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【 ORIGINAL ARTICLE 】

Determinants of Insufficient Optimal Medical Therapy after Acute Myocardial Infarction

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Abstract:

Objective Although the importance of evidence-based optimal medical therapy (OMT) after acute myocardial infarction (AMI) has been recognized, the prescription rate of OMT is not sufficiently high in real-word clinical settings. The purpose of this study was to identify the clinical characteristics of AMI patients who did not receive OMT.

Methods The present study was a retrospective study. OMT was defined as the combination of antiplatelet therapy, angiotensin-converting enzyme (ACE) inhibitors/angiotensin II receptor blockers (ARBs), beta-blockers, and statins at the time of hospital discharge. Non-OMT was defined as the lack of either antiplatelet therapy, ACE inhibitors/ARBs, beta-blockers, or statins.

Results A total of 457 AMI patients were included as the final study population, and 98 patients (22.4%) lacked at least 1 OMT medication. The prescription rates of antiplatelet therapy, ACE inhibitors/ARBs, beta-blockers, and statins were 98.7%, 87.5%, 90.4%, and 96.7%, respectively. In the multivariate logistic regression analysis, age [per 1-year increase: odds ratio (OR) 1.033, 95% confidence interval (CI) 1.007-1.059, p=0.014], hemodialysis (vs. no hemodialysis: OR 2.707, 95% CI 1.082-6.774, p=0.033), estimated glomerular filtration rate <30 mL/min/1.73 m^2 without hemodialysis (OR 4.585, 95% CI 1.975-10.644, p<0.001), AMI caused by vasospastic angina (VSA) (vs. no VSA: OR 13.198, 95% CI 1.809-96.260, p=0.011), and asthma (vs. no asthma: OR 7.241, 95% CI 1.716-30.559, p=0.007) were significantly associated with non-OMT, whereas heart rate on admission (per 1-bpm increase: 0.987, 95% CI 0.975-0.999, p=0.033), any PCI (vs. no PCI: OR 0.156, 95% CI 0.066-0.373, p<0.001), and ST-elevation myocardial infarction (STEMI) (vs. NSTEMI: OR 0.384, 95% CI 0.218-0.675, p=0.001) were inversely associated with non-OMT.

Conclusion An advanced age, VSA, bradycardia, asthma, impaired renal function, non-PCI revascularization, and non-ST-elevation myocardial infarction were significantly associated with non-OMT.

Key words: optimal medical therapy, acute myocardial infarction, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers

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Introduction

Evidence-based optimal medical therapy (OMT) after acute myocardial infarction (AMI) consists of antiplatelet therapy, angiotensin-converting enzyme (ACE) inhibitors/angiotensin II receptor blockers (ARBs), beta-blockers, and statins (1, 2). Since non-adherence to OMT after AMI has been shown to be associated with poor clinical outcomes (3, 4), the importance of OMT is emphasized in contemporary clinical guidelines (5, 6). Nevertheless, the prescription rate of OMT is not sufficiently high in real-word clinical settings. The Tokyo CCU network cohort including 4,329 AMI patients reported that approximately 60% and 40% of AMI patients received ACE inhibitors/ARBs and beta-blockers, respectively (7). However, why OMT is not prescribed has not been fully discussed.

The present study explored the clinical characteristics of

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AMI patients who did not receive OMT at the time of hospital discharge.

Materials and Methods

Study patients

The present study was a retrospective and single-center study. From our medical records, we included AMI patients who were treated at our institution between January 2015 and December 2016. The diagnosis of AMI required the following criteria: symptoms consistent with AMI, elevated cardiac enzymes including Troponin I and/or creatinine kinase (at least a two-fold increase from the normal upper limit), and ST-segment elevation or depression in electrocardiograms compatible with AMI (8, 9). Furthermore, diagnostic ST-segment elevation was defined as new ST elevation at the J point in at least 2 contiguous leads of 2 mm (0.2 mV); all others were defined as not having ST-segment elevation (10, 11). The exclusion criteria were no coronary angiography, in-hospital death, and second or beyond AMI during the study period. OMT was defined as the combination of antiplatelet therapy (at least single), ACE inhibitors/ARBs, beta-blockers, and statins at the time of hospital discharge. Non-OMT was defined as the lack of either antiplatelet therapy, ACE inhibitors/ARBs, beta-blockers, or statins at the time of hospital discharge. We divided the study patients into OMT and non-OMT groups.

