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Identification of Risk Factors Influencing In-Stent Restenosis with Acute Coronary Syndrome Presentation

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Although the angiographic rates of in-stent restenosis (ISR) at later months have reduced dramatically with the introduction of drug-eluting stents (DESs), some patients with ISR after implantation of DES present with acute coronary syndrome (ACS). Here, we sought to identify parameters influencing the likelihood of restenosis with ACS presentation after DES implantation. Stented patients (n=3,817) with DESs in the Korea University Anam Hospital percutaneous coronary intervention registry were reviewed retrospectively for inclusion. In this database, 247 age- and sex-matched patients (6.5%) with ISR were allocated to either the Stable ISR group (n=78) or the ACS ISR group (n=73). Predictors of in-stent restenosis were identified with Cox regression analyses. Age (hazard ratio [HR], 1.14; 95% confidence interval [CI], 1.02 to 1.27; p=0.026), diabetes (HR, 8.40; 95% CI, 1.30 to 54.1; p=0.025), use of aspirin (HR, 0.003; 95% CI, 0.0001 to 0.63; p=0.03), clopidogrel (HR, 0.005; 95% CI, 0.001 to 0.121; p=0.001), renin-angiotensin system (RAS) blocker (HR, 0.02; 95% CI, 0.003 to 0.14; p < 0.001), use of first -generation DES (HR, 0.07; 95% CI, 0.009 to 0.59; p=0.014), and matrix metalloproteinase 2 (MMP-2) levels (HR, 1.120; 95% CI, 1.001 to 1.190; p=0.004) during follow-up angiograms were significant predictors of ISR with ACS presentation during the 3 year follow-up. Age, diabetes, the use of first generation DES, and increased MMP-2 levels were significant predictors of ISR with ACS presentation; moreover, the use of aspirin, clopidogrel, RAS blocker, and the use of second generation DESs prevented ISR with ACS presentation.

Key Words: *Acute Coronary Syndrome; Coronary Restenosis; Drug-Eluting Stents; Matrix Metalloproteinase 2*

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INTRODUCTION

In-stent restenosis (ISR) remains a significant clinical problem especially in patients with multiple risk factors.[1,2] With the introduction of drug-eluting stents (DESs), there has been a considerable reduction in the in-stent restenosis rates and target lesion revascularization. Nevertheless, patients with multiple risk factors continue to show increased rates of restenosis and late lumen loss.[3] Systemic treatments with antiplatelet drugs, statins, angiotensin-converting enzyme inhibitors, or calcium-channel blockers have not shown to be effective in reducing neointimal proliferation.[4-6]

Although mortality from acute coronary syndrome (ACS) has declined substantially, the mortality risk is still estimated to be 5 to 6 times higher in patients who suffer a recurrent coronary event.[7] Moreover, prevalence of ACS in ISR was reported to be high as 60 to 70% and myocardial infarction 5 to 10%.[8] According to a previous study—the Prevention of Restenosis with Tranilast and Its Outcomes (PRESTO) trial—patients with ISR who presented with ACS were older and less often men, had a higher incidences of diabetes, hypertension, tobacco use, previous coronary artery bypass graft surgery, and congestive heart failure.[9] However, the stent type used in this trial was a bare-metal stent (BMS), and none of the lesions were revascularized with a DES. The purpose of this retrospective, age and sex-matched study was to demonstrate predictors of ISR

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with ACS presentation in the era of DESs.

MATERIALS AND METHODS

1. Study patients

A total of 247 patients with ISR were retrospectively screened for inclusion in the study at Korea University Anam Hospital Cardiovascular Center from June 2004 through December 2012. All participating patients received DESs according to the study protocol. Patients who did not fulfill the inclusion criteria (n=39) or who had any of the exclusion criteria (n=102) were excluded. Eligible patients (n=151, 62 women and 99 men) were allocated to either the ISR with ACS group (73 patients) or ISR without ACS group (78 patients) after age and sex-matching (Fig. 1). Standard definitions of ACS including ST-segment elevation myocardial infarction (STEMI), non-ST segment elevation myocardial infarction (NSTEMI), and unstable angina (UA) were used.[10,11] We excluded left main coronary lesions, heart failure (ejection fraction $<45\%$), hepatic dysfunction (AST or ALT $>$ twice the upper limit), cerebrovascular disease, or expected life expectancy of <1 year. Statin intensity was defined as follows: low intensity; simvastatin 10 mg, pravastatin 10-20 mg, pitavastatin 1 mg, fluvastatin 20-40 mg, moderate intensity; atorvastatin 10-20 mg, rosuvastatin 5-10 mg, pravastatin 40-80 mg, simvastatin 20-40 mg, pitavastatin 2-4 mg, high intensity; atorvastatin 40-80 mg, rosuvastatin 20 mg. A renin-angiotensin system (RAS) blocker was defined as any use of angiotensin converting enzyme inhibitors (ACE-I) or angiotensin II receptor blockers (ARB).

