 0.94), but BMS patients were more likely to develop occlusive restenosis (17% vs 33%, p = 0.05). Published by Elsevier Inc. (Am J Cardiol 2022;162:24−30)**

Drug-eluting stents (DES) reduced the risk of in-stent restenosis (ISR) in native coronary artery lesions compared with bare-metal stents (BMS), yet their role in saphenous vein graft (SVG) percutaneous coronary intervention (PCI) has been controversial.[1−10] Randomized trials that mandated 6- to 12-month angiographic follow-up showed that BMS had higher rates of angiographic ISR.[4,9] However, during long-term follow-up, the 2 largest studies showed no difference in clinical events between DES and BMS,[2,5] and another study showed worse outcomes with DES.[10] We compared the clinical, angiographic, and procedural characteristics of patients who did with those who did not develop ISR in the Drug-Eluting Stents in Saphenous Vein Graft Angioplasty (DIVA trial, NCT01121224), a randomized controlled trial conducted at 25 US Department of Veterans Affairs centers. Moreover, we compared the incidence and ISR pattern after DES versus BMS implantation.

DIVA was a prospective, double-blind trial that randomized patients with de novo SVG lesions (50% to 99%

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stenosis of a 2.25 to 4.5 mm diameter) in a 1:1 ratio to receive either DES or BMS. The vast majority of DES were second generation (88%). The full study protocol and primary results have been published;[2,11] patients receiving DES and BMS had similar incidence of the primary endpoint of target vessel failure during a median follow-up of 2.7 years. Nearly all study patients (>99%) were men.

We compared the clinical, angiographic, and procedural characteristics of patients who did with those who did not develop ISR in the DIVA trial. We performed a second analysis comparing the angiographic types of ISR as described by Mehran et al:[12] type IA: lesion ≤10 mm in length at the unscaffolded segment (articulation or gap), type IB: lesion ≤10 mm in length at the proximal or distal margin (but not both), type IC: lesion ≤10 mm in length at the body of the stent, type ID: lesion ≤10 mm in length to both margins (proximal and distal), type II: lesion >10 mm confined to the stent, type III: lesion >10 mm in length that extends beyond the margins of the stent, type IV: total occlusion. Focal ISR includes types IA, IB, IC, and ID, and diffuse ISR includes types II, III, and IV. Repeat angiography was driven by clinical symptoms, and the presence of ISR was indicated by the interventional cardiologist/primary investigator of each center and adjudicated by the core laboratory. Binary ISR was defined as ≥50% angiographic reduction in lumen diameter after stent implantation. Quantitative coronary analysis was performed using the Cardiovascular Angiography Analysis System (version 8.1, Pie Medical Imaging, Maastricht, The Netherlands).

Categorical variables were expressed as percentages and compared using Pearson's chi-square test or 2-tail Fisher's exact test. Continuous variables were presented as mean ± SD or median (interquartile range) and were compared using *t* test or Wilcoxon rank-sum test, as appropriate. Time to event analysis was used to examine the association between use of DES and ISR after adjusting for confounding variables selected on univariable association ($p < 0.1$). SAS 9.2 (TS2M3; SAS Institute, Cary, North Carolina) and R version 3.4.4 were used for the analyses. A two-sided p value of 0.05 was considered statistically significant.

Of the 575 patients who underwent stenting of de novo SVG lesions in the DIVA trial, 119 (21%) developed ISR during a median follow-up of 2.7 years (126 restenotic lesions in 119 grafts, out of 688 treated lesions in 597 grafts). Of note, 58 of 279 patients (21%) with DES and 61 of 296 patients (21%) with BMS developed ISR during the follow-up period ($p = 0.89$) (Figure 1).

The clinical characteristics of the study patients are summarized in Table 1. There was no difference in the prevalence of cardiovascular risk factors; however, patients without ISR were more likely to have heart failure. The SVG age was older in the DES group (14.19 ± 6.77 vs 11.56 ± 5.97 years, $p = 0.02$).

