Clinical Presentation and Outcomes of Coronary In-Stent Restenosis Across 3-Stent Generations

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Background—Clinical presentation of bare metal stent in-stent restenosis (ISR) in patients undergoing target lesion revascularization is well characterized and negatively affects on outcomes, whereas the presentation and outcomes of first- and second-generation drug-eluting stents (DESs) remains under-reported.

Methods and Results—The study included 909 patients (1077 ISR lesions) distributed as follows: bare metal stent (n=388), first-generation DES (n=425), and second-generation DES (n=96), categorized into acute coronary syndrome (ACS) or non-ACS presentation mode at the time of first target lesion revascularization. ACS was further classified as myocardial infarction (MI) and unstable angina. For bare metal stent, first-generation DES and second-generation DES, ACS was the clinical presentation in 67.8%, 71.0%, and 66.7% of patients, respectively (P=0.470), whereas MI occurred in 10.6%, 10.1%, and 5.2% of patients, respectively (P=0.273). The correlates for MI as ISR presentation were current smokers (odds ratio, 3.02; 95% confidence interval [CI], 1.78–5.13; P<0.001), and chronic renal failure (odds ratio, 2.73; 95% CI, 1.60–4.70; P=0.001), with a protective trend for the second-generation DES ISR (odds ratio, 0.35; 95% CI, 0.12–1.03; P=0.060). ACS presentations had an independent effect on major adverse cardiac events (death, MI, and re-target lesion revascularization) at 6 months (MI versus non-ACS: adjusted hazard ratio, 4.06; 95% CI, 1.84–8.94; P<0.001; unstable angina versus non-ACS: adjusted hazard ratio, 1.98; 95% CI, 1.01–3.87; P=0.046).

Conclusions—ISR clinical presentation is similar irrespective of stent type. MI as ISR presentation seems to be associated with patient and not device-related factors. ACS as ISR presentation has an independent effect on major adverse cardiac events, suggesting that ISR remains a hazard and should be minimized. (Circ Cardiovasc Interv. 2014;7:768-776.)

Key Words: drug-eluting stents • restenosis • stents

In-stent restenosis (ISR) is a critical drawback of coronary stents and remains the leading cause of unplanned, repeat procedures in the drug-eluting stent (DES) era in the United States. Although initially described as benign, this theory has been challenged by studies showing a high incidence of acute coronary syndromes (ACSs) as bare metal stent (BMS) ISR clinical presentation. Moreover, the BMS ISR effect on outcome was related to its ACS presentation mode.

First-generation DES reduced restenosis rates by decreasing the neointimal hyperplasia volume. As a result, DES ISR is usually a focal phenomenon compared with the more diffuse pattern of BMS ISR. Nonetheless, ISR after first-generation DES is associated with a distinct process linked with escalating and persistent inflammatory vessel wall reaction, fibrin deposition, and earlier and more frequent neointimal proliferation. These surrogate findings may enhance the vulnerability of the first-generation DES ISR neointima, thereby increasing the ACS presentation propensity.

By contrast, second-generation DES convey a safer preclinical performance with less prominent inflammatory reaction.

Although these mechanistic studies provide insight into the vascular response associated with the different devices, it is the ISR presentation that ultimately leads to patient readmission and repeat revascularization. However, it is presently unclear whether the 3-stent generations show similar ISR clinical presentation and whether the ISR presentation mode is independently associated with worse outcomes. Therefore, the aims of this study are to (1) compare the clinical presentation among BMS, first-, and second-generation DES ISR in patients undergoing target lesion revascularization (TLR); (2) describe the correlates of acute myocardial infarction (MI) as ISR presentation; and (3) investigate the ISR clinical presentation effect on outcome as assessed by the incidence of major adverse cardiac events (MACE) and death/Q wave MI (QWMI) at 6 months.
Clinical Presentation of In-Stent Restenosis

WHAT IS KNOWN

- The observation that there is a high incidence of acute coronary syndrome in the clinical presentation of in-stent restenosis (ISR) challenged the paradigm that this was a benign process.
- Although the first-generation drug-eluting stent has resulted in reduced hyperplasia volume and restenosis, evidence suggests that the neointimal tissue is more vulnerable to rupture, leading to acute events.

WHAT THE STUDY ADDS

- Overall, ISR clinical presentation is similar across all 3-stent generations. Current smokers and chronic renal failure were associated with more malignant ISR presentations.
- The lower likelihood of second-generation drug-eluting stents ISR to present as myocardial infarction may be the net benefit of reduced hyperplasia and less vulnerable neointimal tissue.
- Outcome after ISR is mostly related to acute coronary syndrome mode of presentation and hinges on patient risk factors.

