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Clinical presentation of patients with in-stent restenosis in the drug-eluting stent era

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ABSTRACT: Background. Drug-eluting stents (DES) represent a significant improvement in the treatment of coronary artery disease as they decrease restenosis rates by approximately 50% compared with bare metal stents. In-stent restenosis (ISR) is perceived to be a benign phenomenon because it is a gradual process and may lead to angina pectoris. With bare metal stents, ISR has been associated with myocardial infarction in approximately 10% to 15% of cases. Comparable data with DES are lacking. Methods. From April 2003 to December 2005, 42 out of 889 patients (4.7%) with DES ISR were identified at our institution. We excluded 3 orthotopic heart transplant patients who had ISR. Therefore, the final analysis included 39 patients. Results. The mean age was 66 ± 10 years, 77% were male, and 33% were diabetic. A mean of 1.8 ± 0.9 stents were implanted with a total stent length of 39 ± 24 mm. The mean time from percutaneous coronary intervention to detection of ISR was 396 ± 290 days. At a mean from follow-up of 35 ± 10 months, 8% were asymptomatic, 77% presented with angina pectoris, 5% with unstable angina, and 10% with non-ST-segment elevation myocardial infarction. Conclusions. In the DES era, although most patients with ISR have stable symptoms, myocardial infarction occurred in 10%, suggesting that ISR is not a benign clinical entity. DES with improved designs or drug elution systems that further decrease the incidence of ISR are needed.

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One of the main limitations of percutaneous coronary intervention (PCI) is in-stent restenosis (ISR), which occurs in between 22% to 31.6% of cases utilizing bare metal stents. 1,2 Although ISR is considered to be a gradual and progressive phenomenon, unstable angina was the presentation in 26% of patients with ISR after PCI with bare metal stents, and myocardial infarction occurred in 9.5% to 19.4%.3,4 The ISR rate after PCI with drug-eluting stents (DES) is reported between 3.2% to 5.5%.5,6 However, the clinical presentation of patients who present with ISR after PCI with DES is not well

described. The purpose of this study was to analyze the clinical presentation of patients with ISR after PCI with DES.

Methods: From April 2003 to December 2005, 475 out of 889 (53.4%) patients had follow-up angiography, of whom 42 out of 889 patients (4.7%) underwent PCI with DES — sirolimus-eluting stent (Cypher, Cordis, Miami, Florida) or paclitaxel-eluting stent (Taxus, Boston Scientific, Natick, Massachusetts) for ISR at UCLA Medical Center. Clinical follow up at 6 months was available in 78%. Patient demographic, medical, and procedural data were recorded in a computerized cardiovascular database. Data on clinical follow up were obtained from institutional medical records as well as records from the referring physicians and physicians who assumed care of patients after PCI. The United States Social Security Death Index (available at: http://ssdi.genealogy.rootsweb.com) was used to obtain longterm patient mortality data. We excluded 3 orthotopic heart transplant patients who had ISR. Therefore, the final analysis included 39 patients. Repeat angiography was performed when clinically indicated either because of recurrent symptoms, markedly abnormal stress test, or surveillance angiography after orthotopic heart transplantation. The Institutional Review Board approved the use of the database review for this study. The primary endpoint of the study was the type of clinical presentation of patients with ISR. Patients were identified as being asymptomatic or presenting with angina pectoris, unstable angina, or myocardial infarction. In-stent restenosis was defined as a stenosis of >50% located within the stent or within 5 mm of the stent edges by visual estimation by experienced coronary angiographers. The World Health Organization and American College of Cardiology/American Heart Association definition of myocardial infarction was used.7 Two of the 3 criteria were required for the diagnosis of myocardial infarction: ischemic chest pain, significant electrocardiographic changes, or an elevated biochemical marker such as creatine kinase-MB or troponin. Myocardial infarction was further divided into ST-segment-elevation myocardial infarction if the admission electrocardiogram showed ≥ 1 mm ST-segment elevation in ≥ 2 contiguous leads, or non-ST-elevation myocardial infarction if ST-segment elevations were not present on the admission electrocardiogram. Major adverse cardiac events were defined as death, myocardial infarction, or target lesion revascularization.

Statistical analysis. Continuous data are expressed as mean ± standard deviation (SD), and categorical variables are presented as frequency and percent. Statistical analyses were performed using SAS, version 9.1 (SAS Institute, Cary, North Carolina).

Results Baseline patient characteristics. The mean age was 66 ± 10 years, 77% were male, 33% had diabetes, 17% had peripheral arterial disease, 60% had previous PCI prior to the index procedure, and 24% had previous coronary artery bypass surgery (Table 1). The mean ejection fraction was 46 ± 18%.

Procedural characteristics. Sirolimus-eluting stents were used in 65% of cases, paclitaxel-eluting stents were used in 33% of cases, and both sirolimus- and paclitaxel-eluting stents were used in 2% of cases (Table 2). The mean number of stents used per case was 1.8 ± 0.9, and the mean stent length per case was 39 ± 24 mm.