The most common target graft recipient vessel was the circumflex/obtuse marginal for both groups (41% vs 40% for no SVG ISR group and SVG ISR group, respectively), followed by the right coronary artery/posterior descending artery (37% vs 34%) and the left anterior descending/diagonal artery (22% vs 25%, $p = 0.67$ for all comparisons). Furthermore, the location of the SVG target lesion was similar in the no SVG ISR group and the SVG ISR group (21% vs 27%, 70% vs 65% and 9% vs 8% for aortic/ostial, body and coronary anastomosis, $p = 0.30$ for all comparisons). Lesions in the ISR group patients were less likely to have Thrombolysis In Myocardial Infarction (TIMI) 3 flow before the intervention (83% vs 77%, $p < 0.01$), whereas there was no difference in poststenting TIMI flow between the 2 groups (TIMI 3 flow 98% vs 100%, $p = 0.26$).

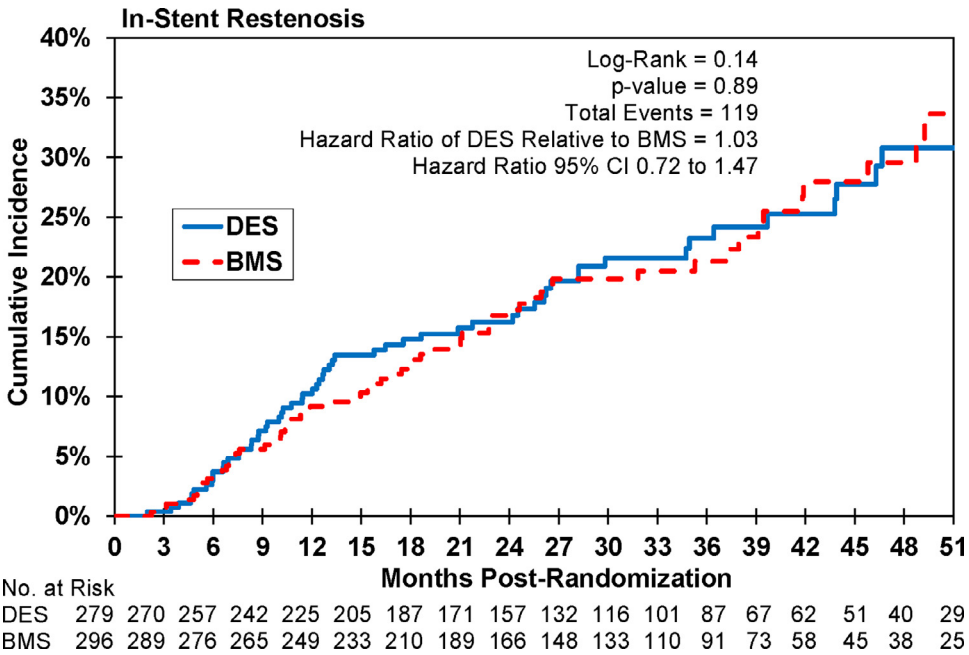


Figure 1. Kaplan-Meier plot of cumulative incidence curves for patients who received DESs or BMSs for ISR. CI = confidence interval; No. = number.

Table 1
Clinical characteristics of the study patients classified according to the occurrence of in-stent restenosis