Methods

Study Design and Sample Population

This retrospective study included consecutive patients with clinical culprit ISR lesions from April 2003 to May 2013, who were readmitted for TLR by means of percutaneous coronary intervention. Participants were categorized by initial stent type into BMS, first- or second-generation DES ISR. Our study, whose flow chart is summarized in Figure 1, was approved by the local institutional review board.

The first-generation DES group included patients whose initial procedure treatment consisted of either sirolimus (Cypher, Cordis; Johnson and Johnson, Miami Lakes, FL) or paclitaxel-eluting stents (Taxus Express or Liberté; Boston Scientific Corp, Natick, MA). The second-generation DES included patients treated with everolimus (Xience V; Abbott, Santa Clara, CA, or PROMUS Element; Boston Scientific Corp) or zotarolimus-eluting stents (Endeavor; Medtronic Inc, Minneapolis, MN). We excluded patients treated with combinations of stents.

ISR Clinical Presentation at the Time of First TLR

The ISR clinical presentations at the time of first TLR were initially divided into 2 categories: ACS or non-ACS with ACS further categorized as unstable angina (UA) or MI. Non-ACS presentations included stable angina and silent ischemia.

Stable angina was defined as typical chest pain occurring on physical exertion and relieved by rest or nitrates. Silent ischemia was defined as abnormal functional testing attributed to the ISR lesion. UA was defined as typical chest pain of recent onset or chest pain of increasing duration or intensity 2 weeks before hospitalization that was refractory to medications and was associated with ST-segment dynamic electrocardiographic abnormalities.

MI was defined according to current standards as either non-ST-segment-elevation MI or ST-segment-elevation MI. The former was indicated by the presence of symptoms in association with altered cardiac markers (troponin >0.045 ng/mL) or which required prompt intervention, the latter by ST-segment elevation or new or presumably new left-bundle branch block.

Outcome Definitions

The first TLR (at the time of ISR clinical presentation and at the index ISR treatment) and the second TLR or re-TLR (6 months after index ISR treatment) were defined as repeat intervention because of myocardial ischemia with angiographic ISR (diameter of stenosis >50% within the stent or the 5-mm proximal or distal stent borders). MI after index ISR treatment was defined as an elevation in creatine kinase-MB of twice the upper limit (2.6 ng/mL). MI was further categorized as QWMI if new Q waves deeper than ≥1 mm occurred in ≥2 contiguous leads; otherwise non-QWMI was diagnosed. MACE after the index ISR treatment was defined as a composite of all-cause death, MI, and re-TLR at 6 months. MI as ISR presentation was not included in the cumulative events. All deaths were considered cardiac unless otherwise documented. Chronic renal failure (CRF) was defined as serum creatinine>2.0 mg/dL. Congestive heart failure (CHF) was defined as evidence of fluid retention from cardiac causes categorized according to New York Heart Association class. Stent thrombosis was defined in accordance with the Academic Research Consortium as definite or probable.

Procedure and Adjunctive Therapies

All patients were treated with aspirin and thienopyridines, in particular, clopidogrel (300–600 mg) before the procedure. The periprocedural antiaggregation included either heparin with a bolus dose of 60 U/kg and additional dose(s) to achieve an activated clotting time of 200 to 300 s or bivalirudin 0.75 mg/kg followed by an infusion of 1.75 mg/kg per hour during the procedure. Percutaneous coronary intervention was performed using the standard techniques; the TLR and re-TLR treatment was left to the physician’s discretion, but options included a new stent, cutting-balloon, or brachytherapy. Adjunctive devices were used according to the physician’s discretion. Angiographic success was defined as the presence of thrombolysis in MI 3 flow and final angiographic lesion diameter <30%.

Data Collection and Clinical Follow-Up

Patients’ demographics, risk factors, clinical characteristics, and procedural details were prospectively recorded in a dedicated system controlled by independent database administrators. Follow-up was conducted at 30 days and 6 months after the first TLR (index ISR treatment) by telephone contact. All adverse events were systematically adjudicated by interventional cardiologists who were unaware of study objectives.

Study Objectives

The primary objective of this study was to determine the ISR clinical presentation that drove the first TLR for the different stent generations. The secondary objectives were the description of the correlates with MI as ISR clinical presentation mode and the effect of the ISR presentation on the incidence of MACE, death/QWMI, and re-TLR at 6 months.