Clinical characteristics. The mean time from PCI to detection of ISR was 13 ± 10 months. The mean time from PCI to follow up was 35 ± 10 months. Eight percent were

asymptomatic, 77% presented with angina pectoris, 5% with unstable angina, and 10% with non-ST-segment elevation myocardial infarction. No patients presented with ST-segment elevation myocardial infarction or had angiographic evidence of stent thrombosis in patients who had ISR. The overall incidence of angiographic stent thrombosis in the 889 patients was 0.4%. The 3 asymptomatic patients underwent coronary angiography because ischemia was detected on stress testing. All 3 patients underwent repeat PCI with DES and were free from major adverse cardiac events at the end of follow up. Out of the 30 patients who presented with angina pectoris, 24 underwent repeat PCI (23 underwent repeat PCI with DES and one had balloon angioplasty) and 6 patients (20%) underwent coronary artery bypass surgery. Three patients (10%) developed recurrent symptoms (one patient underwent repeat PCI, one bypass surgery, and another had transmyocardial laser revascularization). Six (15%) patients presented with acute coronary syndrome (2 with unstable angina and 4 with myocardial infarction). Among the 4 patients who presented with myocardial infarction, 2 underwent balloon angioplasty. The mean troponin I was 6 ± 8 ng/mL. Three patients (8%) with myocardial infarction died from other causes. An 86-year-old female patient with a pericardial tumor infiltrating the left ventricle died on day 991. An 87- year-old female with multiple medical problems who was admitted for lower gastrointestinal bleeding and acute renal failure, died on day 486 at a nursing home after care was withdrawn. A 76-year-old male died from pneumonia on day 1032.

Discussion: This report describes 39 patients who developed ISR after undergoing PCI with DES. Most of these patients with ISR after PCI with DES were either asymptomatic or had angina pectoris. However, ISR is not always clinically benign, as 10% of patients presented with non-ST elevation myocardial infarction. Patients who presented with myocardial infarction had a higher mortality rate than patients who were asymptomatic or presented with angina pectoris, but the cause of death was due to underlying comorbid disease and was not primarily due to the MI. Although ISR is uncommon in the DES era, with a 50% reduction compared with bare metal stents,5,6 rates of ISR remain high in diabetic patients,8 left main lesions involving the distal bifurcation,9 and small vessels.8 Neointimal hyperplasia is suspected as the main cause of ISR, usually requiring several months to develop.10 Moreover, it is generally believed that ISR manifests clinically as angina pectoris. Klugherz et al reported ISR and target vessel revascularization occurred at 5.4 months with bare metal stents.11 In our study, the mean time for ISR was over 13 months. Bossi et al reported that stable angina was the clinical presentation in 43% of patients who developed ISR after PCI with bare metal stent.12 This is compared to the 77% of patients in our study who presented with stable angina. The later presentation of ISR and the higher percentage of patients presenting with angina pectoris in our study may reflect a less aggressive form of neointimal hyperplasia with DES. When ISR occurs with DES, it is usually more focal compared with bare metal stents.5,6,13 Myocardial infarction due to ISR is usually due to sudden compromise of the vessel lumen due to rapid plaque growth with subsequent formation of occlusive or sub-occlusive thrombus. Tissue factor, which is highly thrombogenic, has been identified in the tissue inside the stent, and therefore may provide a stimulus for thrombus formation and myocardial infarction.14 Thrombus was visible on angiography in 9% of patients with ISR.4 Although DES attenuate neointimal hyperplasia, they are also associated with delayed

endothelialization, incomplete neointimal healing, and hypersensitivity reactions which may lead to myocardial infarction and death due to late stent thrombosis. We report a myocardial infarction rate of 10% in patient who have ISR, which is consistent with previous studies that have reported myocardial infarction as the clinical presentation in 10% to 19% of cases.3,4 The development of restenosis after PCI is not always associated with the recurrence of anginal symptoms.15 Less severe lesions on follow-up angiography were identified as a predictor of asymptomatic restenosis. Moderate non-critical lesions (50–60% restenosis) are typically associated with good clinical outcomes and the potential for lesion regression over time.16 The ideal treatment for asymptomatic patients with ISR is unknown. In our series, repeat PCI was performed in 5 asymptomatic patients with ISR. Lee et al. evaluated the utility of deferring repeat PCI in 98 asymptomatic patients with moderate non-critical ISR (< 70% diameter stenosis).17 There was no significant difference in target lesion revascularization, new lesion revascularization, event-free survival (cardiac death, nonfatal myocardial infarction, repeat revascularization), and percentage of patients requiring antianginal medications between the group of patients with moderate non-critical ISR that had PCI deferred until clinical recurrence of symptoms, compared with the group of patients without evidence of ISR on angiography. This suggests that it may be acceptable to defer repeat PCI in these patients until symptoms recur.

Limitations: This study was a single-center, retrospective analysis with a small number of patients. Angiographic followup was not performed on all patients who underwent PCI. Therefore, the true incidence of ISR and the breakdown of clinical presentation of ISR with DES are unknown as patients with ISR who did not undergo repeat coronary angiography may have been asymptomatic.
Furthermore, the true incidence of stent thrombosis is unknown because autopsy was not performed on all patients who died with no obvious cause. It is possible that ISR could present as death, and therefore be under-reported in this study. The rate of ISR reported from randomized controlled trials with DES with protocol-mandated angiography was 3.2% to 5.5%.5,6 Intravascular ultrasound was not performed on all patients. Therefore, information such as whether DES implantation resulted in incomplete stent apposition,18 late stent malapposition,19 or stent fracture,20 was not available. Only 17% of patients had intravascular ultrasound performed. Therefore, it was not possible to determine if inadequate expansion was partly responsible for ISR.
Conclusion: Although most patients with ISR after PCI with DES are either asymptomatic or have stable symptoms, ISR is not a completely benign clinical entity as patients presented with myocardial infarction 10% of the time. Drug-eluting stents with improved designs or drug elution systems that further decrease the incidence of ISR are needed.

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