| Variables | Total(N = 688 lesions, 597 grafts, 575 subjects) | No SVG in-stent restenosis (N = 462 lesions, 478 grafts, 456 subjects) | SVG in-stent restenosis (N = 126 lesions, 119 grafts, 119 subjects) | p Value |
|---|---|---|---|---|
| Age* (years) | 68.60 ± 7.56 | 68.93 ± 7.63 | 67.30 ± 7.18 | 0.04 |
| Men | 573 (100%) | 454 (100%) | 119 (100%) | 1.00 |
| White | 498 (89%) | 395 (90%) | 103 (88%) | 0.63 |
| Black | 46 (9%) | 37 (10%) | 9 (8%) | 0.68 |
| Hispanic | 30 (5%) | 24 (5%) | 6 (5%) | 1.00 |
| Body mass index (kg/m$^2$) | 30.51 ± 5.5 | 30.28 ± 5.36 | 31.42 ± 5.96 | 0.13 |
| Years since most recent coronary artery bypass graft surgery | 13.36 ± 6.74 | 13.5 ± 6.81 | 12.84 ± 6.48 | 0.41 |
| Number of narrowed coronary vessels | | | | 0.51 |
| 1 | 11 (2%) | 10 (2%) | 1 (1%) | |
| 2 | 54 (9%) | 41 (9%) | 13 (11%) | |
| 3 | 495 (86%) | 391 (86%) | 104 (87%) | |
| First stage chest pain indication for PCI | | | | 0.83 |
| Stable angina pectoris | 217 (38%) | 176 (39%) | 41 (34%) | |
| Unstable angina pectoris | 177 (31%) | 140 (31%) | 37 (31%) | |
| Non-STEMI | 135 (23%) | 104 (23%) | 31 (26%) | |
| Other | 46 (8%) | 36 (8%) | 10 (8%) | |
| Hypertension | 553 (96%) | 439 (96%) | 114 (96%) | 0.79 |
| Hyperlipidemia | 559 (97%) | 443 (97%) | 116 (97%) | 1.00 |
| Diabetes mellitus | 345 (60%) | 271 (59%) | 74 (62%) | 0.58 |
| Current smoker | 129 (22%) | 99 (22%) | 30 (25%) | 0.42 |
| Prior myocardial infarction | 304 (53%) | 240 (53%) | 64 (54%) | 0.82 |
| History of atrial fibrillation | 105 (18%) | 85 (19%) | 20 (17%) | 0.64 |
| Congestive heart failure | 204 (35%) | 172 (38%) | 32 (27%) | 0.03 |
| Ejection fraction* | 49.49 ± 13.32 | 48.90 ± 13.52 | 51.87 ± 12.29 | 0.12 |
| Peripheral arterial disease | 103 (18%) | 81 (18%) | 22 (18%) | 0.85 |

CAD = coronary artery disease; Non-STEMI = ST-segment elevation myocardial infarction; SVG = saphenous vein graft.
* Mean ± SD.

The procedural characteristics of the index procedure are outlined in Table 2. The ISR group had more target SVG lesions, more stents implanted in target SVG lesions, and longer total stent length. The median highest inflation pressure for the largest balloon in target lesions was similar between the no-ISR and the ISR group (14 [4, 28] vs 12 [5, 24] atmospheres, p = 0.45). On multivariable analysis, only total stent length of all subjects' target lesions was independently associated with the development of ISR (Table 3).

There was no difference in clinical presentation between DES and BMS patients (Figure 2). The ISR pattern according to Mehran classification is illustrated in Table 4. BMS patients presented more often with pattern IV ISR (total occlusion), whereas pattern II ISR (>10 mm confined to the stent) was more common for patients with DES. The rate of focal and diffuse ISR was similar in the 2 study groups. Patients with lesions classified as IC and IV according to Mehran classification were more likely to present with stable angina, whereas those with Mehran IB and ID lesions presented more frequently with non-ST−segment elevation myocardial infarction and those with Mehran II lesions with unstable angina (Figure 2). The ISR treatments were also similar in the DES and BMS groups, with the exception that a higher percentage of lesions remained without revascularization in the BMS group (Figure 3).

The major findings of our study are that in patients undergoing stenting of de novo SVG lesions; (1) the risk of ISR during a 2.7-year median follow-up period was 21% without difference between patients randomized to BMS versus DES, (2) baseline TIMI <3 flow and longer stent length were associated with higher risk for ISR, and (3) patients receiving BMS were more likely to develop occlusive restenosis.