This study was approved by the institutional review board and written informed consent was waived because of the retrospective study design. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Definition

Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or medical treatment for hypertension (9). Dyslipidemia was defined as a total cholesterol level ≥220 mg/dL or a low-density lipoprotein cholesterol level ≥140 mg/dL or medical treatment for dyslipidemia (9). Diabetes mellitus was defined as a hemoglobin A1c level ≥6.5% (as NGSP value) or medical treatment for diabetes mellitus (12). We also calculated the estimated glomerular filtration rate (eGFR) from the serum creatinine levels, age, weight, and gender using the following formula: $eGFR=194\times Cr^{-1.094}\times age^{-0.287}$ (male), $eGFR=194\times Cr^{-1.094}\times age^{-0.287}\times 0.739$ (female) (13). An impaired renal function was defined as an eGFR <60 mL/min/1.73 m^2 (12). Shock was defined as systolic blood pressure ≤90 mmHg, need for vasopressors to maintain blood pressure, need for percutaneous mechanical support, or attempted cardiopulmonary resuscitation.

Statistical analyses

Data are shown as the mean±standard deviation or percentage. Categorical variables are presented as numbers (percentages) and compared using Pearson's χ^2 test. The Kolmogorov-Smirnov test was performed to determine if the continuous variables were normally distributed. Normally distributed continuous variables were compared between the groups using the unpaired Student's *t*-test. Otherwise, continuous variables were compared using the Mann-Whitney U test. Multivariate logistic regression analyses were performed to identify the determinants of non-OMT. In this model, the non-OMT group was used as the dependent variable. The multivariate logistic regression model included covariates found to have significant differences between the OMT and non-OMT groups (defined as $p<0.05$). The odds ratios (ORs) and 95% confidence intervals (CIs) were also calculated. A p value <0.05 was considered statistically significant. We analyzed all data using the SPSS software program, ver. 24, for Windows (SPSS, Chicago, USA).

Results

During the study period, a total of 504 AMI patients were treated at our institution. Of those, 457 AMI patients were included as the final study population and divided into the OMT group (n=359) and non-OMT group (n=98) (Figure). Table 1 shows the comparison of the background characteristics between the two groups. The mean age was significantly older in the non-OMT group (74±12 years old) than in the OMT group (68±12 years old) (p<0.001). The eGFR was significantly lower in the non-OMT group (52.3±31.7 mL/min/1.73 m^2) than in the OMT group (65.9±26.5 mL/min/1.73 m^2) (p<0.001). The heart rate on admission was significantly lower in the non-OMT group (72±24 bpm) than in the OMT group (80±23 bpm) (p=0.001). The prevalence of ST-elevation myocardial infarction (STEMI) was significantly lower in the non-OMT group (40.8%) than in the OMT group (65.5%) (p<0.001). The prevalence of AMI caused by vasospastic angina (VSA) was significantly greater in the non-OMT group (12.2%) than in the OMT group (0.6%) (p<0.001). Hemoglobin levels on admission was significantly lower in the non-OMT group (12.4±2.2 g/dL) than in the OMT group (13.5±1.9 g/dL) (p<0.001). The prevalence of a history of malignancy was significantly greater in the non-OMT group (21.4%) than in the OMT group (13.4%) (p=0.048). Blood transfusion during admission was more frequently performed in the non-OMT group (34.7%) than in the OMT group (8.9%) (p<0.001).

Table 2 shows the comparison of the lesion and therapeutic characteristics between the OMT and non-OMT groups. Percutaneous coronary intervention (PCI) was more frequently selected in the OMT group (95.5%) than in the non-OMT group (71.4%). Peak creatinine kinase (CK) and creatinine kinase-myocardial band (CK-MB) levels were significantly greater in the OMT group than in the non-OMT group. In the overall study population, the prescription rates of antiplatelet therapy, ACE inhibitors/ARBs, beta-blockers, and statins were 98.7%, 87.5%, 90.4%, and 96.7%, respectively. In addition, we compared the clinical characteristics between patients who did and did not receive antiplatelet

