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Incidence and Clinical Predictors of Stent Restenosis and Early Stent Occlusion in Patients with Acute Myocardial Infarction treated by Bare Metal Stents: Importance of Infarct location and Serum Creatinine Level

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Abstract

Background: Bare Metal Stents (BMS) have been commonly used for recanalization of an infarct-related artery in Japanese patients with Acute Myocardial Infarction (AMI). We sought to examine predictors of binary restenosis and early Stent Occlusion (SO) in these patients.

Methods: Among 242 consecutive patients with AMI treated by BMS implantation as reperfusion therapy, 226 underwent either ischemia-driven or follow-up coronary angiography within 8 months. Restenosis change in the stented segment was found in 56. Among them, 10 patients had early SO on an angiogram. Multivariate analysis was performed to obtain predictors of restenosis and early SO.

Results: Predictors for restenosis were Left Anterior Descending Artery (LAD) involvement (odds ratio (OR) 2.32, p=0.024), serum creatinine (SCr) on admission (OR 1.29 per 0.1mg/dl increase, p=0.001), and stent size (OR 0.43 per 0.5mm increase, p=0.001). Those for early SO were left main trunk or LAD involvement (OR 27.0, p=0.029), SCr (OR 1.65 per 0.1mg/dl increase, p=0.005) and leukocyte count (OR 1.28 per 1,000/microliter increase, p=0.037) on admission. SCr was significantly higher in patients with early SO than in those with restenosis (median 1.05, Interquartile Range (IQR) 0.80-1.10 vs. median 0.80, IQR 0.70-1.00, p=0.035).

Conclusion: In patients with AMI treated with BMS, both restenosis and early SO were increased by anterior wall involvement and elevation of SCr level. Higher SCr may be subject to more occlusive changes. It is suggested that in early SO, an inflammatory mechanism may be involved.

Keywords: Acute myocardial infarction; Bare metal stent; Stent occlusion; Restenosis

Introduction

Emergency percutaneous coronary intervention has become an established standard reperfusion therapy for patients with Acute Myocardial Infarction (AMI), especially since cardiologists started to use stents, which can stabilize coronary patency. As compared to uncoated Bare Metal Stents (BMS), many studies [1-7] have shown that Drug-Eluting Stent (DES) implantation at the infarct-related lesion can reduce target lesion revascularization markedly during a 1 to 3 year follow-up period. However, there is accumulating evidence that raises concerns regarding a higher risk of stent thrombosis after DES placement, especially in the setting of AMI [3-6, 8, 9]. Compared with restenosis without complete occlusion, unexpected abrupt coronary closure caused by Stent Occlusion (SO) may need urgent recanalization because it can involve sudden hemodynamic deterioration, leading to death.

This risk can be avoided to a great extent if BMS is used appropriately for reperfusion therapy by knowing the predictors of stent restenosis and SO. In Japan, the Ministry of Health, Labor, and Welfare did not accept DES use in the setting of AMI by the medical care insurance system for a long time. Here, under such circumstances, we report the predictors of binary restenosis and early SO at infarct-related lesions treated with BMS in patients with AMI.

Methods

Patients

Between October 1999 and March 2013, 242 consecutive patients

with AMI underwent emergency percutaneous coronary intervention as reperfusion therapy within 24 hours of symptom onset and received uncoated BMS at the infarct-related lesion to successfully obtain Thrombolysis in Myocardial Infarction trial 3 flow grade with residual stenosis of <50%. AMI was diagnosed when patients complained of chest pain of ≥ 20 minutes but ≤ 24 hours duration that was unresponsive to sublingual nitroglycerin and was associated with ST segment elevation ≥ 1 mm in ≥ 2 contiguous ECG leads or ST depression in leads V1 to V4 consistent with posterior wall infarction. Those whose body temperature exceeding 38°C, who were too restless for catheterization, or who had bleeding tendency due to hepatic or hematologic disorder were excluded.

Groups

Among these 242 patients, 226 underwent either ischemia-driven or planned follow-up coronary angiography within 8 months. Thus,

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this study was performed in these patients (182 men and 44 women, mean age, 63 ± 10 years). All patients gave written informed consent. Comparisons were performed between patients with and without either angiographic restenosis or early SO.