Statistical Analysis

Binary variables are reported by counts and percentages, whereas the continuous variables are presented as mean±SD. Differences in binary data were tested by either χ² or Fisher exact test as appropriate in a 3- or 2-way group analysis. ANOVA was used for continuous variables. First, we estimated the frequency of patients who had a previous BMS, first- or second-generation DES among those who present with ACS and non-ACS at the time of first TLR. Second, the correlates for MI as ISR presentation were tested in a univariable, followed by a multivariable, logistic regression. The ISR stent type was forced into the final model. Third, we assessed the time-to-event survival of MACE, death/QWMI, and re-TLR according to ISR presentation mode by the Kaplan–Meier method and by the log-rank test. The adjusted effect of the ISR presentation on MACE, death/QWMI, and re-TLR was tested in Cox regression allowing covariates with a P<0.20. All variables respected the assumption of the proportional hazards functions. Exploratory survival curves for MACE, death/QWMI, and re-TLR were also generated stratifying by ACS and non-ACS. A value of P≤0.05 was considered indicative of statistical significance. All analyses were conducted using SAS Software version 9.2 (SAS Institute, Cary, NC).
Results

Clinical and Angiographic Characteristics at the Time of First TLR

The study comprised 909 patients with 1077 clinically driven TLR because of ISR. The BMS ISR cohort included 388 patients, whereas the first- and second-generation DES ISR groups comprised 425 and 96 patients, respectively. Patient characteristics at the time of TLR are represented in Table 1. Overall, the second-generation DES ISR group was characterized by a higher prevalence of comorbidities, such as diabetes mellitus and CRF.

Table 1. Patient Demographics and Clinical Characteristics at the Time of First Target Lesion Revascularization

<table>
<thead>
<tr>
<th>Demographics</th>
<th>BMS ISR (n=388)</th>
<th>First-Generation DES ISR (n=425)</th>
<th>Second-Generation DES ISR (n=96)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>258 (66.5%)</td>
<td>262 (61.8%)</td>
<td>62 (64.6%)</td>
<td>0.376</td>
</tr>
<tr>
<td>Age, y</td>
<td>66±11</td>
<td>65±11</td>
<td>64±11</td>
<td>0.431</td>
</tr>
<tr>
<td>Black</td>
<td>111 (28.6%)</td>
<td>129 (30.4%)</td>
<td>47 (46.9%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Risk factors/clinical characteristics</td>
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<td></td>
<td></td>
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<tr>
<td>Current smoker</td>
<td>77 (19.8%)</td>
<td>74 (17.4%)</td>
<td>18 (17.7%)</td>
<td>0.657</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>363 (93.6%)</td>
<td>402 (94.6%)</td>
<td>93 (96.9%)</td>
<td>0.436</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>162 (42.3%)</td>
<td>188 (44.3%)</td>
<td>59 (61.5%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Insulin-treated diabetes mellitus</td>
<td>54 (14.1%)</td>
<td>86 (20.3%)</td>
<td>31 (32.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypercholesterolemia†</td>
<td>365 (94.6%)</td>
<td>407 (96.0%)</td>
<td>90 (93.8%)</td>
<td>0.510</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>80 (20.8%)</td>
<td>102 (24.2%)</td>
<td>27 (28.1%)</td>
<td>0.247</td>
</tr>
<tr>
<td>Chronic renal insufficiency</td>
<td>70 (18.1%)</td>
<td>88 (20.8%)</td>
<td>28 (29.2%)</td>
<td>0.054</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>68 (17.9%)</td>
<td>74 (17.6%)</td>
<td>14 (14.6%)</td>
<td>0.733</td>
</tr>
<tr>
<td>NYHA class III/IV</td>
<td>30 (7.9%)</td>
<td>28 (6.7%)</td>
<td>6 (6.3%)</td>
<td>0.741</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>47±14</td>
<td>49±14</td>
<td>46±17</td>
<td>0.235</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>209 (56.8%)</td>
<td>189 (49.1%)</td>
<td>36 (38.7%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Previous coronary artery bypass graft</td>
<td>138 (35.8%)</td>
<td>170 (40.2%)</td>
<td>35 (36.5%)</td>
<td>0.424</td>
</tr>
<tr>
<td>Lipid profile, mg/dL, mean±SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>156±47</td>
<td>155±45</td>
<td>148±47</td>
<td>0.414</td>
</tr>
<tr>
<td>LDL</td>
<td>86±33</td>
<td>86±35</td>
<td>76±29</td>
<td>0.065</td>
</tr>
<tr>
<td>HDL</td>
<td>43±15</td>
<td>43±18</td>
<td>45±17</td>
<td>0.828</td>
</tr>
</tbody>
</table>

BMS indicates bare metal stent; DES, drug-eluting stent; HDL, high-density lipoprotein; ISR, in-stent restenosis; LDL, low-density lipoprotein; and NYHA, New York Heart Association.