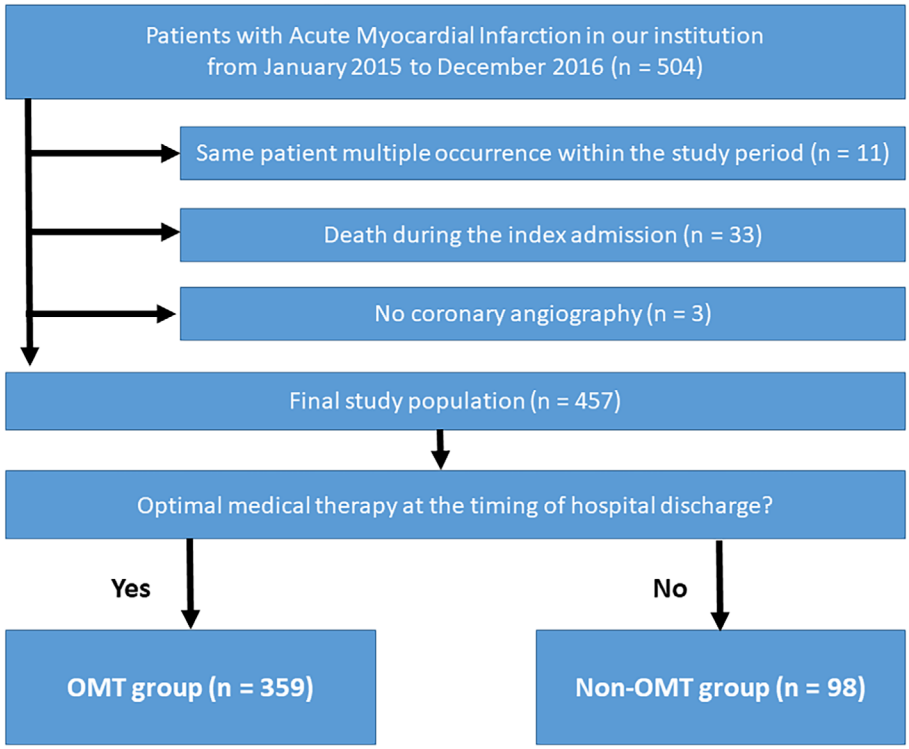

Figure. **Patient flowchart.**

therapy (Supplementary material 1), between patients who did and did not receive ACE inhibitors/ARBs (Supplementary material 2), between patients who did and did not receive beta-blockers (Supplementary material 3), and between patients who did and did not receive statins (Supplementary material 4).

Table 3 shows the results of a multivariate logistic regression analysis to identify the determinants of non-OMT group. Age (per 1-year increase: OR 1.033, 95% CI 1.007-1.059, p=0.014), hemodialysis (vs. no hemodialysis: OR 2.707, 95% CI 1.082-6.774, p=0.033), eGFR<30 mL/min/1.73 m^2 without hemodialysis (OR 4.585, 95% CI 1.975-10.644, p<0.001), AMI caused by VSA (vs. no VSA: OR 13.198, 95% CI 1.809-96.260, p=0.011), and asthma (vs. no asthma: OR 7.241, 95% CI 1.716-30.559, p=0.007) were significantly associated with non-OMT, whereas heart rate on admission (per 1-bpm increase: 0.987, 95% CI 0.975-0.999, p=0.033), any PCI (vs. no PCI: OR 0.156, 95% CI 0.066-0.373, p<0.001), and STEMI (vs. NSTEMI: OR 0.384, 95% CI 0.218-0.675, p=0.001) were inversely associated with non-OMT.

Discussion

A total of 457 AMI patients were included in the present study and divided into 359 patients (78.6%) who had sufficient OMT and 98 (22.4%) who did not have sufficient OMT at the time of hospital discharge. While the prescription rate of each OMT medication was reasonably high (87.5-98.7%), more than 20% of study patients lacked at least 1 OMT medication. Aging, AMI caused by VSA, asthma, and an impaired renal function were significantly associated with non-OMT, whereas heart rate, any PCI, and STEMI were inversely associated with non-OMT. It may be important to recognize the above factors as risk factors for insufficient OMT.

