Clinical characteristics of early and late drug-eluting stent in-stent restenosis and mid-term prognosis after repeated percutaneous coronary intervention

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Abstract

Background: The mechanism and characteristics of early and late drug-eluting stent in-stent restenosis (DES-ISR) have not been fully clarified. Whether there are different outcomes among those patients being irrespective of their repeated treatments remain a knowledge gap.

Methods: A total of 250 patients who underwent initial stent implantation in our hospital, and then were readmitted to receive treatment for the reason of recurrent significant DES-ISR in 2016 were involved. The patients were categorized as early ISR (<12 months; E-ISR; $n = 32$) and late ISR (≥12 months; L-ISR; $n = 218$). Associations between patient characteristics and clinical performance, as well as clinical outcomes after a repeated percutaneous coronary intervention (PCI) were evaluated. Primary composite endpoint of major adverse cardiac events (MACEs) included cardiac death, non-fatal myocardial infarction (MI), or target lesion revascularization (TLR).

Results: Most baseline characteristics are similar in both groups, except for the period of ISR, initial pre-procedure thrombolysis in myocardial infarction, and some serum biochemical indicators. The incidence of MACE (37.5% *vs.* 5.5%; $P < 0.001$) and TLR (37.5% *vs.* 5.0%; $P < 0.001$) is higher in the E-ISR group. After multivariate analysis, E-ISR (odds ratio [OR], 13.267; [95% CI 4.984–35.311]; $P < 0.001$) and left ventricular systolic dysfunction (odds ratio [OR], 6.317; [95% CI 1.145–34.843]; $P = 0.034$) are the independent predictors for MACE among DES-ISR patients in the mid-term follow-up of 12 months.

Conclusions: Early ISR and left ventricular systolic dysfunction are associated with MACE during the mid-term follow-up period for DES-ISR patients. The results may benefit the risk stratification and secondary prevention for DES-ISR patients in clinical practice.

Keywords: In-stent restenosis; Neointimal hyperplasia; Risk factors; Drug-eluting stent

Introduction

Currently, coronary stenting has been recommended as a primary strategy of revascularization for patients with coronary artery disease.[1,2] Despite the excellent efficacy regarding the reduction of the incidence of in-stent restenosis (ISR) in the era of plain balloon angioplasty and bare metal stents (BMS) implantation, drug-eluting in-stent restenosis (DES-ISR) affects approximately 5% to 10% of the patients undergoing percutaneous coronary intervention (PCI).[3-5] In addition to that, considering the large population treated with DES, treatment of ISR after DES implantation is yet a major challenge.[6] Even though many studies have addressed the incidence, mechanism and optimal treatment of DES-ISR, the prognosis of it, on the other hand, covers a wide range, as DES-ISR is related to worse outcomes than BMS-ISR, which has resulted in the development of treatment strategies including DES or drug coated balloon (DCB).[7,8] These treatment strategies show a varied and abundant body of evidence supporting the utilization in clinical treatment. Nevertheless, it is yet unclear whether the occurrence time of DES-ISR and other risk factors are the bane of poor clinical outcomes following repeated percutaneous coronary intervention (PCI), and a few previous studies in clinical trial settings addressing the issue can not sufficiently reflect the real-word situation.[9-11] Therefore, in the present study, we seek to shed light on the potential relationship between

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early and late DES-ISR, and identify patients at risk of adverse outcomes during the mid-term follow-up period after repeated PCI.

Methods

Study design and patient selection

This study was approved by the Institution Review Board of Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, and written informed consent was obtained from each patient enrolled in the study. In this retrospective single center study, there were 297 consecutive patients with significant ISR who had initial stent implantation and needed secondary intervention in our center within the entire year of 2016. Forty-seven patients were excluded from the present study for the reasons as follows: ISR lesions resulted from bare metal stent, no need of PCI, and loss to follow-up. Thus, 250 patients requiring PCI for the treatment of DES-ISR were included in this study. The study cohort was divided into two categories of early ISR (<12 months; E-ISR; $n = 32$) and late ISR (≥12 months; L-ISR; $n = 218$), depending on the time of ISR after initial DES implantation.