The primary end point of the study was to compare various risk factors between the patients with ISR who presented with ACS or stable angina. Moreover, biomarkers known to predict ACS such as matrix metalloproteinase-2 (MMP-2), MMP-9,[12,13] myeloperoxidase (MPO),[14,15] interleukin-6 (IL-6),[16,17] adiponectin,[18,19] tumour necrosis factor-α (TNF-α)[17,20] and high-sensitivity C-reactive protein (hsCRP) 19 were compared between the two groups. Our study only tried to find the statistical significance among the biomarkers because the reference range of biomarkers were not confidentially determined and the pathological range varied with studies researching the same biomarkers.

2. Angiographic analysis

Procedural success was defined as residual stenosis of $<15\%$ in the absence of closure during the first 48 hours after the procedure. Two identical orthogonal views were obtained after intracoronary administration of nitrates and stored on digital CD-ROM. All angiographic and clinical data were analyzed by people blinded to the treatment. End-diastolic frames were chosen for quantitative analysis. This was performed using a computer-based TCS system, Version 2.02 (Medcon Inc., Tel-Aviv, Israel). The reference diameter, minimal luminal diameter, percentage of stenosis, and lesion length were calculated as the average value of the two orthogonal views. The same views and calibrations were used at follow-up angiography. The average diameter of normal segments proximal and distal to the treated lesion was used as the reference diameter. The Gensini score was calculated based on a previous report.[21] Lesions were characterized according to the modified American College of Cardiology/American Heart Association classification.[22] Restenosis was defined as a stenosis of $>$ 50% of the luminal diameter, and Mehran classification was used for description of in-stent restenosis patterns.[23]

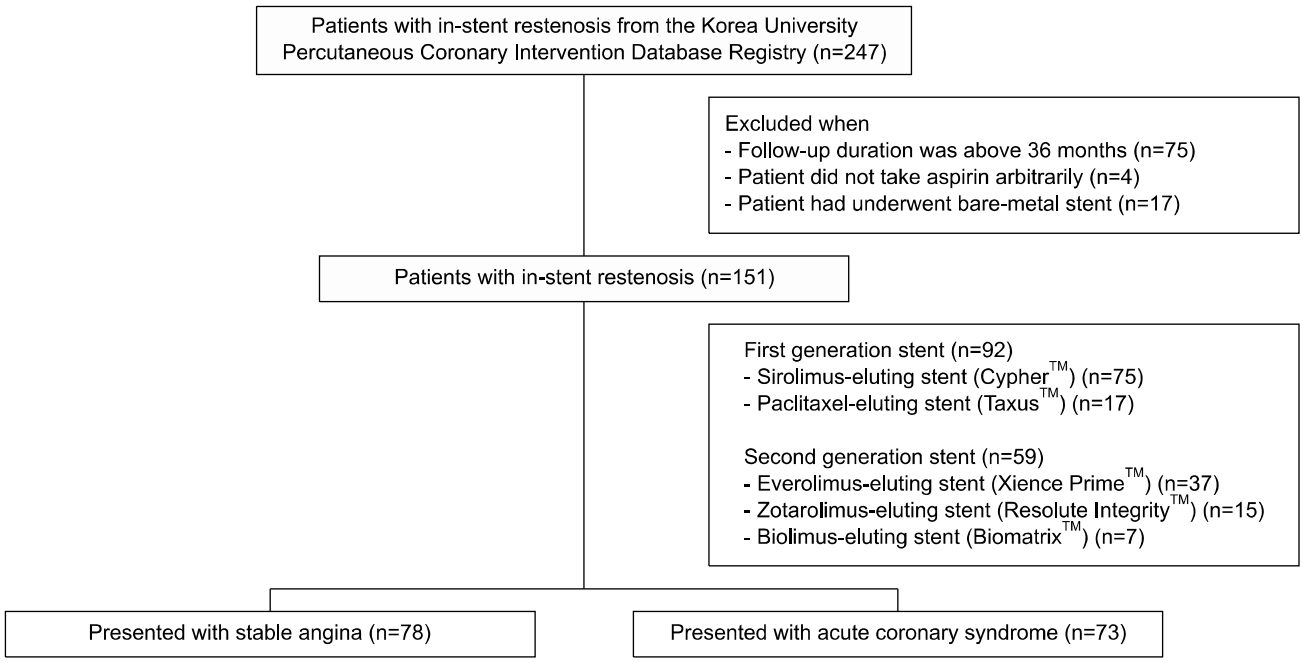

FIG. 1. Study design.

Balloon angioplasty and stent implantation were performed according to standard clinical practice.