In the present study, aging was associated with non-OMT. Since we prescribe OMT for better clinical outcomes in AMI patients, we might hesitate to prescribe OMT for the very elderly. Yan et al. also reported that advanced age was a negative independent predictor of OMT (14). The association between AMI caused by VSA and non-OMT may be explained by the association between VSA and beta-blockers. Although no studies have proven a cause-and-effect relationship between beta-blockers and VSA, several case reports suggest that beta-blockers may provoke coronary spasm (15, 16). The administration of beta-blockers alone for VSA was reported to be class III in clinical guidelines (17). Therefore, we tended to avoid administering beta-blockers to patients with AMI caused by VSA without coronary artery stenosis, especially when the left ventricular function was preserved. We might also avoid introducing antiplatelet therapy to patients with AMI caused by VSA without coronary artery stenosis. The association between asthma and non-OMT may be explained by the association between asthma and beta-blockers, as beta-blockers are generally contraindicated in patients with asthma.

The association between the heart rate and non-OMT may be explained by the non-administration of beta-blockers. Generally, we did not administer beta-blockers to patients with bradycardia (<50 bpm). In fact, a recent Japanese multicenter registry reported that the introduction of beta-

Table 1. Comparison of Patient Characteristics between the OMT and Non-OMT Groups.

Patient characteristics	All (n=457)	OMT group (n=359)	Non-OMT group (n=98)	p value
Age, years	70±12	68±12	74±12	<0.001
Male sex, n (%)	343 (75.1)	269 (74.9)	74 (75.5)	0.906
Hypertension, n (%)	385 (84.2)	307 (85.5)	78 (79.6)	0.154
Hyperlipidemia, n (%)	318 (69.6)	254 (70.8)	64 (65.3)	0.299
Diabetes mellitus, n (%)	203 (44.4)	161 (44.8)	42 (42.9)	0.725
Chronic obstructive pulmonary disease, n (%)	14 (3.1)	11 (3.1)	3 (3.1)	1.000
Asthma, n (%)	12 (2.6)	5 (1.4)	7 (7.1)	0.005
Chronic kidney disease, n (%)	197 (43.1)	139 (38.7)	58 (59.2)	<0.001
Serum creatinine, mg/dL	1.6±4.4	1.5±4.8	2.1±2.6	<0.001
eGFR, mL/min/1.73 m^2	62.9±28.2	65.9±26.5	52.3±31.7	<0.001
Hemodialysis, n (%)	30 (6.6)	17 (4.7)	13 (13.3)	0.003
Hemoglobin levels on admission, g/dL	13.3±2.0	13.5±1.9	12.4±2.2	<0.001
Potassium levels (mEq/L)	4.2±0.6	4.2±0.5	4.3±0.6	0.095
Atrial fibrillation, n (%)	67 (14.7)	47 (13.1)	20 (20.4)	0.070
Current smoking, n (%)	144 (31.5)	120 (33.4)	24 (24.5)	0.091
History of malignancy, n (%)	69 (15.1)	48 (13.4)	21 (21.4)	0.048
Previous PCI, n (%)	90 (19.7)	64 (17.8)	26 (26.5)	0.055
Previous CABG, n (%)	17 (3.7)	10 (2.8)	7 (7.1)	0.065
Previous myocardial infarction, n (%)	75 (16.4)	55 (15.3)	20 (20.4)	0.228
STEMI, n (%)	275 (60.2)	235 (65.5)	40 (40.8)	<0.001
NSTEMI, n (%)	182 (39.8)	124 (34.5)	58 (59.2)	<0.001
AMI caused by vasospastic angina, n (%)	14 (3.1)	2 (0.6)	12 (12.2)	<0.001
Killip 1 or 2, n (%)	369 (80.7)	294 (81.9)	75 (76.5)	0.233
Systolic blood pressure on admission, mmHg	138±33	140±33	130±35	0.021
Diastolic blood pressure on admission, mmHg	79±21	80±21	72±22	0.001
Heart rate on admission, bpm	79±23	80±23	72±24	0.001
Shock status, n (%)	62 (13.6)	45 (12.5)	17 (17.3)	0.218
Cardio-pulmonary arrest, n (%)	21 (4.6)	15 (4.2)	6 (6.1)	0.417
Catecholamine use before coronary angiography, n (%)	44 (9.6)	30 (8.4)	14 (14.3)	0.078
Use of intra-aortic balloon pumping, n (%)	61 (13.3)	44 (12.3)	17 (17.3)	0.189
Use of veno-arterial extra-corporeal membrane oxygenation, n (%)	11 (2.4)	6 (1.7)	5 (5.1)	0.063
Blood transfusion during hospitalization, n (%)	66 (14.4)	32 (8.9)	34 (34.7)	<0.001

Categorical variables were compared using the Pearson χ^2 test. Normally distributed continuous variables were compared using the unpaired Student's t test. Non-normally distributed continuous variables were compared using the Mann-Whitney U test.