Definitions and PCI

Definitions were mainly proposed based on the Academic Research Consortium criteria.[12] According to the Academic Research Consortium and the third universal definition of MI,[13] the primary endpoint was a major adverse cardiac events (MACEs), defined as a composite of myocardial infarction (MI), cardiovascular death, and target lesion revascularization (TLR). The left ventricular systolic dysfunction was defined as ejection function lower than 50% evaluated by the echocardiography. The intervention strategies were at the discretion of the operators, based on angiographic findings including a >50% diameter stenosis with evidence of myocardial ischemia, such as ischemic symptoms, electrocardiogram changes, elevated cardiac troponin over the standard level and a positive stress test, or a ≥70% diameter stenosis assessed by quantitative coronary angiography (QCA) without either ischemic symptoms. PCI was performed by standard techniques via radial approach in most cases. If patients did not take adequate therapy of long-term aspirin and P2Y12 inhibitors, they were treated with a loaded dose of aspirin (300 mg) and clopidogrel (300 to 600 mg) or ticagrelor (180 mg) at least 24 h before the operation. During PCI, 100 IU/kg of unfractionated heparin was used for anticoagulation. After procedure, aspirin 100 mg per day was continued indefinitely. The recommended treatment duration of clopidogrel (75 mg daily) or ticagrelor (90 mg twice daily) was at least 1 year after the index PCI. Success of PCI was defined as <30% angiographic stenosis and thrombolysis in myocardial infarction (TIMI) flow grade 3 in the culprit vessel after interventions, with patients leaving the cardiac catheterization laboratory alive.[14]

Data collection and clinical follow-up

Detailed data on patients including demographic data, history, clinical presentation, angiographic findings, and in-hospital conditions were obtained from the medical record. Echocardiography and blood samples including biochemical test, blood routine, coagulation and lipid profile were taken at admission. The ratio of neutrophils to lymphocytes in the same blood sample obtained using an automated blood cell counter. Patients were followed on a regular basis. After 12 months of index PCI, a follow-up was organized in the outpatient clinics using a predefined questionnaire, and telephonic contact was also adopted for scheduled review. The validated dataset eventually entered into analysis.

Statistical analysis

Continuous variables were expressed as the mean value ± standard deviation for parametric variables, and median value with range was used for nonparametric variables. Categorical data were expressed as counts and proportions. Comparison of parametric variables between two groups was performed by means of independent samples *t* test, and Mann-Whitney *U* test was adopted for nonparametric variables. Categorical variables were compared by the chi-square test or Fisher exact test. Due to the reason that time variables from the secondary PCI to the occurrence of MACE events were not statistically accurate by telephonic contact, survival analysis and Cox regression analysis were not performed. Multiple logistic regression analysis was applied to determine the independent predictors of MACE in all DES-ISR patients during the mid-term follow-up period. A variable which was significant in univariate analysis was included in the analysis as well. Traditional cardiac factors and some potential clinical characteristics in the present study were also included in the multivariate analysis by Forward: LR method. Variables with known prognostic value $P < 0.05$ (two-sided) were considered statistically significant. All statistical analyses were performed using SPSS version 24.0 software (SPSS Inc., Chicago, IL, USA).

Results

Demographical and baseline characteristics

Among the total study population, 32 patients (12.8%) were categorized as E-ISR and 218 patients (87.2%) were categorized as L-ISR. The very small and disproportionate E-ISR might be owing to the low incidence of DES-ISR and our rigorous selection criteria according to which the patients received only first and second coronary intervention in our center in the year of 2016, and had completed the 1-year follow-up. There were significant differences in the median time interval from initial PCI to index interventions between the E-ISR and L-ISR groups (0.8 years *vs.* 5.1 years, respectively; $P < 0.001$). The other baseline clinical characteristics were similar in both groups as summarized in Table 1.

Echocardiograph and blood sample characteristics

Echocardiographic data were obtained during hospitalization. As shown in Table 2, there were higher rates of regional wall motion abnormality and left ventricular

Table 1: Demographic and clinical characteristics of DES-ISR patients after PCI.