SVG lesions are associated with high risk for restenosis and re-occlusion.[13,14] A potential explanation is the different pathophysiology and physical history of SVG compared with native coronary artery disease. SVG disease develops in the following stages: (1) thrombosis during the first month, (2) intimal hyperplasia within 4 to 6 weeks after coronary artery bypass graft, and (3) atherosclerosis beyond the first year.[15] Although atherosclerosis in coronary arteries takes decades to develop, accelerated atherosclerosis, especially in the adjacent stented segments, is observed in SVGs within months to years, often in a more concentric and diffuse pattern with less well-defined fibrous cap and large hemorrhagic necrotic cores that predispose to plaque rupture and thrombosis.[16−18]

Compared with BMS, DES reduce neointimal thickness in SVGs but also cause delayed healing characterized by persistent fibrin deposition, uncovered stent struts, and incomplete endothelialization.[19] Late in-stent neointimal growth may in part explain the “catch-up” phenomenon that occurs beyond 2 years in SVGs treated with DES. In addition, neoatherosclerosis is more common and occurs earlier and in a more diffuse pattern across the stented segments in DES than BMS, contributing to late DES

Table 2
Index procedure characteristics classified according to the presence of in-stent restenosis

| Index procedure characteristics | Total(N = 688 lesions, 597 grafts, 575 subjects) | No SVG in-stent restenosis (N = 462 lesions, 478 grafts, 456 subjects) | SVG in-stent restenosis (N = 126 lesions, 119 grafts, 119 subjects) | p Value |
|---|---|---|---|---|
| Arterial access | | | | |
| Femoral | 529 (92%) | 419 (92%) | 110 (92%) | 0.87 |
| Radial | 42 (7%) | 33 (7%) | 9 (8%) | |
| Other | 4 (1%) | 4 (1%) | 0 (0%) | |
| Anticoagulant | | | | |
| Unfractionated heparin | 332 (58%) | 259 (57%) | 73 (61%) | 0.37 |
| Bivalirudin | 251 (44%) | 200 (44%) | 51 (43%) | 0.84 |
| Glycoprotein IIb/IIIa inhibitor | 84 (15%) | 62 (14%) | 22 (18%) | 0.18 |
| Staged PCI | 64 (11%) | 48 (11%) | 16 (13%) | 0.37 |
| Hemodynamic support During PCI | 4 (1%) | 4 (1%) | 0 (0%) | 0.59 |
| Embolic protection device used in at least 1 target lesion | 410 (71%) | 325 (71%) | 85 (71%) | 0.97 |
| Number of target SVGs intervened per subject* | 1.04 ± 0.19 | 1.04 ± 0.18 | 1.05 ± 0.22 | 0.44 |
| Number of subjects who underwent PCI of more than 1 target SVG lesion | 96 (17%) | 67 (15%) | 29 (24%) | 0.01 |
| Number of target SVG lesions intervened per subject* | 1.20 ± 0.48 | 1.16 ± 0.42 | 1.33 ± 0.64 | <0.01 |
| Number of stents inserted in target SVG lesions per subject* | 1.36 ± 0.70 | 1.31 ± 0.66 | 1.52 ± 0.80 | <0.01 |
| Number of non-target SVG lesions intervened per subject* | 1.37 ± 0.65 | 1.40 ± 0.69 | 1.29 ± 0.46 | 0.72 |
| Type of DES used in target lesions | | | | |
| First generation | 23 (4%) | 15 (3%) | 8 (7%) | 0.11 |
| Second generation | 265 (46%) | 210 (46%) | 55 (46%) | 0.97 |
| Total length of stents inserted in target lesions per subject* (mm) | 26.83 ± 18.62 | 25.64 ± 17.42 | 31.37 ± 22.11 | 0.01 |
| Target lesion stent diameter* (mm) | 3.40 ± 0.53 | 3.40 ± 0.53 | 3.37 ± 0.52 | 0.43 |
| Angiographic success | 685 (100%) | 559 (99%) | 126 (100%) | 1.00 |
| Intravascular imaging utilization | | | | |
| Intravascular ultrasound | 116 (20%) | 87 (19%) | 29 (24%) | 0.20 |
| Optical coherence tomography | 9 (2%) | 8 (2%) | 1 (1%) | 0.69 |
| Any procedural complication | 31 (5%) | 25 (5%) | 6 (5%) | 0.85 |
| Periprocedural myocardial infarction, n (%) | 28 (5%) | 21 (5%) | 7 (6%) | 0.56 |

DES = drug-eluting stents., PCI, percutaneous coronary intervention; SVG, saphenous vein graft.
* Mean ± SD.

failure,[20,21] although in our study, there was not a difference in diffuse disease between DES and BMS. According to the DIVA trial inclusion criteria, stenosed SVGs had to have a 2.25 to 4.5 mm diameter. Mean target lesion stent diameter was 3.4 ± 0.5 mm. To date, no SVG dedicated DES have been developed. The relatively high rates of stent failure underline the need for developing such stents.