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

3. Laboratory analysis and inflammatory markers

Venous blood samples were drawn from each patient after overnight fasting at the beginning of the study. Biomarkers predicting ACS were obtained at both index PCI and ISR PCI. Blood samples were centrifuged to obtain serum, and the serum was stored at −80°C. TNF-α was measured using a sandwich enzyme-linked immunosorbent assay (ELISA) with a sensitivity of 0.13 pg/mL (ALPCO Diagnostics, Salem, NH, USA). Undetectable TNF-α values in 2 patients were recorded as 0.13 pg/mL. High-sensitivity IL-6 was also measured using a sandwich ELISA with a sensitivity of 0.16 pg/mL (ALPCO Diagnostics, Salem, NH, USA). The hsCRP levels were quantified using a latex nephelometer II (Dade Behring Inc., Newark, DE, USA). The serum adiponectin level was assessed by radioimmunoassay (Linco Research, Inc. St. Charles, MO, USA) with a sensitivity of 0.78 ng/mL. The intra- and inter-assay coefficients of variation for the radioimmunoassay were 9.3% and 15.3%, respectively.

Cytokine protein levels such as MMP2 and MMP-9 were quantified using Luminex's xMAP Technology with the Milliplex kits (Millipore, Billerica, MA, USA) similar to the sandwich ELISA procedure according to the manufacturer's instructions. In brief, 5 μg of total protein per sample was mixed with the capture antibody conjugated beads before adding the phycoerythrin/streptavidin-con-

TABLE 1. Patients characteristics of study subjects

Variable	Stable angina (n=78)	Acute coronary syndrome (n=73)	p-value
Age (years)	61.3±8.4	61.1±10.3	0.921
Male, n (%)	51 (64.6)	48 (66.7)	0.785
Smoking, n (%)			
Ex-smoker	20 (25.6)	16 (22.2)	0.579
Current smoker	18 (23.1)	22 (30.6)	
Hypertension, n (%)	39 (50.0)	43 (59.7)	0.232
Diabetes mellitus, n (%)	27 (35.5)	29 (42.0)	0.694
Medications, n (%)			
Aspirin	76 (97.4)	70 (96.0)	0.673
Clopidogrel	67 (85.9)	58 (79.5)	0.389
DAPT	67 (85.9)	58 (79.5)	0.389
RAS blocker	59 (75.6)	53 (72.6)	0.712
Stain	73 (93.6)	65 (89.0)	0.391
High statin intensity	0	4 (5.7)	0.798
Generation of previously implanted DES, n (%)			
First generation	35 (44.9)	57 (78.1)	<0.001
Second generation	43 (55.1)	16 (21.9)	
Laboratory data			
Hemoglobin (g/dL)	13.2±1.83	14.5±10.2	0.262
Creatinine (mg/dL)	0.95±0.20	0.97±0.29	0.631
HbA1c (%)	7.49±18.71	10.85±24.30	0.346
ESR (mm/hr)	36.19±41.52	34.49±41.73	0.802
Total cholesterol (mg/dL)	136.50±49.03	140.49±61.12	0.643
Triglyceride (mg/dL)	110.79±81.92	109.79±67.60	0.936
HDL cholesterol (mg/dL)	40.97±15.03	40.78±15.76	0.934
LDL cholesterol (mg/dL)	72.87±29.80	85.64±42.15	0.035
Diagnosis, n (%)			
Unstable angina		63 (86.4)	
NSTEMI		6 (8.0)	
STEMI		4 (5.7)	
Stent thrombosis		7 (9.6)	

DAPT: dual antiplatelet therapy, RAS: renin-angiotensin system, DES: drug-eluting stent, HbA1c: glycated hemoglobin, ESR: erythrocyte sedimentation rate, LDL: low-density lipoprotein, HDL: high-density lipoprotein, NSTEMI: non-ST segment elevation myocardial infarction, STEMI: ST segment elevation myocardial infarction.

jugated reporter antibody. The double-labeled beads were separated and quantitated in a Luminex xMAP flow cytometer. The MPO serum levels were measured with ELISA according to manufacturer's suggestions (Calbiochem, Millipore, Billerica, MA, USA). This assay provides a detection limit of 1.5 μg/L.

4. Statistical analysis

Data are expressed as mean±SD for continuous variables, and data for the categorical variables are expressed as the number and the percentage of patients. A Chi-square test was used for categorical variables. The results between the two groups were compared via an unpaired Student's *t* test, and the comparisons before and after treatment were analyzed with a paired *t* test. Angiographic analyses were performed according to the number of patients available for each analysis. A Cox regression analysis of hazard ratios (HRs) was applied to verify the independent predictors for ACS. Adjusted factors for the Cox regression analysis were age, smoking history, diabetes mellitus, RAS blocker, first generation DES, and LDL cholesterol level. These are common risk factors of ACS development. A P-value of less than 0.05 was considered statistically significant. SPSS software (version 18.0) was used for analyses (SPSS Inc., Chicago, Illinois, USA).