Variables	Early ISR ($n=32$)	Late ISR ($n=218$)	P
Age (years)	58.5 (48.8–63.8)	61 (54.0–67.0)	0.103
Male	22 (22.0)	176 (80.7)	0.119
BMI (kg/m^2)	26.2 (24.0–28.1)	25.8 (24.1–27.7)	0.844
Diabetes mellitus	12 (37.5)	83 (38.1)	0.950
Hypertension	21 (65.6)	150 (68.8)	0.718
Dyslipidemia	26 (81.3)	196 (89.9)	0.144
Apoplexy	5 (15.6)	29 (13.3)	0.782
Atrial fibrillation	2 (6.3)	9 (4.1)	0.637
CKD	1 (3.1)	4 (1.8)	0.499
Prior MI	12 (37.5)	65 (29.8)	0.379
Prior CABG	1 (3.1)	7 (3.2)	1.000
Prior surgery	4 (12.5)	42 (19.3)	0.356
Peripheral vascular history	1 (3.1)	15 (6.9)	0.702
History of smoking	17 (53.1)	134 (61.5)	0.368
Smoking within 1 month	7 (21.9)	51 (23.4)	0.849
History of drinking	11 (34.4)	113 (51.8)	0.065
Family history of CHD	7 (21.9)	44 (20.2)	0.825
History of interruption APT	0 (0)	24 (11.0)	0.052
Symptoms on admission			0.088
Stable angina	12 (37.5)	39 (17.9)	–
Unstable angina	19 (59.4)	165 (75.7)	–
NSTEMI	1 (3.1)	8 (3.7)	–
STEMI	0 (0)	6 (2.8)	–
Killip class >II or NYHA class >II	10 (31.3)	100 (45.9)	0.120
Prior PCI counts	1 (1–2)	1 (1–2)	0.929
Stent amounts	3 (2–4)	2 (1–4)	0.110
Stented vessel counts	1 (1–2)	2 (1–2)	0.639
In-hospital time (days)	5 (3–6)	4 (3–5)	0.221
Period of ISR (years)	0.8 (0.5–0.9)	5.1 (2.4–7.5)	<0.001

Data are presented as median (range) or *n* (%). APT: Antiplatelet therapy; BMI: Body mass index; CABG: Coronary artery bypass grafting; CKD: Chronic kidney disease; DES: Drug-eluting stent; ISR: In-stent restenosis; MI: Myocardial infarction; NSTEMI: Non-ST-segment elevated myocardial infarction; NYHA: New York Heart Association; PCI: Percutaneous coronary intervention; STEMI: ST-segment elevated myocardial infarction.

systolic or diastolic dysfunction in the E-ISR group in comparison to the L-ISR patients (9.4% *vs.* 22.1%, $P=0.095$; 0 *vs.* 4.1%, $P=0.609$; 0 *vs.* 5.1%, $P=0.368$). However, there were no differences in left ventricular ejection fraction, left atrial or ventricular diameters between the two groups. In terms of blood profile at admission, the patients in E-ISR group had significantly higher standard of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and erythrocyte sedimentation rate (ESR) (21.5 [19.0–27.5] IU/L *vs.* 19.0 [16.0–23.0] IU/L, $P=0.029$; 30.0 [23.0–41.0] IU/L *vs.* 23.0 [16.0–33.0] IU/L, $P=0.017$; 8.5 [5.0–15.8] mm/h *vs.* 6.0 [2.0–12.0] mm/h, $P=0.026$), whereas low density lipoprotein cholesterol (LDL-C) level tended to be higher in the L-ISR than the E-ISR group (2.0 [1.3–2.4] mmol/L *vs.* 2.3 [1.8–2.9] mmol/L, $P=0.035$). Other laboratory parameters were similar in both groups.

Characteristics of PCI and clinical outcomes

There were no significant differences in baseline performances and angiographic characteristics between the two groups, except the pre-procedure TIMI flow grade 0 of prior PCI tended to be more in the E-ISR group than the L-ISR group (31.3% *vs.* 14.7%, $P=0.019$). Treatment of DES-ISR and the outcome of index PCI did not differ significantly between the two groups as shown in Table 3. Over the retrospective mid-term follow-up of 12 months after the secondary PCI, the primary endpoint of MACE occurred significantly more frequently in the E-ISR group than the L-ISR group (37.5% *vs.* 5.5%, $P<0.001$). However, the difference in MACE between the two groups was mainly driven by the TLR (37.5% *vs.* 5.0%, $P<0.001$, respectively). In addition, the re-hospitalization rate tended to be higher in the E-ISR group, too. As for the other components of primary endpoint, except only one case of cardiac death happened in the L-ISR group, there was no occurrence in the non-fatal MI, and no significant differences were found between the two groups as summarized in Table 3.