OMT: optimal medical therapy, eGFR: estimate glomerular filtration rate, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft surgery, STEMI: ST-segment elevation myocardial infarction, NSTEMI: non-ST-segment elevation myocardial infarction, AMI: acute myocardial infarction

blockers was associated with poor clinical outcomes in AMI patients whose admission heart rate was <50 bpm (18). The association between an impaired renal function and non-OMT may be explained by the non-administration of ACE inhibitors/ARBs. While we understand the importance of administering ACE inhibitors/ARBs to patients with an impaired renal function (19), we might hesitate to administer ACE inhibitors/ARBs to patients with an impaired renal function, as the use of ACE inhibitors/ARBs during coronary angiography may increase the incidence of contrast-induced acute kidney injury (20). Furthermore, patients with hemodialysis might have hypotension during hemodialysis.

PCI for revascularization was inversely associated with non-OMT, suggesting that AMI patients who underwent CABG for revascularization might not receive OMT. In fact, CABG during hospitalization is reported to be a risk factor for non-OMT (14). One possible explanation for this is that AMI patients who underwent CABG were managed by cardiovascular surgeons during hospitalization. Unlike cardiovascular physicians, cardiovascular surgeons might not administer OMT to patients who underwent CABG. Furthermore, STEMI was inversely associated with non-OMT, indicating that NSTEMI was associated with non-OMT. Because NSTEMI patients included those whose troponin I levels were significantly elevated while their CK levels were normal, the left ventricular systolic function was preserved in some NSTEMI patients. While the clinical guidelines strongly recommend administering ACE inhibitors to NSTEMI patients with a left ventricular ejection fraction < 40% (21), the significance of ACE inhibitors for NSTEMI patients with a normal left ventricular ejection fraction has not been established. Therefore, we might not administer

Table 2. Comparison of Lesion and Therapeutic Characteristics between the OMT and Non-OMT Groups.

	All (n=457)	OMT group (n=359)	Non-OMT group (n=98)	p value
Infarct related artery				0.876
Left main-left anterior descending artery, n (%)	237 (51.9)	188 (52.4)	49 (50.0)	
Left circumflex artery, n (%)	58 (12.7)	47 (13.1)	11 (11.2)	
Right coronary artery, n (%)	158 (34.6)	121 (33.7)	37 (37.8)	
Bypass graft vessel, n (%)	4 (0.9)	3 (0.8)	1 (1.0)	
Number of narrowed coronary arteries				0.445
1	246 (53.9)	190 (53.1)	56 (57.1)	
2	135 (29.6)	111 (31.0)	24 (24.5)	
3	75 (16.4)	57 (15.9)	18 (18.4)	
Type of revascularization				<0.001
PCI only, n (%)	411 (89.9)	343 (95.5)	68 (69.4)	
CABG, n (%)	17 (3.7)	6 (1.7)	11 (11.2)	
PCI and CABG, n (%)	2 (0.4)	0 (0.0)	2 (2.0)	
Medication and others, n (%)	27 (5.9)	10 (2.8)	17 (17.3)	
Any PCI, n (%)	413 (90.4)	343 (95.5)	70 (71.4)	<0.001
Type of PCI (n=413)				0.053
Drug-eluting stent use, n (%)	369 (89.3)	312 (91.0)	57 (81.4)	
Bare metal stent use, n (%)	18 (4.4)	12 (3.5)	6 (8.6)	
Others, n (%)	26 (6.3)	19 (5.5)	7 (10.0)	
Final TIMI-3 flow, n (%)	424 (92.8)	333 (92.8)	91 (92.9)	0.973
Outcomes				
Peak creatinine kinase level, mU/mL	1,468±2,336	1,622±2,536	902±1,226	0.001
Peak creatinine kinase-myocardial band level, mU/mL	128±175	144±186	67±110	<0.001
Left ventricular ejection fraction, (%)	55.0±13.8	55.5±13.4	53.0±13.2	0.077
Length of hospital stay, days	11±11	10±8	16±16	0.002
Medication at discharge				
Antiplatelet therapy (at least single)	451 (98.7)	359 (100)	92 (93.9)	-
ACE inhibitors/ARBs	400 (87.5)	359 (100)	41 (41.8)	-
Beta-blockers	413 (90.4)	359 (100)	54 (55.1)	-
Statins	442 (96.7)	359 (100)	83 (84.7)	-