The incidence of 6- to 12-month ISR for BMS and DES ranges from 19% to 61% and 11% to 12%, respectively.[6,9,22–26] In our study, 21% of the patients with BMS and 21% of the patients with DES developed ISR during a median follow-up period of 2.7 years. This occurred despite using second generation DES in 88% of the DES patient group, unlike previous studies that used first generation (sirolimus or paclitaxel-eluting stents).[27–29] In contrast with other studies that mandated follow-up with angiography at 6 to 12 months in DIVA, repeat angiography was not mandated but was instead performed only if clinically indicated.

Approximately 1 of 3 patients who developed SVG ISR did not undergo revascularization, which may reflect the high risk of repeat SVG failure or challenges associated with acute SVG treatment, especially for completely occluded SVGs, which are unlikely to remain patent even if repeat PCI is successful (Figure 3). In addition, corresponding coronary artery lesions are often severely calcified or represent complex chronic total occlusion lesions that need special expertise to be recanalized, discouraging interventional cardiologists from proceeding with PCI.

Data on prognostic factors for SVG ISR remain scarce. Diabetes mellitus, minimal lumen diameter before stent implantation, low TIMI status before intervention, intermittent vessel occlusion, and use of BMS over DES have been associated with higher risk for ISR.[6,9,10,13,21–25,30] In our study, TIMI flow <3 prestenting and higher number and length of stents were associated with higher risk for ISR. However, on multivariable analysis, only stent length remained independently associated with ISR. Similar to our study, previous studies comparing older generation DES with BMS in SVG interventions did not demonstrate an independent association of diabetes mellitus with ISR,[9,23] likely owing to different pathophysiology of ISR in coronary arteries compared with SVGs.

Table 3
Multivariable analysis of time to in-stent restenosis during the entire follow-up period

| Variable | HR (95% CI) | p Value |
|---|---|---|
| Randomized to DES | 1.02 (0.71, 1.46) | 0.93 |
| Age | 0.98 (0.96, 1.01) | 0.24 |
| Diabetes | 0.96 (0.66, 1.41) | 0.84 |
| Current smoker | 1.09 (0.71, 1.67) | 0.70 |
| EGFR<60 ml/min/1.73 $m^2$ | 1.51 (0.99, 2.31) | 0.0575 |
| Total stent length (mm) | 1.02 (1.01, 1.02) | 0.0005 |
| 2.25 mm <=Stent diameter <3 mm | 1.4 (0.81, 2.42) | 0.23 |
| 3.5 mm <=Stent diameter <4 mm | 1.17 (0.7, 1.93) | 0.55 |
| Stent diameter >=4 mm | 0.79 (0.45, 1.39) | 0.41 |
| Aortic/ostial lesion | 1.49 (0.99, 2.24) | 0.0557 |
| Coronary anastomosis lesion | 1.08 (0.58, 2.03) | 0.81 |

DES = drug-eluting stent; EGFR = estimated glomerular filtration rate.

Although the overall incidence of ISR was similar with BMS and DES in DIVA, occlusive restenosis was more common in the BMS group (17% vs 33%, p = 0.05). This is similar to the Stenting of Saphenous Vein Graft (SOS) trial,[6] in which occlusive restenosis occurred in 24% of BMS patients versus 6% of DES patients after 12 months. In the Reduction of Restenosis In Saphenous Vein Grafts With Cypher Sirolimus-Eluting Stent (RRISC) trial[9], 10 of 16 BMS restenotic lesions (62.5%) were diffuse, with 2 (12.5%) being total occlusions, and 6 (37.5%) were characterized as focal, whereas most ISR cases in the sirolimus-eluting stent group were focal (5 out of 6 lesions [83.3%], vs 1 out of 6 [16.7%], diffuse). This finding suggests that DES may have an advantage over BMS in SVG lesions, even though there was no difference in the overall incidence of major adverse cardiac events.