Multivariate analysis and predictors

Logistic regression analysis was performed to determine the independent predictors of MACE during the mid-term follow-up period in DES-ISR patients. The characteristics variables comprised of traditional cardiovascular disease risk factors, such as hypertension, hyperlipidemia, diabetes mellitus, and other clinical features including early/late

Table 2: Echocardiographic and blood parameters of DES-ISR patients after PCI.

Variables	Early ISR ($n = 32$)	Late ISR ($n = 218$)	*P* value
LVEF on admission (%)	63 (60–65)	63 (60–65)	0.417
Diameter of left atrial (mm)	35 (33–38)	36 (34–38)	0.436
Diastolic diameter of left ventricle (mm)	47.5 (46.3–50)	48 (45–51)	0.602
Regional wall motion abnormality	3 (9.4)	48 (22.1)	0.095
Left ventricular diastolic dysfunction	0	11 (5.1)	0.368
Left ventricular systolic dysfunction	0	9 (4.1)	0.609
WBC (10^3/μL)	6.3 (5.0–7.5)	6.5 (5.3–7.6)	0.691
NLR	2.2 (1.9–3.0)	2.3 (1.7–3.1)	0.973
RBC (10^6/μL)	4.7 ± 0.5	4.8 ± 0.5	0.256
Hemoglobin (g/L)	142.7 ± 14.8	146.5 ± 14.5	0.173
PLT (10^3/μL)	219 (167–279)	207.5 (180.3–242.8)	0.651
CK-MB (IU/L)	11.5 (9–16)	11 (9–13)	0.460
Serum creatinine max (μmol/L)	73.5 (63.8–93.9)	79.4 (71.2–89.7)	0.258
AST (IU/L)	21.5 (19.0–27.5)	19.0 (16.0–23.0)	0.029
ALT (IU/L)	30.0 (23.0–41.0)	23.0 (16.0–33.0)	0.017
Uric acid (μmol/L)	343.6 (288.3–412.1)	345.6 (293.4–404.3)	0.954
Triglyceride (mmol/L)	1.3 (0.9–2.1)	1.5 (1.1–1.9)	0.435
Total cholesterol (mmol/L)	3.5 (3.0–4.1)	3.8 (3.3–4.7)	0.105
LDL-C (mmol/L)	2.0 (1.3–2.4)	2.3 (1.8–2.9)	0.035
HDL-C (mmol/L)	1.2 (0.9–1.3)	1.1 (0.9–1.3)	0.444
hsCRP (mg/L)	1.3 (0.8–3.1)	1.7 (0.8–2.6)	0.606
ESR (mm/h)	8.5 (5.0–15.8)	6.0 (2.0–12.0)	0.026
NT-proBNP (pg/mL)	97.8 (39.8–308.3)	88.0 (41.3–156.7)	0.589
HbA1c (%)	6 (5.6–7.2)	6.1 (5.7–7.0)	0.873
Glucose (mmol/L)	5.6 (4.9–7.4)	5.9 (5.2–7.3)	0.260
Aptt (s)	35.2 (31.9–37.7)	34.3 (32.4–37.0)	0.498
INR	1.0 (0.9–1.0)	1.0 (0.9–1.0)	0.426
D-dimer (μg/mL)	0.3 (0.3–0.4)	0.3 (0.2–0.5)	0.769
Fibrinogen (g/L)	3.3 (2.9–3.6)	3.3 (2.8–3.9)	0.649

Data are presented as mean ± standard deviation, *n* (%) or median (range). ALT: Alanine aminotransferase; Aptt: Activated partial thromboplastin time; AST: Aspartate aminotransferase; CK-MB: Creatine kinase isoenzyme; DES: Drug-eluting stent; ESR: Erythrocyte sedimentation rate; HbA1c: Glycosylated hemoglobin; HDL-C: High-density lipoprotein cholesterol; hsCRP: High sensitivity C reactive protein; INR: International normalized ratio; ISR: In-stent restenosis; LDL-C: Low-density lipoprotein cholesterol; LVEF: Left ventricular ejection fraction; NLR: Ratio of neutrophil to lymphocyte; NT-proBNP: N-terminal pro-B natriuretic peptide; PLT: Platelets; RBC: Red blood cell; WBC: White blood cell.