*Blood pressure >140/90 mm Hg or the use of antihypertensive therapy.
†Fasting cholesterol >250 mg/dL or the use of lipid-lowering therapy.
compared with other groups. Notably, the prevalence of insulin-dependent diabetic patients in the second-generation DES ISR cohort was 32.3% compared with 20.3% and 14.1% in the first-generation DES and BMS ISR groups, respectively.

Table 2 shows the angiographic characteristics according to ISR type at the time of first TLR. The vessel territory was similar across the 3 ISR generations. Patients with DES ISR were more likely to be treated with brachytherapy, whereas patients with BMS ISR more often received a new DES. In addition, when a new stent was chosen as the TLR treatment modality, a gradient was shown across the 3 ISR stent generations, with significantly longer stents implanted in BMS ISR lesions compared with those chosen for DES ISR lesions.

**BMS, First-, and Second-Generation DES ISR Clinical Presentation at the Time of First TLR**

Overall, ISR clinical presentation was similar in all 3-stent generations with ACS accounting for 67.8% of BMS, 71% of first-, and 66.7% of second-generation DES ISR ($P=0.470$). Among the ACS presentations, although not statistically significant, second-generation DES ISR patients were less likely to present with MI compared with the BMS and first-generation groups (5.2% versus 10.6% and 10.1%; $P=0.273$; Figure 2).

As the severity of ISR presentation grew, so did the frequency of clinical comorbidities (Table 3). Patients presenting with MI were more likely to be current smokers, to have CRF, previous MI, and CHF. In addition, patients with MI were...
less likely to be treated with an additional DES, and none had undergone brachytherapy at the index ISR treatment. On the contrary, the use of glycoprotein IIb/IIIa in MI presentations was 35× higher when compared with non-ACS presentations.

MI as ISR Clinical Presentation Frequency and Correlates

MI as ISR presentation occurred in 9.8% of our cohort. Of those, 3.7% were characterized as ST-segment–elevation MI and 6.1% as non–ST-segment–elevation MI. We analyzed the independent correlates for MI as ISR presentation, testing lesion, devices, and patient variables (Table 4). The independent correlates were current smokers (odds ratio, 3.02; 95% confidence interval [CI], 1.78–5.13; \( P < 0.001 \)) and CRF (odds ratio, 2.73; 95% CI, 1.60–4.70; \( P < 0.001 \)). Notably, when comparing the DES ISR stent generations with BMS ISR as the reference, there was a trend toward the second-generation DES as a protective factor against MI (odds ratio, 0.35; 95% CI, [0.12–1.03]; \( P = 0.060 \)).

Effect of ISR Clinical Presentation at the Time of First TLR on Outcome

Individually, 83.5% of adverse events were concentrated in ACS ISR clinical presentation strata (Table 5). Overall, a more severe ISR diagnosis generated a worse outcome. ISR patients presenting with MI had a 2.1-fold increased risk (hazard ratio [HR], 2.05; 95% CI, 1.14–3.68; \( P = 0.007 \)) of MACE at 6 months (adjusted for black, previous MI, CRF, CHF, peripheral vascular disease, saphenous vein graft, ISR location, current smoker, and stent type) compared with patients presenting with UA, and a 4.1-fold increased risk (HR, 4.06; 95% CI, 1.84–8.94; \( P < 0.001 \)) compared with non-ACS. In addition, a gradient effect was noted, with a 2-fold higher incidence of MACE in UA compared with non-ACS (HR, 1.98; 95% CI, 1.01–3.87; \( P = 0.046 \); Figure 3).

Strikingly, there was a higher incidence of death/QWMI in patients presenting with MI (adjusted for previous MI, peripheral vascular disease, CRF, CHF, and stent type) compared with UA (HR, 4.25; 95% CI, 2.09–8.67; \( P < 0.001 \)) and non-ACS (HR, 4.06; 95% CI, 1.84–8.94; \( P = 0.001 \); Figure 3). However, comparing UA to non-ACS showed no statistically significant difference in the rates of death/QWMI at 6 months. Nevertheless, a trend was found in the incidence of re-TLR when comparing UA with non-ACS (adjusted for age, CHF, current smoker, saphenous vein graft, ISR location and stent type; HR, 2.23; 95% CI, 0.98–5.04; \( P = 0.058 \)). Notably, the 10-year time interval did not influence ISR clinical presentation or the incidence of MACE (Figure 5).