RESULTS

1. Study patients

Baseline characteristics of the 151 patients included in this study are presented in Table 1. The baseline level of low-density lipoprotein (LDL) cholesterol was higher in ACS group compared to that of SA (90.8±35.7 mg/dL in SA group vs 75.3±35.6 mg/dL in ACS group, p=0.005).

TABLE 2. Angiographic characteristics of study subjects

Variable	Stable Angina (n=78)	Acute coronary syndrome (n=73)	p-value
Interval between index and second procedure (months)	16.8±15.9	18.9±16.3	0.41
Before index procedure			
Gensini score	30.9±21.0	38.6±22.3	0.032
Number of target vessel, n (%)			0.028
One vessel	50 (65.8)	32 (44.4)	
Two vessel	22 (28.9)	35 (48.6)	
Three vessel	3 (5.3)	5 (6.9)	
Reference diameter (mm)	2.67±0.44	2.55±0.62	0.181
Minimal lumen diameter (mm)	0.68±0.53	0.69±0.48	0.932
Percentage of stenosis (%)	74.0±0.21	70.0±0.25	0.263
Mean lesion length (mm)	27.7±16.0	32.8±19.6	0.084
Immediately after index procedure			
Minimal lumen diameter (mm)	2.87±0.46	2.89±0.35	0.275
Percentage of stenosis (%)	3.5±2.9	9.3±13.3	0.126
Second procedure			
Number of target vessel, n (%)			0.927
One vessel	71 (93.4)	67 (93.1)	
Two vessel	5 (6.6)	5 (6.9)	
Three vessel	0 (0)	0 (0)	
Location of ISR, n (%)			
Left anterior descending artery	50 (61.0)	50 (64.1)	0.688
Left circumflex artery	18 (22.0)	18 (23.1)	0.869
Right coronary artery	14 (17.1)	14 (17.9)	0.880
Reference diameter (mm)	2.65±0.62	2.49±0.60	0.111
Minimal lumen diameter (mm)	0.76±0.51	0.65±0.51	0.172
Percentage of stenosis (%)	71.1±21.1	72.2±0.24	0.783
ISR lesion length (mm)	17.3±8.16	22.2±13.2	0.023
Restenosis pattern, n (%)			0.884
Ia	3 (3.8)	1 (1.4)	
Ib	24 (30.4)	25 (35.2)	
Ic	22 (27.8)	11 (15.5)	
Id	5 (6.3)	10 (14.1)	
II	7 (8.9)	11 (15.5)	
III	11 (13.9)	4 (5.6)	
IV	7 (8.9)	9 (12.7)	

ISR: in-stent restenosis.

Compared to second generation DESs, a first generation DES implanted at an index procedure was more closely related to ACS presentation in the following procedure in the ACS group (78.1% in first generation DES vs 21.9% in second generation DES, $p < 0.001$). In the index procedure, 151 patients underwent percutaneous coronary intervention with first generation DESs (n=92) or second generation DESs (n=59) (Fig. 1). Sirolimus eluting stents (n=75) and everlorimus eluting stents (n=37) were most common in implanted stents in the first and the second generation DESs, respectively.

Within the ACS group, patients' characteristics of UA versus myocardial infarction (MI) in the acute coronary syndrome group were also analyzed (Supplement Table 1). Compared to UA, MI, which contains STEMI and NSTEMI, had significantly higher incidence with first generation DESs in index procedures (55.3% in UA group vs 91.7% in MI group, p=0.017). Patients' baseline characteristics were also compared between stent generations (Supplement Table 2). On medication, use of clopidogrel (76.1% in first vs 93.2% in second generation DES, p=0.007) and dual antiplatelet therapy (76.1% in first vs 89.8% in second generation DES, p=0.034) was higher in the second generation DES group. Although the use of statin or statin intensity was similar between two groups, LDL cholesterol levels were significantly lower in the second generation DES group (90.2±34.8 mg/dL in first vs 72.8±25.6 mg/dL in second generation DES, p=0.001).

2. Angiographic characteristics

Table 2 lists the results of quantitative coronary angiography. The baseline Gensini score was significantly higher in the ACS group than in the SA group (38.5±22.3 vs. 30.9±21.0, p=0.03). More patients in the ACS group had two-vessel disease (48.6% vs. 28.9%, p=0.028). There were no significant differences in reference diameter, minimal lumen diameter, percentage of stenosis, and mean lesion length during the index and follow-up procedure except that the ISR lesion length was longer in ACS group (22.2±13.2 mm vs. 17.3±8.16 mm, p=0.023). However, there was no significant difference between the two groups in terms of restenosis pattern.

3. Comparison of Inflammatory Biomarkers

None of the biomarkers showed a significant difference between the two groups (Table 3). However, IL-6 level tended to be lower in the ACS group compared to the SA group at the index procedure (25.29±54.92 pg/mL vs. 5.25±5.82 pg/mL, p=0.066). We also studied the impact of procedure timing on biomarker levels, but there was no significant difference between the index and the follow-up procedure.