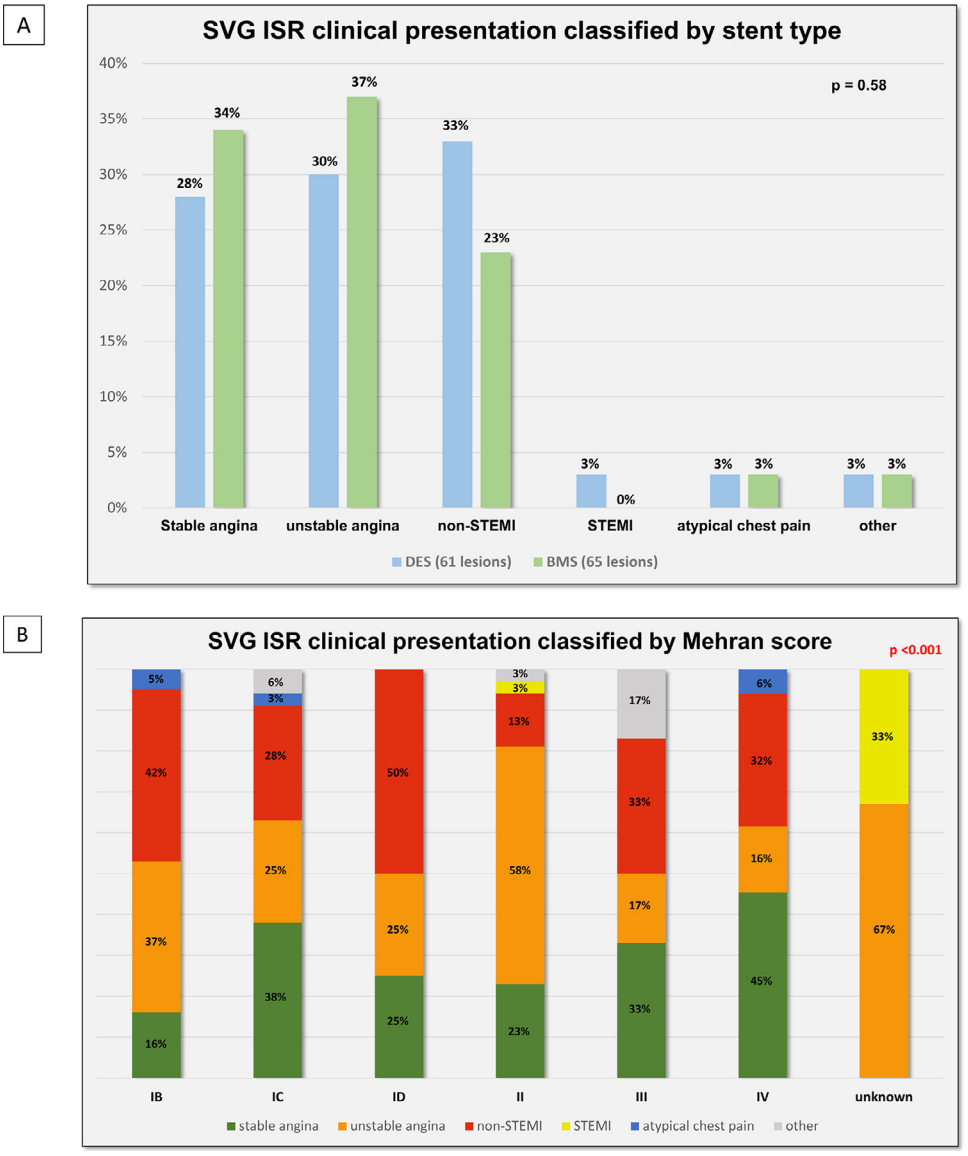


Figure 2. SVG ISR clinical presentation according to stent type (*A*) and Mehran score (*B*). STEMI = ST-segment elevation myocardial infarction.