We further stratified the analysis into ACS and non-ACS ISR presentations according to the BMS, first- and second-generation DES ISR. Patients with non-ACS presentations had a lower incidence of adverse events and similar outcomes irrespective of the ISR type (\( P = 0.899 \)). On the contrary, among the ACS ISR presentations, a higher incidence of MACE was found in first- and second-generation DES ISR patients when compared with the BMS ISR cohort (\( P = 0.009 \)).

### Table 3. Baseline Clinical Findings According to In-Stent Restenosis Presentation Severity

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Non-ACS (n=277)</th>
<th>Unstable Angina (n=540)</th>
<th>Myocardial Infarction (n=89)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>195 (70.4%)</td>
<td>327 (60.7%)</td>
<td>57 (64.0%)</td>
<td>0.023</td>
</tr>
<tr>
<td>Age, y</td>
<td>66±10</td>
<td>65±11</td>
<td>64±12</td>
<td>0.169</td>
</tr>
<tr>
<td>Black</td>
<td>74 (26.7%)</td>
<td>177 (32.8%)</td>
<td>33 (37.1%)</td>
<td>0.099</td>
</tr>
<tr>
<td>Risk factors/clinical characteristics</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>39 (14.1%)</td>
<td>99 (18.3%)</td>
<td>30 (33.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>253 (91.3%)</td>
<td>518 (95.9%)</td>
<td>84 (94.4%)</td>
<td>0.026</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>118 (43.2%)</td>
<td>247 (46.0%)</td>
<td>42 (47.2%)</td>
<td>0.702</td>
</tr>
<tr>
<td>Insulin-treated</td>
<td>46 (16.8%)</td>
<td>103 (19.2%)</td>
<td>21 (23.6%)</td>
<td>0.358</td>
</tr>
<tr>
<td>Hypercholesterolemia†</td>
<td>261 (94.2%)</td>
<td>514 (95.5%)</td>
<td>84 (95.5%)</td>
<td>0.703</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>69 (25.1%)</td>
<td>120 (22.4%)</td>
<td>20 (22.5%)</td>
<td>0.678</td>
</tr>
<tr>
<td>Chronic renal insufficiency</td>
<td>39 (14.1%)</td>
<td>112 (20.8%)</td>
<td>34 (38.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>38 (13.9%)</td>
<td>91 (17.1%)</td>
<td>27 (30.7%)</td>
<td>0.001</td>
</tr>
<tr>
<td>NYHA class III/IV</td>
<td>15 (5.5%)</td>
<td>36 (6.8%)</td>
<td>13 (14.8%)</td>
<td>0.012</td>
</tr>
<tr>
<td>Left ventricular ejection fraction,%</td>
<td>50±13</td>
<td>48±14</td>
<td>41±15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>119 (45.2%)</td>
<td>258 (51.7%)</td>
<td>56 (67.5%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Previous coronary artery bypass graft</td>
<td>107 (38.8%)</td>
<td>199 (37.1%)</td>
<td>35 (39.3%)</td>
<td>0.861</td>
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<td>Lipid profile, mg/dL, mean±SD</td>
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<tr>
<td>Total cholesterol</td>
<td>148±44</td>
<td>158±47</td>
<td>157±45</td>
<td>0.029</td>
</tr>
<tr>
<td>LDL</td>
<td>78±26</td>
<td>89±35</td>
<td>93±41</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL</td>
<td>42±16</td>
<td>45±18</td>
<td>40±16</td>
<td>0.042</td>
</tr>
</tbody>
</table>

ACS indicates acute coronary syndrome; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and NYHA, New York Heart Association.

*Blood pressure >140/90 mm Hg or the use of antihypertensive therapy.

†Fasting cholesterol >250 mg/dL or the use of lipid-lowering therapy.
difference appeared as a consequence of a higher re-TLR rate in those patients compared with BMS ISR (8.6% versus 8.3% and 3.1%; \(P=0.018\)) because no difference in death/QWMI was found (\(P=0.137\); Figures I–III in the Data Supplement).

No single case of stent thrombosis was found among second-generation DES ISR patients undergoing TLR.