Categorical variables were compared using the Pearson χ^2 test. Normally distributed continuous variables were compared using the unpaired Student's t test. Non-normally distributed continuous variables were compared using the Mann-Whitney U test. OMT: optimal medical therapy, TIMI: thrombolysis in myocardial infarction, ACE: angiotensin converting enzyme, ARBs: angiotensin II receptor blockers

Table 3. Multivariate Logistic Regression Analysis to Identify the Determinants of Non-OMT Group.

Variables	Multivariate logistic regression analysis		
	Odds ratio	95% confidence interval	p value
Age (per 1 year increase)	1.033	1.007-1.059	0.014
Systolic blood pressure on admission (per 1 mmHg increase)	0.994	0.986-1.003	0.202
Heart rate on admission (per 1 bpm increase)	0.987	0.975-0.999	0.033
Hemoglobin levels on admission (per 1 g/dL increase)	0.885	0.756-1.036	0.129
Hemodialysis (vs. non-hemodialysis)	2.707	1.082-6.774	0.033
eGFR<30 mL/min/1.73 m^2 without hemodialysis	4.585	1.975-10.644	<0.001
Any PCI (vs. no PCI)	0.156	0.066-0.373	<0.001
AMI caused by Vasospastic angina (vs. no vasospastic angina)	13.198	1.809-96.260	0.011
STEMI (vs. NSTEMI)	0.384	0.218-0.675	0.001
Asthma (vs. no asthma)	7.241	1.716-30.559	0.007
History of malignancy (vs. no malignancy)	1.684	0.843-3.362	0.140

OMT: optimal medical therapy, PCI: percutaneous coronary intervention, eGFR: estimate glomerular filtration rate, AMI: acute myocardial infarction, STEMI: ST-segment elevation myocardial infarction, NSTEMI: non-ST-segment elevation myocardial infarction

ACE inhibitors/ARBs to NSTEMI patients without a reduced ejection fraction.

The clinical implications of the present study should be noted. As we discussed above, some reasons for non-OMT

might be unavoidable, especially for patients with AMI caused by VSA. However, there is likely room for improvement, especially for patients with an advanced age. Since Japan is becoming a super-aged society (22), secondary prevention for elderly patients should be prioritized, not only for achieving better clinical outcomes but also for reducing medical expenses. However, whether or not OMT is equally effective for the frail elderly, especially for the bedridden elderly, is unclear. A comprehensive discussion regarding OMT for the elderly is warranted, as healthcare resources will be considerably limited in a super-aged society (22).

Study limitations

Several limitations associated with the present study warrant mention. Because this study was a single-center retrospective observational study, there was a risk of selection bias. Our prescription rates of ACE inhibitors/ARBs (87.5%) and beta blockers (90.4%) were considerably higher than the prescription rates of ACE inhibitors/ARBs (60%) and beta blockers (40%) in contemporary Japanese AMI registries (7), partly because we introduced a novel acute myocardial infarction risk stratification system (nARS) in April 2015 (23, 24). In the nARS, the early introduction of ACE inhibitors/ARBs was strongly encouraged by our daily conference (23). Therefore, the reasons for non-OMT in our study may be different from those in contemporary Japanese AMI registries. The present study focused on the OMT at the time of hospital discharge. We were unable to conduct monitoring to see whether or not OMT was maintained after hospital discharge. Finally, because we did not routinely check the low-density lipoprotein cholesterol levels following statin administration during hospitalization, the statin dose might not have been titrated at the time of hospital discharge.

Conclusion

Although the prescription rate of each OMT medication was reasonably high (87.5-98.7%), 22.4% of AMI patients lacked at least 1 OMT medication. An advanced age, VSA, bradycardia, asthma, impaired renal function, non-PCI revascularization, and NSTEMI were significantly associated with non-OMT.

Author's disclosure of potential Conflicts of Interest (COI).
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