Evaluation of optimal medical therapy in acute myocardial infarction patients with prior stroke

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complications in a Multicenter registry of patients discharged with diagnosis of Acute
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Abstract

Background: Treatment of acute myocardial infarction (AMI) patients with prior stroke is a common clinical dilemma. Currently, the application of optimal medical therapy (OMT) and its impact on clinical outcomes are not clear in this patient population.

Methods: We retrieved 765 AMI patients with prior stroke who underwent percutaneous coronary intervention (PCI) during the index hospitalization from the international multicenter BleeMACS registry. All of the subjects were divided into two groups based on the prescription they were given prior to discharge. Baseline characteristics and procedural variables were compared between the OMT and non-OMT groups. Mortality, re-AMI, major adverse cardiovascular events (MACE), and bleeding were followed-up for 1 year.

Results: Approximately 5% of all patients presenting with AMI were admitted to the hospital for ischemic stroke. Although the prescription rate of each OMT medication was reasonably high (73.3%–97.3%), 47.7% lacked at least one OMT medication. Patients receiving OMT showed a significantly decreased occurrence of mortality (4.5% vs 15.1%, $p < 0.001$), re-AMI (4.2% vs 9.3%, $p = 0.004$), and the composite endpoint of death/re-AMI (8.6% vs 20.5%, $p < 0.001$) compared to those without OMT. No significant difference was observed between the groups regarding bleeding. After adjusting for confounding factors, OMT was the independent protective factor of 1-year mortality, while age was the independent risk factors.

Conclusions: OMT at discharge was associated with a significantly lower 1-year mortality of patients with AMI and prior stroke in clinical practice. However, OMT was provided to just half of the eligible patients, leaving room for substantial improvement.

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Introduction

Atherosclerosis is a systemic disease that often occurs at more than one vascular site, and thus should be considered an integral disease. The presence of more than one affected vascular bed, including any combination of the following: coronary artery disease (CAD), cerebrovascular disease (CVD), and peripheral arterial disease (PAD), has been termed polyvascular disease (PolyVD).[1]

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Patients with PolyVD have a higher risk of cardiovascular events and worse prognosis.[2] Any acute atherosclerotic event increases the risk for another in the same or different vascular bed.[3] CAD complicated with CVD is very common in clinical work. One-third of patients with ischemic stroke with no cardiovascular history have more than 50% coronary stenosis, and 3% are at risk of developing myocardial infarction (MI) within a year.[4] Moreover, the leading cause of mortality following an acute ischemic stroke is MI.[5,6] Although interventional procedures have greatly developed in both areas, the prognosis still remains unsatisfactory.

Guidelines recommend optimal medical therapy in patients with ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI) to improve the prognosis. This is defined as a combination of aspirin, any P2Y12 inhibitor, statin, beta-blocker, and angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB).[7,8] Despite being recommended by the guidelines, the optimal evidence-based medical therapy is prescribed at suboptimal rates, particularly in patients with high-risk features.[9] Concerns regarding an increased risk of bleeding or recurrent stroke in patients with a stroke history might make this situation even worse. Since the related data are limited, we aim to evaluate the application of OMT and its impact on the prognosis in acute MI (AMI) patients with prior stroke.

Methods

Registry design
A sub-analysis was performed using the database of Bleeding complications in a Multicenter registry of patients discharged with diagnosis of Acute Coronary Syndrome (BleeMACS) registry.[10] BleeMACS is an investigator-initiated international multicenter registry that retrospectively enrolled 15,401 consecutive acute coronary syndrome (ACS) patients who underwent percutaneous coronary intervention (PCI) during the index hospitalization. Patients were enrolled from 15 centers in 10 countries from around the world including Canada, Brazil, Germany, Poland, Netherlands, Spain, Italy, Greece, China, and Japan. The BleeMACS webpage (http://bleemacs.wix.com/registry) as well as clinicaltrials.gov (NCT02466854) could be searched for details of the registry.

Ethics and consent statements
This registry was formed by the fusion of several ACS registries, each with the approval of its local ethics committee (2015009X). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the institution's human research committee. As the retrospective nature of our study, written informed consent was waived by the ethics committee.