Table 4
Type of in-stent restenosis among DES vs BMS patients according to the Mehran classification

| Type of in-stent restenosis | Total with in-stent restenosis (N = 126 lesions, 119 subjects) | DES(N = 61 lesions, 58 subjects) | BMS(N = 65 lesions, 61 subjects) | p Value |
|---|---|---|---|---|
| Lesion Mehran classification (% of in-stent restenosis) | | | | |
| IA | 0 (0%) | 0 (0%) | 0 (0%) | 0.19 |
| IB | 19 (15%) | 9 (15%) | 10 (15%) | |
| IC | 32 (25%) | 15 (25%) | 17 (26%) | |
| ID | 4 (3%) | 2 (3%) | 2 (3%) | |
| II | 31 (25%) | 21 (34%) | 10 (15%) | |
| III | 6 (5%) | 3 (5%) | 3 (5%) | |
| IV | 31 (25%) | 10 (16%) | 21 (32%) | |
| Unknown* | 3 (2%) | 1 (2%) | 2 (3%) | |
| Focal (IA, IB, IC, or ID) | 55 (44%) | 26 (43%) | 29 (45%) | 0.94 |
| Diffuse (II, III, or IV) | 68 (54%) | 34 (56%) | 34 (52%) | |
| Unknown* | 3 (2%) | 1 (2%) | 2 (3%) | |
| Subject Mehran classification (% of had in-stent restenosis) | | | | |
| IA | 0 (0%) | 0 (0%) | 0 (0%) | N/A |
| IB | 19 (16%) | 9 (16%) | 10 (16%) | 0.90 |
| IC | 31 (26%) | 14 (24%) | 17 (28%) | 0.64 |
| ID | 4 (3%) | 2 (3%) | 2 (3%) | 1.00 |
| II | 31 (26%) | 21 (36%) | 10 (16%) | 0.01 |
| III | 6 (5%) | 3 (5%) | 3 (5%) | 1.00 |
| IV | 30 (25%) | 10 (17%) | 20 (33%) | 0.05 |
| Unknown* | 3 (3%) | 1 (2%) | 2 (3%) | 1.00 |
| Focal (IA, IB, IC, or ID) | 54 (45%) | 25 (43%) | 29 (48%) | 0.68 |
| Diffuse (II, III, or IV) | 66 (55%) | 33 (57%) | 33 (54%) | 0.94 |

BMS = bare-metal stents; DES = drug-eluting stents.
* There were 3 in-stent restenosis that could not be confirmed due to lack of imaging files.

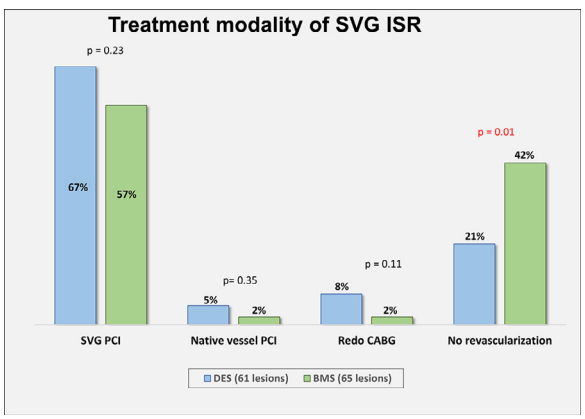


Figure 3. Treatment strategies for ISR SVG. CABG = coronary artery bypass surgery.

The main limitation of our study was the relatively small number of patients with ISR. In addition, nearly all patients were men, which limits the extrapolation of the results to women. Our study is further limited by its post hoc nature and the difference in terms of years since last coronary artery bypass graft among patients in the DES and BMS group. Intravascular ultrasound or optical coherence tomography was not used per protocol to clarify the mechanism of stent failure. Finally, BMS are rarely used currently; however, our study suggests that DES may have an advantage (less occlusive restenosis) over BMS in SVGs, supporting their use in this setting.

In conclusion, longer stent length was associated with higher risk of ISR after SVG PCI. Furthermore, although patients who had BMS stents had the same incidence of ISR as patients who had DES, the patients with BMS stents were more likely to develop occlusive restenosis.

## Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2021.09.024.

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