Within the ACS group, biomarkers of UA versus MI in the acute coronary syndrome group were compared (Supplement Table 3). None of biomarkers except adiponectin in the index procedure (3.3±2.0 in UA group vs 6.6±1.6 in MI group, p=0.041) showed significant differences between the UA and MI group. Regarding stent generation, MMP-9 showed significant differences in both index (96.1±50.7 ng/mL in first vs 51.7±47.6 ng/mL in second generation DES, p=0.006) and second (96.5±68.5 ng/mL in first vs 49.1±35.5 ng/mL in second generation DES, p=0.001) procedures (Supplement Table 4).

4. Predictors for ISR with ACS presentation

The result of risk factor using Cox-regression analysis is shown in Table 4. Of the medications, aspirin (HR: 0.003, 95% CI: 0.0001 to 0.63, p=0.034) as well as clopidogrel (HR: 0.005, 95% CI: 0.0001 to 0.121, p=0.001) and RAS blocker (HR: 0.02, 95% CI: 0.003 to 0.14, p=0.0001) lowered the risk of ISR with ACS presentation. With respect to stent type

TABLE 3. Biomarkers in index and second procedure according to clinical presentation

Variables	Stable angina (n=78)	Acute coronary syndrome (n=73)	p-value
Index procedure			
hsCRP (mg/dL)	26.62±42.84	26.65±41.93	0.996
TNF-alpha (pg/mL)	15.30±12.00	11.52±8.75	0.302
IL-6 (pg/mL)	25.29±54.92	5.25±5.82	0.066
MMP-2 (ng/mL)	52.2±13.8	53.0±15.4	0.867
MMP-9 (ng/mL)	66.1±47.4	83.2±64.0	0.336
Adiponectin (μg/mL)	4.3±2.2	3.6±2.2	0.299
Myeloperoxidase (μg/L)	446.0±62.1	420.8±60.9	0.206
Second procedure			
hsCRP (mg/dL)	12.85±31.44	14.09±32.37	0.812
TNF-alpha (pg/mL)	9.49±6.27	18.09±34.83	0.132
IL-6 (pg/mL)	14.29±40.16	5.40±7.21	0.175
MMP-2 (ng/mL)	58.1±15.6	62.6±16.9	0.279
MMP-9 (ng/mL)	67.0±56.8	81.8±62.5	0.334
Adiponectin (μg/mL)	4.1±2.1	4.4±2.5	0.679
Myeloperoxidase (μg/L)	428.6±69.3	415.2±88.3	0.500

hsCRP: high-sensitivity C-reactive protein, TNF: tumor necrosis factor, IL: interleukin, MMP: matrix metalloproteinase.

at the index procedure, the second generation of DESs had lower risks for ISR. The ACS presentation was compared to the first generation DESs (HR: 0.07, 95% CI: 0.009 to 0.59, p=0.014) (Fig. 2A). We conducted a subgroup analysis for patients who had SES and EES. In subgroup analysis, EES at the index procedure lowered the risk of ISR with ACS presentation (HR: 0.41, 95% CI: 0.19 to 0.89, p=0.026) (Fig. 2B). High levels of MMP-2 during the second procedure could predict the ISR with ACS presentation (HR: 1.12, 95% CI: 1.001 to 1.19, p=0.004).

TABLE 4. Cox regression analysis of risk factors for occurrence of acute coronary syndrome

Variables	HR	95% CI	p-value
Age	1.14	1.02-1.27	0.026
Male	0.45	0.05-4.37	0.491
Smoking	1.30	0.15-11.4	0.812
Hypertension	0.28	0.05-1.61	0.163
Diabetes mellitus	8.40	1.30-54.1	0.025
Medications			
Aspirin	0.003	0.0001-0.63	0.034
Clopidogrel	0.005	0.001-0.121	0.001
Statin	0.19	0.01-2.63	0.225
Relative doses of statin	0.99	0.96-1.02	0.916
RAS blocker	0.02	0.003-0.14	0.0001
Stent			
Gensini score	1.03	0.98-1.09	0.217
Total length of stents	0.99	0.97-1.01	0.358
Second generation stent	0.07	0.009-0.59	0.014
Laboratory data			
LDL	1.03	0.998-1.06	0.064
MMP-2 during second procedure	1.12	1.001-1.19	0.004

HR: hazard ratio, CI: confidence intervals, RAS: renin-angiotension system, LDL: low-density lipoprotein, MMP: matrix metalloproteinase.

DISCUSSION

To the best of our knowledge, this is the first study to investigate multiple predictors of ISR with ACS presentation after DES implantation. Our study demonstrated that patients who had second generation DESs in index PCI, prescription of aspirin, clopidogrel, and RAS blocker were associated with a lower risk of ISR upon ACS presentation. Older age and diabetes mellitus had predictive power for ISR with ACS presentation. Of the biomarkers, only increased MMP-2 in the ISR period was associated with ISR in the ACS presentation.