ISR, age, gender, BMI, CKD, history of smoking, presentation with MI, echocardiographic features, neutrophils to lymphocytes ratio, ESR, implanting stent, and the success of index PCI were included into multivariate logistic analysis using the Forward: LR method. As shown in Table 4, the E-ISR (odds ratio [OR], 13.267; 95% confidence interval [CI] 4.984–35.311; $P < 0.001$) and left ventricular systolic dysfunction (odds ratio [OR], 6.317; 95% confidence interval [CI] 1.145–34.843; $P = 0.034$) were performed as independent risk factors of MACE during the mid-term follow-up in DES-ISR patients.

Discussion

To the best of our knowledge, this study is among the first to explore clinical characteristics between early and late DES-ISR, as well as predictors for the mid-term MACE in DES-ISR after repeated PCI in a real world situation, irrespective of the type of treatment adopted for DES-ISR. The main findings are as follows: (1) Baseline characteristics of the study between the E-ISR and L-ISR groups are almost similar except some laboratory parameters and prior TIMI flow. (2) Compared to the patients in L-ISR group, the patients in the E-ISR group suffer significantly more MACE in mid-term clinical follow-up, mainly driven by a higher proportion of TLR. (3) The early ISR and left ventricular systolic dysfunction are found as independent risk factors of MACE over the mid-term follow-up in DES-ISR patients after repeated PCI.

Restenosis remains one of the clinical intractable and unresolved issues. Treatment of patients with DES-ISR is more challenging than that of patients with BMS-ISR.[10,15,16] DES-ISR is characterized by delayed vessel healing due to the stent components such as the durable polymer which has a time lag presentation typically after 2 years as compared to BMS-ISR which is typically approximately 6 to 8 months to present.[17] Vascular injury and ensued inflammation in the intima induces the initial stimuli for vascular smooth muscle (SMC) proliferation and activation, and, consequently, the SMC and myofibroblast migrate form an extracellular matrix (ECM) and neointimal layer covered by the endothelial cell over the stented segment.[18,19] Those complicated pathogenic processes result in variable time of onset and character-

Table 3: Characteristics of PCI and clinical outcomes in patients with DES-ISR at 12-month follow-up after treatment.

Variables	Early ISR ($n=32$)	Late ISR ($n=218$)	*P* value
Prior PCI characteristics			
Single vessel lesion	5 (15.6)	46 (21.1)	0.473
Including lesion of LM	3 (9.4)	8 (3.7)	0.154
Calcific lesions	15 (46.9)	121 (55.5)	0.360
Pre-Procedure TIMI flow grade*			
0	10 (31.3)	32 (14.7)	0.019
1–2	5 (15.6)	34 (15.6)	1.000
3	17 (53.1)	150 (68.8)	0.079
Post-procedural TIMI flow grade 3	32 (100)	218 (100)	–
Residual stenosis >30%	0	1 (0.5)	1.000
Complication	0	1 (0.5)	1.000
Treatment for ISR			0.652
Implanting stent	22 (68.8)	141 (64.7)	–
Balloon angioplasty	10 (31.2)	77 (35.3)	–
Presentation with MI	1 (3.1)	14 (6.4)	0.701
Outcome of index PCI			0.615
Success	30 (93.8)	207 (95.0)	–
Part success	1 (3.1)	8 (3.7)	–
Failure	1 (3.1)	3 (1.4)	–
Follow-up at 12 months			
Re-hospitalization	12 (37.5)	16 (7.3)	<0.001
MACE events	12 (37.5)	12 (5.5)	<0.001
Cardiac death	0	1 (0.5)	1.000
Non-fatal MI	0	0	–
Target lesion revascularization	12 (37.5)	11 (5.0)	<0.001
Stent thrombosis	0	1 (0.5)	1.000

* There were two cases in late ISR lacking the pre-TIMI flow grade. Data are presented as *n* (%). DES: Drug-eluting stent; ISR: In–stent restenosis; LM: Left main coronary artery; MACE: Major adverse cardiac events; PCI: Percutaneous coronary intervention; TIMI: Thrombolysis in myocardial infarction.