Therapeutic method

Percutaneous coronary intervention was only performed for The Infarct-Related Artery (IRA). After the procedure the patients were transferred to the coronary care unit and monitored. Heparin was continuously infused to maintain the activated clotting time ≥ 200 seconds for ≥ 24 hours. At the same time, intravenous isosorbide dinitrate and nicorandil were administered. Patients received oral aspirin (100 mg/ day), either ticlopidine (200 mg/day) or clopidogrel (75 mg/ day), and calcium antagonist after the procedure. If recurrent chest pain unrelieved by nitrates lasted ≥ 20 minutes and was accompanied by ≥ 1 mm ST elevation or depression in the infarct-related territory, the patient underwent emergency angiography and, if necessary, additional coronary intervention.

Clinical observation indicators

Coronary artery diameters were measured on end-diastolic frames and percent diameter stenosis was calculated after maximal dilation obtained by isosorbide dinitrate administration. It was defined as follows: (reference diameter – minimal luminal diameter)/reference diameter × 100. A diseased vessel was defined as one with >70% narrowing. Binary restenosis was defined as >50% luminal narrowing at the infarct-related lesion, including the implanted stent and 5 mm proximal and distal to the stent edges of the target vessel on the follow-up angiogram. Early SO was defined as stent thrombotic occlusion within the stented segment, confirmed with angiographic proof of vessel occlusion within 30 days after the index procedure. This study complied with the Declaration of Helsinki and was approved by the ethics committee of our institution.

Statistical analysis

Continuous variables were tested for normal distribution using the Shapiro-Wilk test. Data with normal distribution are presented as the mean ± SD; non-normally distributed data are presented as the median and interquartile range (IQR). Between-group comparisons of normally distributed variables were made with two-sided Student's t test for unpaired data, and those of variables not normally distributed were made by the Mann-Whitney test. Categorical variables were compared with the chi-square or Fisher's exact test (whenever an expected cell value was <5). Multivariate logistic regression analysis was performed to correlate binary restenosis and early SO with clinical and angiographic variables. The model was built entering variables that demonstrated p ≤ 0.15 in univariate analysis by means of a stepwise forward selection procedure. Statistical significance was accepted as p<0.05. All tests were performed by SPSS 11J statistical software (Tokyo, Japan).

Results

Binary restenosis and SO

Among 226 study patients who received BMS implantation as reperfusion therapy, 56 had binary restenosis, including reocclusion in the stented portion confirmed on either ischemia-driven or planned follow-up coronary angiogram. Ten patients had early SO and underwent another coronary intervention successfully. Among them, however, two patients with left main coronary artery occlusion died due to pneumonia or multi-organ failure secondary to cardiac pump failure 33 days and 4 months after BMS implantation, respectively. Beyond 30 days, very late SO occurred in another two patients with right coronary artery occlusion (2.5 and 9 years after coronary intervention) requiring reperfusion therapy.

Predictors of binary restenosis

No significant intergroup differences were present with regard to coronary risk factors and infarct size, although the percentage of male and aged patients tended to be greater and that of hyperlipidemia tended to be smaller in the restenosis group than in the non-restenosis group (Table 1).

Laboratory examinations on admission showed significantly higher Serum Creatinine (SCr) (p=0.012) and slightly higher C-reactive protein (p=0.065) in the restenosis group. (Table 2).

In this group, the frequency of the Left Anterior Descending Artery (LAD) as IRA was significantly higher (64% vs. 44%, p=0.009) and implanted BMS size was significantly smaller (p <0.001) (Table 3).

Multivariate analysis, which excluded gender, age, hyperlipidemia, and C-reactive protein on admission in the final model, revealed an SCr level on admission (odds ratio (OR) of 1.29 per 0.1 mg/dl increase, p=0.001), LAD involvement (OR 2.32, p=0.024), stent size (OR 0.43 per 0.5 mm increase, p=0.001) as three independent correlates of binary restenosis (Table 4).