Although DES is known to be superior to BMS in suppressing neointimal proliferation, recent studies have shown that there were differences among different types of DESs in the rate of ISR development.[24,25] According to previous studies, second generation DESs (zotarolimus and everolimus-eluting stents) showed a low restenosis rate compared to the first generation DESs (sirolimus and paclitaxel-eluting stents). However, in a study of 12-month follow up after stent implantation, cardiac death and MI did not show any significant difference between patients who were implanted with zotarolimus-eluting stents (ZES) and paclitaxel-eluting stents (PES); TLR did show a difference.[25]

In our study, patients who developed ISR after the second generation DESs demonstrated significantly fewer ACS presentations than the first generation DESs (22.2% vs 54.4%, p=0.0001) (HR 0.07, CI 0.009-0.59, p=0.014). This is the first result of superior clinical outcome of second generation DES in clinical presentation after ISR, which improves the safety and efficacy of early generation devices.[26]

Several studies have shown that pharmacologic therapy with ACE-I or ARB reduced neointima proliferation and restenosis after stent implantation.[27,28] We speculated that the tissue renin-angiotensin system inside the stent might play a role in neointima formation. Although each drug

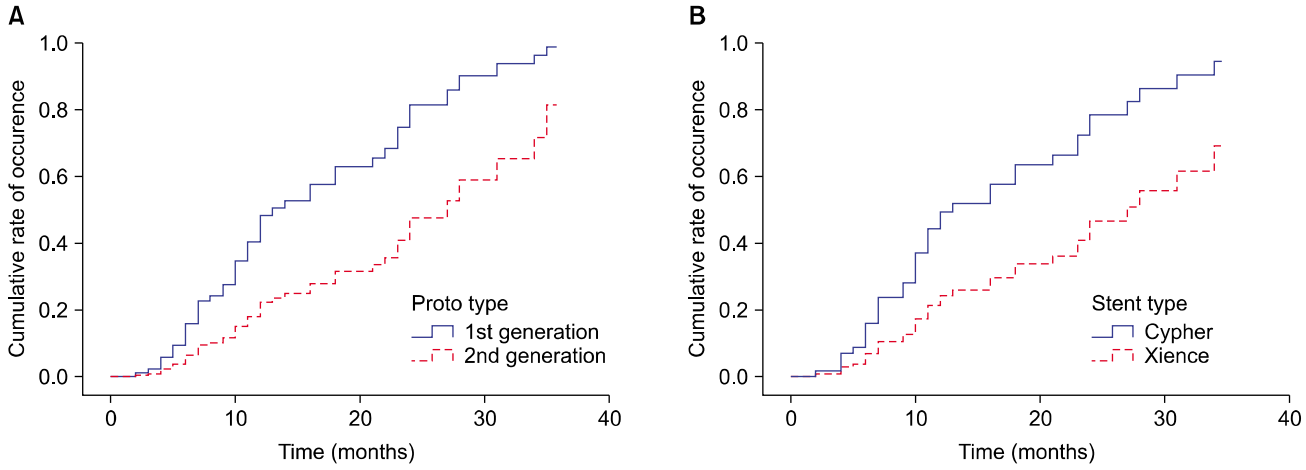

FIG. 2. Cumulative rate of occurrence analyzed by Cox regression analysis. (A) shows the difference of cumulative occurrence rates in acute coronary syndrome between first and second generation stents. (B) shows differences between the Cypher and Xience prime stent.

showed specific effects, the plaque-stabilizing effects of ACE-I and ARB were equivalent and increased the thickness of the fibrous cap and collagen content in the plaque. This decreased the number of plaque macrophages.[29] These facts may explain why our patients who used RAS blockers in ISR had a lower risk of ACS (HR 0.02, CI 0.003-0.14, p=0.0001). On the other hand, statin use was not a significant predictor of ISR with ACS presentation. It is known that statins have a significant reduction in coronary heart disease events including mechanisms of low-density lipoprotein (LDL) reduction or a variety of LDL-independent mechanisms—these are the so-called pleiotropic effects.[30] Considering the difference of LDL levels between 2 groups, which was higher in ACS group, it seems that statins may not have been administered sufficiently enough to lower LDL levels. As a result, statin use did not play a major role in lowering the risk of ACS presentation in ISR.

MMP-2 and MMP-9 are increased in vascular smooth muscle and inflammatory cells and contribute to the development and complications of atherosclerosis. Moreover, patients with ACS had significantly greater levels of MMP-9 and MMP-2 than both SA patients and healthy control subjects.[12,13] In our study, only MMP-2 had a higher risk of ACS development (HR 1.12, CI 1.001-1.19, p=0.004).