Table 4: Results of univariate analysis of MACE at mid-term follow-up in DES-ISR patients.

Variables	OR	95% CI	*P* value
Age	0.982	0.942–1.023	0.382
Male	0.998	0.354–2.812	0.997
BMI	1.000	0.878–1.140	0.996
Early ISR	10.300	4.095–25.910	<0.001
Hypertension	0.916	0.375–2.240	0.848
Hyperlipidemia	0.871	0.242–3.129	0.832
Diabetes mellitus	0.646	0.257–1.620	0.351
CKD	–	–	0.999
History of smoking	0.754	0.323–1.757	0.512
Presentation with MI	0.658	0.083–5.238	0.693
Left ventricular diastolic dysfunction	–	–	0.999
Left ventricular systolic dysfunction	2.980	0.581–15.269	0.190
NLR	0.795	0.503–1.257	0.327
ESR	0.992	0.948–1.038	0.720
Implanting stent	0.723	0.307–1.704	0.459
Success of index PCI	0.324	0.083–1.270	0.106

95% CI: 95% confidence interval; BMI: Body mass index; CKD: Chronic kidney disease; DES: Drug-eluting stent; ESR: Erythrocyte sedimentation rate; ISR: In-stent restenosis; MACE: Major adverse cardiac events; MI: Myocardial infarction; NLR: Ratio of neutrophil to lymphocyte; OR: Odds ratio; PCI: Percutaneous coronary intervention.

istics in DES-ISR. Some studies even have found that DES-ISR has a predominantly focal morphological pattern, with onset after 6 to 9 months and increasing up to 2 years after stent implantation.[20,21] In our study, there is a short interval of duration of period of ISR from 0.5 to 0.9 years in the early DES-ISR group. Also, there is a long interval from 2.4 to 7.5 years in the late DES-ISR group. Multifarious neoatherosclerosis could be a mechanism for the different clinical outcomes after repeated PCI, and this may relate to risk factor control rather than a function of procedure. Hence, it may also confound our observation study.

Intravascular imaging by optical coherence technology (OCT) has given further insight into the significant differences between lesion morphological characteristics of early and late ISR. There are predominantly heterogeneous tissue patterns and higher incidence of neoatherosclerosis in late DES-ISR.[22,23] In contrast, the primary OCT finding in early DES-ISR is reported to be homogeneous backscatter, which is related to the neointima rich in SMC.[22,24] The occurrence of neoatherosclerosis is independently associated to the time interval after stent implantation, and neoatherosclerosis has been a novel underlying substrate of DES-ISR happened up to one of six patients presenting with ISR.[25] Furthermore, DES-ISR with neoatherosclerosis has also been reported to cause poorer acute results after intervention. However, in the current study, we find a significantly higher MACE event in early DES-ISR patients, mainly driven by higher TLR rates, which is in line with a recent report by Koch *et al*[26] where clinical outcomes at 12 months after treatment of DES-ISR with DCB showed significantly higher clinical event rates in patients with early DES-ISR as compared to those with late DES-ISR. Concerning the underlying substrate of early ISR found by OCT, neointimal proliferation might contribute predominantly to the cause of worse outcomes. On the one hand, the reason of higher MACE in early ISR could be the earlier ISR. Stent underexpansion, if uncorrected by appropriate stent upsizing, could entail the higher re-re ISR and MACE event. Although the PSP technology, known as "Prepare lesion, Size appropriately, Post-dilate", has been well carried out as a routine in our center, the lack of invasive imaging which is too expensive to guide treatment for primary PCI could impact on the higher adverse events. On the other hand, it can also be deduced that the increasing incidences of MACE in E-ISR group could be related to modification of ECM and neointima, which has been accelerating neoatherosclerosis process. Permeability of plasma lipoproteins is usually regarded as the most probable mechanism to accelerate neoatherosclerosis, and larger ECM accumulation binding between lipoprotein and proteoglycans is another likely contributor to the promotion of neoatherosclerosis.[27,28] The serum lipid profile might affect the neointimal plaque characteristics and outcomes after PCI. In accordance with previous OCT studies which have found a lower cholesterol level and heterogeneous intima in the E-ISR group,[23,29] our data also show that low-density lipoprotein cholesterol (LDL-C) concentrations differ significantly between the E-ISR and L-ISR groups (2.0 [1.3–2.4] mmol/L *vs*. 2.3 [1.8–2.9] mmol/L, $P = 0.035$), and the total cholesterol (TC) tends to be numerically higher in the L-ISR group than the E-ISR group (3.8 [3.3–4.7] mmol/L *vs*. 3.5 [3.0–4.1] mmol/L, respectively, $P = 0.105$). However, the hyperlipidemia does not perform as the risk factor of MACE after multivariate analysis in the present study.