	Restenosis group(n=56)	Non-restenosis group(n=170)	p	Early SO group(n=10)	Non-early SO group(n=216)	p
Men (%)	49(88)	133 (78)	0.129	10 (100)	172 (80)	0.216
Age (yrs)	65.3 ± 9.4	62.7 ± 10.5	0.103	61.9 ± 11.4	63.4 ± 10.2	0.647
Current smoker (%)	26 (46)	93 (55)	0.282	4 (40)	115 (53)	0.523
Hypertension (%)	33 (59)	82 (48)	0.165	5 (50)	110 (51)	1.000
Hyperlipidemia (%)	29 (52)	110 (65)	0.085	4 (40)	135 (63)	0.189
Diabetes mellitus (%)	16 (29)	50 (29)	0.905	3 (30)	63 (29)	1.000
Hyperuricemia (%)	6 (11)	18 (11)	0.979	2 (20)	22 (10)	0.288
Prior MI (%)	2 (4)	9 (5)	1.000	0 (0)	11 (5)	1.000
Previous CABG (%)	0 (0)	1 (1)	1.000	0 (0)	1 (1)	1.000
Cardiogenic shock (%)	7 (13)	16 (9)	0.507	3 (30)	20 (9)	0.069
Peak CK (IU/l)	3173 (1659-4586)	3180 (1979-5201)	0.452	4004 (2078-7547)	3161 (1835-4935)	0.372
Peak CKMB (IU/l)	268 (177-469)	308 (166-461)	0.618	258 (198-635)	298 (165-459)	0.703

Abbreviations: CABG: coronary artery bypass grafting; MI: myocardial infarction; SO: stent occlusion

Table 1: Baseline characteristics of the study population.

	Restenosis group(n=56)	Non-restenosis group(n=170)	p	Early SO group(n=10)	Non-early SO group(n=216)	p
Glucose (mg/dl)	154 (135-206)	166 (139-211)	0.397	163 (137-258)	165 (138-210)	0.818
Creatinine (mg/dl)	0.8 (0.7-1.0)	0.8 (0.6-0.9)	0.012	1.1 (0.8-1.1)	0.8 (0.6-0.9)	0.003
CRP (mg/dl)	0.16 (0.08-0.37)	0.12 (0.06-0.27)	0.065	0.08 (0.05-0.24)	0.13 (0.06-0.30)	0.382
Hemoglobin (g/dl)	14.5 ±1.6	14.4 ± 1.7	0.568	14.5 ± 1.2	14.4 ± 1.7	0.914
Platelets (/microl)	22.9 (20.1-26.3)	23.1 (19.6-27.4)	0.688	25.3 (21.6-28.8)	23.0 (19.6-27.2)	0.357
White Blood Cells (/microl)	11000 (8610-13430)	10000 (7660-12730)	0.207	13650 (8840-16450)	10300 (8110-12700)	0.041
Neutrophils (/microl)	7060 (5420-10080)	6650 (4620-9380)	0.356	10450 (4820-12660)	6830 (4780-9340)	0.121
Lymphocytes (/microl)	2100 (1540-3010)	2070 (1250-3010)	0.692	2010 (1670-3650)	2080 (1360-3000)	0.703
Monocytes (/microl)	525 (407-762)	509 (341-732)	0.409	565 (380-864)	509 (380-734)	0.457
Eosinophils (/microl)	68 (25-163)	89 (20-160)	0.482	22 (2-134)	87 (24-162)	0.112

Abbreviations: CRP: C-reactive protein; SO: stent occlusion

Table 2: Laboratory findings on admission.

	Restenosis group(n=56)	Non-restenosis group(n=170)	p	Early SO group(n=10)	Non-early SO group(n=216)	p
Multi-vessel disease (%)	28 (50)	71 (42)	0.281	7 (70)	92(43)	0.109
Target (%) (LMCA/LAD/RCA/Cx)	3/36/12/5 (5/64/21/9)	0/75/77/18 (0/44/45/11)	<0.001	3/6/1/0 (30/60/10/0)	0/105/88/23 (0/49/41/11)	<0.001
LAD (%)	36 (64)	75 (44)	0.009			
LMCA or LAD (%)				9 (90)	105 (49)	0.019
Proximal segment (%)	34 (61)	88 (52)	0.244	6 (60)	116 (54)	0.756
Bifurcation lesion (%)	22 (39)	55 (32)	0.901	4 (40)	73 (34)	0.738
Initial TIMI flow grade 0/1 (%)	47 (84)	132 (78)	0.315	7 (70)	172 (80)	0.437
Poor collaterals (%)	33 (59)	114 (67)	0.268	6 (60)	141 (65)	0.743
IABP support (%)	5 (9)	9 (5)	0.181	3 (30)	11 (5)	<0.001
Time to PCI (min)	236 (196-367)	244 (179-381)	0.849	218 (199-343)	245 (180-379)	0.816
Single stent placement (%)	54 (96)	164 (97)	1.000	10 (100)	208 (96)	1.000
Stent size (mm)	3.00 (2.50-3.00)	3.00 (3.00-3.50)	<0.001	3.00 (2.50-3.50)	3.00 (2.75-3.50)	0.407
Stent length (mm)	15 (13-18)	15 (14-18)	0.453	15 (12-18)	15 (14-18)	0.455