### Discussion

The current study of a large cohort of 909 patients undergoing TLR with 1077 culprit ISR lesions is the first to compare the ISR clinical presentation mode across 3-stent generations. There were several notable findings: (1) The ISR clinical presentation mode is similar in BMS, first-, and second-generation DES ISR; (2)

### Table 4. Correlates of Myocardial Infarction ISR Presentation (vs Unstable Angina and Nonacute Coronary Syndrome)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariable Analysis</th>
<th>Multivariable Analysis</th>
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<tbody>
<tr>
<td></td>
<td>Odds Ratio</td>
<td>Lower 95% CI</td>
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<td>Patient based</td>
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</tr>
<tr>
<td>Age, y</td>
<td>1.00</td>
<td>0.98</td>
</tr>
<tr>
<td>Men</td>
<td>1.00</td>
<td>0.63</td>
</tr>
<tr>
<td>Black</td>
<td>1.33</td>
<td>0.84</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.09</td>
<td>0.70</td>
</tr>
<tr>
<td>Current smoker</td>
<td>2.51</td>
<td>1.56</td>
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<tr>
<td>Previous myocardial infarction</td>
<td>2.11</td>
<td>1.31</td>
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<tr>
<td>Chronic renal failure</td>
<td>2.71</td>
<td>1.71</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td>2.36</td>
<td>1.42</td>
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<tr>
<td>Peripheral vascular disease</td>
<td>0.96</td>
<td>0.57</td>
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<tr>
<td>Statin use</td>
<td>0.63</td>
<td>0.32</td>
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<tr>
<td>BMS (reference)</td>
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<tr>
<td>First-generation-DES</td>
<td>0.95</td>
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<td>Second-generation-DES</td>
<td>0.49</td>
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<tr>
<td>Left anterior descending</td>
<td>0.88</td>
<td>0.54</td>
</tr>
<tr>
<td>Saphenous vein graft</td>
<td>0.98</td>
<td>0.51</td>
</tr>
<tr>
<td>Proximal ISR location</td>
<td>1.25</td>
<td>0.79</td>
</tr>
</tbody>
</table>

BMS indicates bare metal stent; CI, confidence intervals; DES, drug-eluting stent; and ISR, in-stent restenosis.

### Table 5. Individual and Composite Outcomes According to ACS and Non-ACS ISR Presentations

<table>
<thead>
<tr>
<th></th>
<th>Myocardial Infarction (n=89)</th>
<th>Unstable Angina (n=540)</th>
<th>Non-ACS (n=277)</th>
<th>Myocardial Infarction vs Non-ACS Unadjusted HR (95% CI)</th>
<th>Unstable Angina vs Non-ACS Unadjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MACE</td>
<td>6 (6.7%)</td>
<td>18 (3.3%)</td>
<td>5 (1.8%)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Death</td>
<td>5 (5.6%)</td>
<td>9 (1.7%)</td>
<td>3 (1.1%)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>QWMI</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Death/QWMI</td>
<td>5 (5.6%)</td>
<td>9 (1.7%)</td>
<td>3 (1.1%)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>NQWMI</td>
<td>2 (2.4%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Re-TLR</td>
<td>1 (1.2%)</td>
<td>9 (1.7%)</td>
<td>2 (0.7%)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>0 (0)</td>
<td>2 (0.4%)</td>
<td>0 (0)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>6 mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MACE</td>
<td>19 (21.6%)</td>
<td>52 (9.6%)</td>
<td>14 (5.1%)</td>
<td>4.71 (2.36–9.39)</td>
<td>1.96 (1.09–3.54)</td>
</tr>
<tr>
<td>Death</td>
<td>12 (13.8%)</td>
<td>20 (3.7%)</td>
<td>6 (2.2%)</td>
<td>6.79 (2.55–18.1)</td>
<td>1.74 (0.69–4.33)</td>
</tr>
<tr>
<td>QWMI</td>
<td>3 (3.8%)</td>
<td>1 (0.2%)</td>
<td>1 (0.4%)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Death/QWMI</td>
<td>15 (17.2%)</td>
<td>21 (3.9%)</td>
<td>7 (2.5%)</td>
<td>7.35 (2.99–18.1)</td>
<td>1.57 (0.67–3.68)</td>
</tr>
<tr>
<td>NQWMI</td>
<td>7 (8.9%)</td>
<td>6 (1.1%)</td>
<td>1 (0.4%)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Re-TLR</td>
<td>6 (7.5%)</td>
<td>32 (6.1%)</td>
<td>8 (2.9%)</td>
<td>2.62 (0.91–7.56)</td>
<td>2.11 (0.97–4.58)</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>0 (0)</td>
<td>4 (0.7%)</td>
<td>0 (0)</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

ACS indicates acute coronary syndrome; CI, confidence interval; HR, hazard ratios; ISR, in-stent restenosis; MACE, major adverse cardiac events; NQWMI, Non-Q wave myocardial infarction; QWMI, Q wave myocardial infarction; and TLR, target lesion revascularization.
patient-related, as opposed to stent-related factors, are associated with the severity of ISR presentation; and (3) ACS presentations have a significant and independent effect on MACE at 6 months.