Magalhaes *et al*[30] found that 66.7% of patients presenting with DES-ISR requiring target vessel revascularization had ACS and the incidence of myocardial infarction was 5.2%. Similarly, unstable angina in 59.4% of the E-ISR patients and 75.7% of the L-ISR patients is the main presentation of DES-ISR patients in the current study. In addition, a few patients perform as MI at admission, and the patients with prior MI have no distinct difference in both groups (37.5% *vs*. 29.8%, $P = 0.379$). The factors that influence the ISR can be divided into five categories: patient, lesion, mechanical, pharmacological and biological factors.[31] When it comes to the repeated DES-ISR outcomes, something has changed. Paramasivam *et al*[32] reported that among the clinical and lesion related parameters, age, chronic kidney disease and presentation with MI were related to poor outcomes following DES-ISR. Different from the present study, the aforementioned study did not consider the factor of time interval from stent implantation to ISR. However, there is a pool analysis study similar to the current study that has revealed only early-ISR and clinical presentation with NSTE-ACS as independent predictor of MACE.[26] Moreover, in this study, we find that echocardiographic trait of left ventricular systolic dysfunction and early DES-ISR are independent risk predictors of MACE during the mid-term follow-up in DES-ISR patients. Changes in the structure of the left ventricle during the contractile cycle from end-diastole to end-systole play an important role in the optimization of the cardiac pumping function.[33] It is well known that heart diseases lead to apparent changes in the functional geometry of left ventricle and spatial-temporal coordination of its components resulting from the molecular and cellular remodeling of myocardium.[34] In principle, all cardiac structures are involved in the process of ISR, and the abnormal left ventricle systolic function might be an epitome of damaged and poor cardiac function. Given the association between cardiac dysfunction and poor outcome, it is interesting to find that left systolic dysfunction could be served as risk predictor of subsequent clinical adverse events. However, the mechanism of this relationship could not be further clarified, and more studies are needed in the future. Although the underlying mechanism resulting in these findings remains to be resolved, the early DES-ISR patients seem to be taken care of with an increased clinical surveillance, irrespective of current treatment strategies.

Due to the nature of this single center retrospective cohort, some confounding factors may influence the results. Therefore, the findings should be considered as hypothesis generating. This study has several limitations that should be acknowledged. First, the small sample size and lack of some extensive details such as stent or balloon types of treatment in the current study might not be enough to impact on the strength of observations. Also, the use of telephonic contact when obtaining the information of the follow-up might not be reliable enough, as we could not get

their hospital record to further prove the adverse events. In addition to that, although this study mainly focuses on the mid-term prognosis of DES-ISR to help discriminate those high-risk patients of MACE, the mechanism of the pathological process yet remains unknown. Finally, on account of the lack of intravascular imaging data, we fail to provide further insight changes of those DES-ISR patients. Especially, the characteristics and underlying substrates of DES-ISR need to be clarified in pathology and pathophysiology.

To summarize the current study, the incidence of MACE is higher in the E-ISR group than the L-ISR group. E-ISR and left ventricular systolic dysfunction are associated with the poor outcome during the mid-term follow-up. The results may benefit the risk stratification and secondary prevention for DES-ISR patients in clinical practice.

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Conflicts of interest

None.

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