There are several reasons why only MMP-2 was elevated. A period of ACS presentation to admission may have been delayed. A previous study showed that both MMP-2 and MMP-9 were elevated in early ACS presentation, but only MMP-2 elevation was sustained until day 7. MMP-9 gradually decreased by day 7.[12] Also, considering the strong relationship between MMP-9 and hs-CRP, the hs-CRP level was similar between the 2 groups; therefore, MMP-9 did not show significant differences. Finally, the mechanisms could play a role between MMP-2 and ISR with ACS presentation so that only MMP-2 elevation contributes to the development of ISR with ACS presentation. Although previous studies showed the mechanism of elevated MMP for de novo atherosclerosis, this was not seen in ISR. It can be assumed that elevated MMP can represent plaque rupture or instability in ISR—ACS presentation in ISR is also a consequence of plaque rupture in neo-atherosclerosis.

There are several limitations to this study. First, this is a retrospective analysis and is therefore subject to the limitations pertinent to this type of clinical investigation. Second, this had a small sample size, a nonrandomized design, and a lack of strict entry criteria. Due to the limited prevalence of ISR, patient data was collected over 9 years of the database, which caused heterogeneity with first and second generation. Furthermore, several different DESs were included in the analysis. The differences among DESs could not be assessed because of the small sample size.

CONCLUSION

This study demonstrates that age, diabetes, the use of first generation DESs, and increased MMP-2 levels were significant predictors of ISR with ACS presentation. The use of aspirin, clopidogrel, RAS blocker, and the use of second generation DES prevented ISR with ACS presentation.

CONFLICT OF INTEREST STATEMENT

None declared.

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Supplement table 1. Patients characteristics of unstable angina versus myocardial infarction in acute coronary syndrome group

Variable	Unstable angina (N=63)	Myocardial infarction (N=10)	*P value*
Age (years)	60.8 ± 11.1	62.3 ± 10.5	0.682
Male, n (%)	43 (68.4)	7 (66.7)	0.904
Smoking, n (%)			
Ex-smoker	18 (29.0)	3 (33.3)	0.433
Current smoker	18 (29.0)	2 (16.7)	
Hypertension, n (%)	32 (51.3)	6 (58.3)	0.651
Diabetes mellitus, n (%)	26 (40.8)	6 (58.3)	0.254
Medications, n (%)			
Aspirin	59 (93.4)	10 (100)	0.360
Clopidogrel	52 (82.9)	7 (66.7)	0.186
DAPT	51 (80.26)	7 (66.7)	0.287
RAS blocker	48 (76.3)	9 (91.7)	0.230
Stain	57 (90.8)	8 (83.3)	0.428
High statin intensity	3 (4.0)	2 (16.7)	0.671
Generation of previously implanted DES, n (%)			
First generation	35 (55.3)	9 (91.7)	0.017
Second generation	28 (44.7)	1 (8.3)	
Laboratory data			
Hemoglobin (g/dL)	13.1 ± 1.5	14.1 ± 2.0	0.059
Creatinine (mg/dL)	0.94 ± 0.25	2.07 ± 3.40	0.276
HbA1c (%)	7.2 ± 15.5	12.5 ± 27.5	0.531
ESR (mm/hr)	10.8 ± 10.3	14.6 ± 20.0	0.611
Total cholesterol (mg/dL)	148.7 ± 40.8	168.5 ± 60.5	0.199
Triglyceride (mg/dL)	123.9 ± 75.3	118.7 ± 71.1	0.843
HDL cholesterol (mg/dL)	42.6 ± 10.7	46.9 ± 11.2	0.260
LDL cholesterol (mg/dL)	82.3 ± 33.7	99.1 ± 44.6	0.178

DAPT: dual antiplatelet therapy; RAS: renin-angiotensin system; DES: drug-eluting stent; HbA1c: glycated hemoglobin; ESR: erythrocyte sedimentation rate; LDL: low-density lipoprotein; HDL: high-density lipoprotein

Supplement table 2. Patients characteristics of study subjects between stent generation

Variable	1st generation (N=92)	2nd generation (N=59)	*P value*
Age (years)	61.8 ± 9.1	60.3 ± 9.7	0.347
Male, n (%)	59 (64.1)	40 (67.8)	0.644
Smoking, n (%)			
Ex-smoker	16 (17.4)	20 (33.9)	0.233
Current smoker	31 (33.7)	10 (17)	
Hypertension, n (%)	52 (56.5)	30 (50.9)	0.495
Diabetes mellitus, n (%)	41 (44.6)	21 (35.6)	0.274
Medications, n (%)			
Aspirin	91 (98.9)	55 (93.2)	0.057
Clopidogrel	70 (76.1)	55 (93.2)	0.007
DAPT	70 (76.1)	53 (89.8)	0.034
RAS blocker	69 (75)	43 (72.9)	0.772
Stain	85 (92.4)	55 (93.2)	0.848
High statin intensity	3 (3.3)	2 (3.4)	0.859
Laboratory data			
Hemoglobin (g/dL)	13.1 ± 1.6	13.4 ± 2	0.283
Creatinine (mg/dL)	1.22 ± 1.77	0.98 ± 0.24	0.219
HbA1c (%)	10.4 ± 23.8	7.1 ± 17.7	0.332
ESR (mm/hr)	11.7 ± 10.8	11.2 ± 11.2	0.845
Total cholesterol (mg/dL)	154.2 ± 43.7	140.3 ± 38.2	0.057
Triglyceride (mg/dL)	116.9 ± 74.5	116.2 ± 69.9	0.953
HDL cholesterol (mg/dL)	42.5 ± 10.4	44 ± 11.3	0.416
LDL cholesterol (mg/dL)	90.2 ± 34.8	72.8 ± 25.6	0.001
Diagnosis, n (%)			
Stable angina	39 (42.4)	24 (40.7)	0.238
Unstable angina	42 (45.7)	34 (57.6)	