Abbreviations: Cx: left circumflex artery; IABP: intra-aortic balloon pumping; LAD: left anterior descending artery; LMCA: left main coronary artery; PCI: percutaneous coronary intervention; RCA: right coronary artery; SO: stent occlusion; TIMI: Thrombolysis in Myocardial Infarction

Table 3: Angiographic and procedural characteristics of the study population.

	OR	95% CI	p
Serum creatinine (mg/dl)			
(per 0.1mg/dl increase)	1.29	1.11 to 1.50	0.001
Stent size (mm)			
(per 0.50mm increase)	0.43	0.26 to 0.70	0.001
LAD as IRA	2.32	1.12 to 4.80	0.024

Abbreviations: CI: confidence interval; IRA: infarct-related artery; LAD: left anterior descending artery; OR: odds ratio

Table 4: Predictors of binary restenosis.

Predictors of early SO

No significant differences were present among baseline patient demographics and infarct size between the early SO and non-early SO groups, although patients complicated with cardiogenic shock were slightly more frequent (p=0.069) in the early SO group (Table 1). Laboratory examinations on admission showed significantly higher SCr (p=0.003) and white blood cell count (p=0.041), slightly higher numbers of neutrophils (p=0.121), and slightly lower numbers of eosinophils (p=0.112) in the early SO group (Table 2). In this group, the percentages of either left main coronary artery or LAD involvement (p=0.019) and usage of intra-aortic balloon pumping (p <0.001) were significantly higher and multi-vessel disease tended to be more frequent (p=0.109) (Table 3). Multivariate analysis, which excluded cardiogenic shock and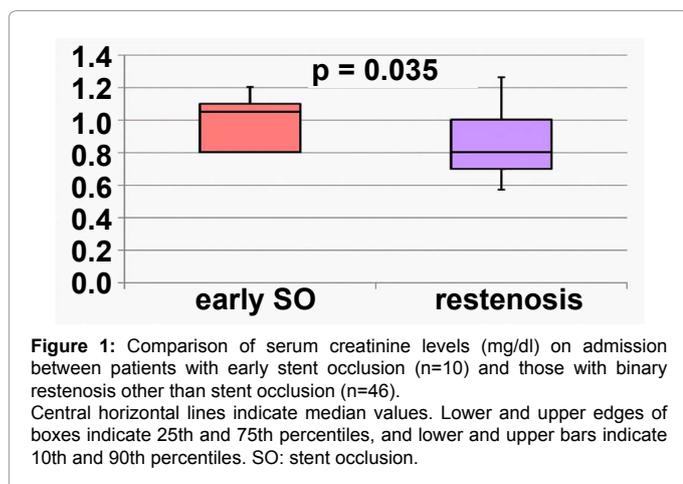 neutrophil count on admission in the final model, revealed the SCr level on admission (OR 1.65 per 0.1mg/dl increase, p=0.005), left main coronary artery or LAD involvement (OR 26.97, p=0.029), white blood cell count (OR 1.28 per 1,000/microliter increase, p=0.037) as three independent correlates of early SO (Table 5).

Here, use of intra-aortic balloon pumping was not included as an independent variable in the analysis because this was significantly more frequently recorded in patients with left main coronary artery or LAD involvement (11.1% vs. 3.3%, p=0.030), indicating a high correlation between the two factors and also, it was at cardiologists' discretion and thus possibly biased. Because the incidence of early SO was quite low, reclassification method was applied for above 3 factors; net reclassification improvement was 0.605, 0.495, and 0.428 for the SCr level, left main coronary artery or LAD involvement, and white blood cell count, respectively (p < 0.001 for each).