**ISR Clinical Presentation Across Stent Generations**

ISR has been described as a nonbenign entity in the BMS era because of the acute nature of its presentation in 36% to 70% of the patients, of whom 1.6% to 18.5% presented with MI.\(^2\)\(^4\)\(^5\) These findings were validated by a cohort study showing a 10-year ISR incidence of 18.1% in which \(\approx 50\%\) of patients presented with ACS.\(^1\)\(^2\)\(^4\)\(^5\) Our study endorses these results, showing that 67.8% of BMS patients presented with ACS, of whom 10.6% were diagnosed with MI.

Although the most common DES ISR clinical presentation remains debatable, in part, because of problems defining terms, and the inclusion of stent thrombosis in some studies,\(^1\)\(^3\) the presentation mode in first-generation DES ISR is reportedly indistinguishable from that of BMS ISR, even given that the latter exhibits a more focal angiographic pattern.\(^8\) Rathore et al\(^1\)\(^4\) reported similar clinical presentation occurs among BMS and DES ISR with an overall ACS rate of 18.2%. These results contrast with those of the Swedish Coronary Angiography Angioplasty Registry in which \(\approx 70\%\) of patients presented with ACS.\(^1\)\(^5\) However, to date, a direct comparison across 3-stent generations has never been done.

Our research underlines ACS as the major ISR presentation mode in first-generation DES and extends this finding to second-generation DES ISR. On the contrary, the second-generation had \(\approx 50\%\) lower likelihood of MI when compared with the BMS cohort, suggesting a more benign presentation.

**Mechanisms of ACS ISR Clinical Presentation**

ISR may trigger an ACS as a result of a superimposed thrombus, aggressive patterns of hyperplasia,\(^4\) or both. BMS ISR culprit areas are rich in macrophage cells, neovascularization, and tissue factor that can trigger an ACS. In fact, thrombus has been documented in 29% of BMS ISR cases\(^3\) and is more commonly found in ACS, as opposed to non-ACS ISR. Instead, a diffuse flow-limiting restenotic lesion per se might be the nidus for thrombus, which may also result in acute presentation.

First-generation DES ISR involves a constellation of features, such as escalating inflammatory reaction, thinner cap...
fibroatheroma, and a larger lipid pool, collectively called neoatherosclerosis that may influence the vulnerability of the neointima. Indeed, 75% of patients with DES ISR presenting with ACS have a disrupted neointima with overlying thrombi.16 Supporting the theory of a thromborestenosis phenomenon, an angiography paired with ISR tissue assessment found a higher incidence of either thrombus or fibrin in first-generation DES ISR compared with BMS ISR.17 Interestingly, the majority of in-stent intimal ruptures do not occur within the DES tightest ISR stenosis,10 challenging the prognostic value of ISR angiographic classification.18 Conversely, second-generation DES demonstrated better vascular healing than first-generation DES, including a lower incidence of thrombus and fibrin deposition. Nonetheless, some optical coherence tomography studies have yielded controversial data on whether neoatherosclerosis occurs at lower rates with second-generation DES than with first-generation DES.19 Indeed, a recent study demonstrated a similar prevalence of neoatherosclerosis in first- and second-generation DES.11 However, no unstable features, such as thin-cap fibroatheroma or ruptured neointima, were documented in the second-generation DES,11 which may partially explain the trend toward a less malignant ISR presentation in our study.