NSTEMI	6 (6.5)	1 (1.7)
STEMI	5 (5.4)	0 (0)
Stent thrombosis	6 (6.5)	2 (3.4)

DAPT: dual antiplatelet therapy; RAS: renin-angiotensin system; HbA1c: glycated hemoglobin; ESR: erythrocyte sedimentation rate; LDL: low-density lipoprotein; HDL: high-density lipoprotein; NSTEMI: non-ST segment elevation myocardial infarction; STEMI: ST segment elevation myocardial infarction

Supplement table 3. Biomarkers in index and second procedure according to clinical presentation

Variables	Unstable Angina (n=63)	Myocardial infarction (n=10)	*P value*
Index procedure			
hsCRP (mg/dL)	2.29 ± 4.8	1.36 ± 3.67	0.527
TNF-alpha (pg/mL)	11.48 ± 9.21	8.77 ± 2.43	0.691
IL-6 (pg/mL)	8.62 ± 12.32	4.49 ± 2.98	0.65
MMP-2 (ng/mL)	50.7 ± 16.3	58.1 ± 20.9	0.56
MMP-9 (ng/mL)	73.4 ± 57.2	75.0 ± 80.7	0.97
Adiponectin (μg/mL)	3.3 ± 2	6.6 ± 1.6	0.041
Myeloperoxidase (μg/L)	437.5 ± 57.9	349.3 ± 11.9	0.051
Second procedure			
hsCRP (mg/dL)	2.85 ± 5.92	14.92 ± 26.46	0.143
TNF-alpha (pg/mL)	14.34 ± 31.63	7.43 ± 3.25	0.255
IL-6 (pg/mL)	7.05 ± 16.89	3.92 ± 1.87	0.335
MMP-2 (ng/mL)	57.7 ± 16.9	64.8 ± 8.8	0.367
MMP-9 (ng/mL)	63.1 ± 55.3	107.7 ± 56.2	0.105
Adiponectin (μg/mL)	3.8 ± 2.1	4.2 ± 2.5	0.722
Myeloperoxidase (μg/L)	420.4 ± 85.3	379.3 ± 93.2	0.331

hsCRP: high-sensitivity C-reactive protein; TNF: tumor necrosis factor; IL:interleukin; MMP: matrix metalloproteinase

Supplement table 4. Biomarkers in index and second procedure according to stent generation

Variables	1st generation DES (n=92)	2nd generation DES (N=59)	*P value*
Index procedure			
hsCRP (mg/dL)	2.28 ± 4.65	0.86 ± 1.42	0.007
TNF-alpha (pg/mL)	11.93 ± 7.7	15.79 ± 13.12	0.244
IL-6 (pg/mL)	15.21 ± 36.2	21.42 ± 52.93	0.667
MMP-2 (ng/mL)	53.9 ± 14.4	51.4 ± 14.2	0.569
MMP-9 (ng/mL)	96.1 ± 50.7	51.7 ± 47.6	0.006
Adiponectin (μg/mL)	3.5 ± 1.8	4.6 ± 2.4	0.125
Myeloperoxidase (μg/L)	441.7 ± 55.8	433.8 ± 68.2	0.687
Second procedure			
hsCRP (mg/dL)	4.03 ± 11.23	2.27 ± 5.77	0.267
TNF-alpha (pg/mL)	14.39 ± 30.68	10.71 ± 6.34	0.511
IL-6 (pg/mL)	9.58 ± 24.76	12.39 ± 38.64	0.728
MMP-2 (ng/mL)	60.3 ± 17.7	59.3 ± 14.7	0.816
MMP-9 (ng/mL)	96.5 ± 68.5	49.1 ± 35.5	0.001
Adiponectin (μg/mL)	4.4 ± 2.2	4.1 ± 2.3	0.664
Myeloperoxidase (μg/L)	421.8 ± 73.8	425.6 ± 80.1	0.842

DES: drug-eluting stent; hsCRP: high-sensitivity C-reactive protein; TNF: tumor necrosis factor; IL:interleukin; MMP: matrix metalloproteinase