	OR	95% CI	p
Serum creatinine (mg/dl)			
(per 0.1mg/dl increase)	1.65	1.17 to 2.33	0.005
LMCA or LAD as IRA	26.97	1.41 to 514.59	0.029
White blood cells			
(per 1000/microl increase)	1.28	1.02 to 1.61	0.037
Multi-vessel disease	5.57	0.89 to 34.90	0.067
Eosinocytes			
(per 20/microl increase)	0.88	0.73 to1.06	0.174

Abbreviations: CI: confidence interval; IRA: infarct-related artery; LAD: left anterior descending artery; LMCA: left main coronary artery; OR: odds ratio.

Table 5: Predictors of early stent occlusion.

Figure 1: Comparison of serum creatinine levels (mg/dl) on admission between patients with early stent occlusion (n=10) and those with binary restenosis other than stent occlusion (n=46).
Central horizontal lines indicate median values. Lower and upper edges of boxes indicate 25th and 75th percentiles, and lower and upper bars indicate 10th and 90th percentiles. SO: stent occlusion.

Serum creatinine level as a common factor in both restenosis and early SO

As shown in Tables 4 and 5, SCr level on admission was an adjusted correlate of both restenosis and early SO. Subsequently, we compared SCr levels between the patients with early SO and those with restenosis but not due to early SO. SCr was significantly higher in the early SO group than in the restenosis group (median 1.05, interquartile range (IQR) 0.80-1.10 vs. median 0.80, IQR 0.70-1.00, p=0.035). (Figure 1).

Discussion

In Japan, the DES use in patients with AMI was contraindicated for a long time in the medical care insurance system by the Ministry of Health, Labor, and Welfare because of its unconfirmed long-term safety, but this restriction was relaxed recently. Thus, AMI has been treated mostly with BMS in the Japanese population.

Many studies [1-7] have shown that uncoated BMS placement is inferior to DES use in terms of reducing target lesion or vessel revascularization during a 1 to 3 year follow-up period after emergency stent implantation at the site of coronary occlusion. No significant difference was observed between BMS and DES in terms of the incidence of death and recurrent AMI [1,2,6,10-12]. On the other hand, accumulating data began to show a higher risk of stent thrombosis in those treated with DES over a 1-year follow-up period [3,6,9]. Kalesan et al. [8] demonstrated in meta-analysis that 1 year after AMI treatment, very late SO is significantly more likely to occur in patients receiving DES than in those with BMS placement. The risk ratio of definite stent thrombosis was 2.10 for DES vs. BMS subsequent to year 1 and interestingly, it was more prominent in trials with industry-

independent funding (risk ratio=3.99). In contrast to restenosis without complete occlusion, once unexpected abrupt coronary closure caused by SO takes place, it may require urgent recanalization because such patients can be complicated with hemodynamic deterioration, leading to death. If such an unexpected event occurs quite a long time after stent implantation when less attention is paid by both cardiologists and patients themselves and antiplatelet agents may be reduced as a result of symptomatic stability, more cautious and closer management must be continued for a longer period of time once patients with AMI are treated with DES, which obviously is accompanied by more financial cost. Thus, it is of importance to elucidate predictors of restenosis and SO in patients receiving BMS as reperfusion therapy for AMI. Selection of patients who can be treated by BMS with a high probability of long-term coronary patency will enable safer and less costly supervision by limiting cases receiving DES, especially beyond 1 year after treatment.

Some studies have reported patient-related clinical factors such as hypertension and diabetes mellitus as predictors of stent restenosis [13,14]. Procedure-related factors such as minimal stent cross-sectional area, stent length, and multiple stenting have been reported as predictors of stent restenosis in many studies [13,15,16] although these factors are influenced by the known lesion-specific predictors of restenosis; vessel diameter <3.5 mm and lesion length [13,14]. In our study, stent size was relevant to restenosis but not to early SO. Consistent with previous reports, we support the idea that BMS can be used for large coronary vessels, whereas in smaller vessels DES might be selected with less frequency of target vessel revascularization.