**Outcomes of ACS Versus Non-ACS ISR Clinical Presentations**

Our study indicates that the outcome of ISR is influenced by its presentation mode. ACS presentations had a higher incidence of MACE and death/QWMI at 6 months compared with non-ACS. A gradient effect on outcome was shown from non-ACS to UA and MI that was accompanied by an increase in the prevalence of comorbidities. Nevertheless, ACS presentation remained independently associated with MACE. Moreover, MI as ISR presentation had an independent effect on death/QWMI at 6 months. These findings are consistent with previous studies, showing that ISR effect may hinge on its presentation mode5,12,14,23 and, in fact, ISR presentation as MI can have a worse outcome than stent thrombosis,24 reinforcing the relevance of ACS presentation in both BMS and DES eras. In the BMS era, the Prevention of REStenosis with Tranilast and its Outcomes (PRESTO) trial documented that patients with ACS had a higher incidence of MACE and death/QWMI at 6 months compared with non-ACS. A gradient effect on outcome was shown from non-ACS to UA and MI that was accompanied by an increase in the prevalence of comorbidities. Nevertheless, ACS presentation remained independently associated with MACE. Moreover, MI as ISR presentation had an independent effect on death/QWMI at 6 months. These findings are consistent with previous studies, showing that ISR effect may hinge on its presentation mode5,12,14,23 and, in fact, ISR presentation as MI can have a worse outcome than stent thrombosis,24 reinforcing the relevance of ACS presentation in both BMS and DES eras.

**Figure 5.** Ten-year time interval of in-stent restenosis clinical presentation and major adverse cardiac events (MACE). ACS indicates acute coronary syndrome.

![Figure 5](http://circinterventions.ahajournals.org/)

**Correlates of MI as ISR Presentation**

The independent correlates for MI as ISR presentation were current smoking and CRF, with second-generation DES ISR and previous MI showing a marginal statistical significance. The association of current smoking with MI at the time of TLR may be related to smoker’s paradox, which describes the dissociation between the clinical symptoms and angiographic findings in this population at the time of TLR.20 Thus, smokers were thought to be less symptomatic on ISR or to have a greater reluctance to seek medical care. Our finding of an incremental smoking prevalence with severity of ISR clinical presentation can be explained by this reluctance until a more dramatic clinical presentation ensues. In addition, smoking has been described as a predictor of neoatherosclerosis after stenting, which might predispose to unstable ISR presentations.19

The other independent factor associated with MI was CRF, a risk factor linked with poor outcomes after percutaneous coronary intervention, even in the DES era. CRF is a predictor of neoatherosclerosis19 and increased lipid neointimal content after stenting.21 These characteristics may explain the CRF association with ACS presentation in the BMS era,2,4 and the late catch-up phenomenon after DES implantation, mainly manifesting as ACS.22 Together, these findings suggest that the ISR clinical presentation is associated with patient- and not device-related factors. Identifying individuals at risk of presenting with malignant forms of ISR may be useful in guiding clinicians through a decision-making process.

**Limitations**

This is an observational study and, therefore, many confounding factors may affect our results; consequently, our
conclusions should be interpreted cautiously and restricted to
the hypothesis-generating domain. Although we systematically
performed an adjudication process with experienced adjudica-
tors, the effect of late stent thrombosis presenting as apparent
restenosis with MI cannot be excluded. Nevertheless, the avail-
ability of high-resolution intravascular imaging challenges the
paradigm that ISR and stent thrombosis are distinct entities.
Moreover, this is the largest cohort study to compare ISR clini-
cal presentation across 3-stent generations >10-year period.

The second-generation ISR group is under-represented, and
therefore the borderline statistical significance for MI reduc-
tion might be considered restrictive compared with the universalclas-
sification, but it is intended to be specific to a clinically relevant
event. A final limitation is the lack of image analysis, which, if
available, would have mechanistically corroborated our findings.

Conclusions

In summary, our results indicate that the clinical presentation
mode of ISR remains similar across 3-stent generations with no
indication of more ACS in DES ISR than BMS ISR. In addition,
presentation with ACS has an independent effect on MACE and
seems to be associated with patient- rather than device-related
factors. These findings reinforce the need for secondary preven-
tion and clinical surveillance after ISR with ACS presentations
and highlight the unmet clinical need for novel technologies to
eradicate ISR, which is gaining new momentum in the DES era.

Disclosures

None.

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Clinical Presentation and Outcomes of Coronary In-Stent Restenosis Across 3-Stent Generations


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SUPPLEMENTAL MATERIAL

Supplemental Figures:

Supplemental Figure 1.

Supplemental Figure 2.

CIRCCVINT/2014/001341/R3
Supplemental Figure 3.

Figure legends

**Figure 1.** Time-to-MACE survival in ACS patients at the time of first TLR by initial stent.

MACE, major adverse cardiac events; ACS, acute coronary syndrome

**Figure 2.** Time-to-re-TLR survival in ACS patients at the time of first TLR by initial stent.

TLR; target lesion revascularization ACS, acute coronary syndrome

**Figure 3.** Time-to-death/QWMI survival in ACS patients at the time of first TLR by initial stent.

QWMI, Q-wave myocardial infarction; ACS, acute coronary syndrome

CIRCCVINT/2014/001341/R3