As shown previously [17] we found an increased restenosis rate when LAD was treated as IRA. We also found that left main coronary artery or LAD involvement was an adjusted predictor of early SO. Namely, AMI, including the anterior region, is associated with both events. Brener et al. [18] reported that the anterior location of AMI was a predictor of death and reinfarction 30 days after primary angioplasty. According to the study by Beinart et al. [19] Killip class >1 on admission was an independent predictor of early SO after coronary stenting during acute coronary syndrome. Interestingly, Smit et al. [20] reported in a previous study that in primary angioplasty for AMI, both LAD as the target vessel and Killip class >1 at presentation were unadjusted predictors of early SO. However, they also showed that after multivariate analysis, the latter was the only independent predictor. Since anterior AMI is more likely to be associated with lower left ventricular function [17] it is likely that LAD involvement promotes early SO through hemodynamic compromise and thereby microcirculatory disturbance of the distal peripheral coronary bed leading to reduced coronary flow reserve. Moreover, since a bigger thrombus can be formed in the IRA of larger caliber, LAD may contain more clot burden to release vasoactive materials such as platelet-derived growth factor, promoting vascular smooth muscle proliferation.

We found that the leukocyte count on admission is another independent predictor of early SO. Since leukocyte increase was shown to be related to microvascular injury [21] and infarct size [22], it is suggested that the increase of white blood cell could serve as a contributing factor to early SO by way of inflammatory reactions producing impaired microvascular perfusion and more necrotic change, leading to left ventricular dysfunction. C-reactive protein on admission, in contrast, was not selected as a predictor here; its elevation follows the leukocyte recruitment and thus, may not be useful as an early-stage surrogate biomarker.

Lastly, we also discovered that the SCr level on admission is an independent predictor of both stent restenosis and early SO. This may

be explained as renal dysfunction is associated with the presence of patient-related predictors of stent restenosis; hypertension and diabetes. In addition, patients complicated with early SO exhibited higher SCr than those with restenosis, although IQR for the former was still in the normal range (Figure 1). Renal insufficiency was reported to increase early, late and very late stent thrombosis [23]. It tended to increase the early SO rate in the setting of ST-elevated AMI treated with DES [24], where renal insufficiency was defined as SCr ≥ 115 micromol/L (=1.3 mg/dl). According to our findings, it is suggested that the higher SCr is on admission, the more occlusive coronary change should be expected and more attention should be paid after primary stenting even if it is not as high as to be regarded as renal dysfunction.

Study Limitations

This is a single-center, retrospective study with a relatively small number of patients, and confirmation by a larger study is warranted. For the same reason, other variables could have been selected as independent predictors of binary stent restenosis or early SO. We did not evaluate later SO here due to its low incidence providing with only weak statistical power in a small population. We found here that stent size is only related to restenosis, not to early SO. In contrast, the anterior location and higher SCr level were correlated with both events. Thus, DES can be used for IRA with reference diameter ≤ 3.0 mm; however, the large amount of intracoronary thrombus in patients with AMI may predispose them to stent malapposition because of stent under sizing or thrombus resolution. This may increase the incidence of later SO. Thus, a randomized study comparing DES and BMS should be performed to elucidate whether the benefit of DES placement in primary reperfusion therapy can be safely maintained for years or whether it is also prone to early SO in those with higher normal or abnormal SCr values, elevated white blood cell counts, or anterior involvement at AMI presentation. The stent type might be cautiously selected considering that very late stent thrombosis is more frequent with DES implantation than BMS over 1 year after the procedure [8]. It could be an option to implant BMS initially as reperfusion therapy with a subsequent angiographic follow-up at 6 months when stent restenosis is most likely to occur [25,26]. DES can be implanted at this stage for more pathologically stabilized in-stent restenosis mainly consisting of neointimal hyperplasia and little thrombotic component.

Conclusion

In patients with AMI treated with BMS, both binary restenosis and early SO were increased by anterior wall involvement and elevation of SCr. Higher SCr may be subject to more occlusive changes even if its value is within the normal range. It is also suggested that in early SO, the inflammatory mechanism reflected by the leukocyte count may be involved while vessel size is not as related as it is to stent restenosis.

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