Patient selection
The AMI patients, including STEMI and NSTEMI with prior stroke, were retrieved from the BleeMACS registry. STEMI was diagnosed if patients had ongoing chest pain and ST-segment elevation > 2 mm in two contiguous precordial leads, > 1 mm in two contiguous limb leads, or a new left bundle branch block (LBBB) on the electrocardiogram (ECG). NSTEMI was defined as elevated cardiac troponin without notable ECG-changes. Stroke referred to prior admission due to ischemic stroke.

All of the patients were divided into two groups based on the prescription received upon discharge. Patients receiving a combination of aspirin, any P2Y12 inhibitor (clopidogrel, prasugrel, or ticagrelor), statin, beta-blocker, and ACEI or ARB were assigned to the OMT group, and others were assigned to the non-OMT group. All patients were followed-up for at least 12 months.

Database management
The clinical and interventional data were recorded, including traditional cardiovascular risk factors, type of AMI, comorbidities, arterial access, and treatment strategy. Data of each center were transferred to the BleeMACS coordinating center at the cardiology department in Santiago de Compostela for further examination and verification. The final database consisting of 61 items was developed covering baseline characteristics and clinical outcomes. Centers that provided forms with more than 5% missing data were not included in the final BleeMACS database.

Endpoints
The primary endpoint was all-cause mortality at 1-year follow-up. The secondary endpoints

included re-AMI and major adverse cardiovascular event (MACE) (a composite of death/MI) at 1 year of follow-up. Bleeding events were also followed-up as a safety indicator.

Sample size calculation and justification
The rule we used for quickly determining sample size is at least 10 cases per variable in this study, in order to obtain results that are likely to be both true and clinically useful.

Statistical analysis
Continuous variables are expressed as means (standard deviations (SD)) and the medium (interquartile range (IQR)) for normally and non-normally distributed data respectively, and the categorical variables are expressed as counts and percentages (%). A comparison of the baseline characteristics between the two groups was performed using a Student *t* test for continuous variables and a Pearson chi-square test or Fisher's exact test for categorical variables. Kaplan-Meier analysis was performed to compare the outcomes between groups. Log-rank test was adopted to compare rates of the endpoints. Cox regression analysis was performed to evaluate the predictive ability of the parameters of interest. Given differences in the baseline characteristics between the two groups, the propensity score matching (PSM) was used to generate two matching cohorts of patients receiving OMT or not. 1:1 PSM was performed using the nearest-neighbor method with a caliper of 0.03. All of the clinical variables (age, sex, type of AMI, hypertension, diabetes mellitus, dyslipidemia, previous AMI, previous PCI, previous coronary artery bypass graft (CABG), congestive heart failure, PAD, chronic kidney disease, malignancy, previous bleeding, and hemoglobin level) as well as procedural data (thrombolysis, procedural access, multi-vessel disease, stent type, and complete revascularization) were incorporated in the analysis. All analyses were performed using SPSS 21.0 (IBM Corp., Armonk, NY, USA). A two-sided *p*-value of <0.05 was considered significant.

Results
A total of 15,401 patients with ACS were included into the BleeMACS registry (Figure 1). Among the 765 (5.0%) patients with AMI and prior

stroke, 400 (52.3%) received OMT upon hospital discharge. More specifically, 744 (97.3%) received aspirin, 723 (94.5%) P2Y12 inhibitor, 687 (89.8%) statin, 561 (73.3%) ACEI/ARB, and 582 (76.1%) beta-blocker. No difference in the OMT prescription was observed between patients diagnosed with STEMI or NSTEMI (53.7% vs 49.6%, $p = 0.286$).

Baseline features
Briefly, most of the baseline characteristics were comparable between the OMT and non-OMT groups, as shown in Table 1. However, patients in the non-OMT group were much older, had more previous bleeding events, presented with higher creatinine levels upon admission, and fewer had used a drug-eluting stent (DES).

Endpoints
OMT was significantly related to improved survival after the 1-year follow-up (Figure 2). Patients receiving OMT showed a significantly decreased occurrence of mortality (4.5% vs 15.1%, $p < 0.001$), re-AMI (4.2% vs 9.3%, $p = 0.004$), and the composite endpoint of death/re-AMI (8.6% vs 20.5%, $p < 0.001$) compared to those without OMT. No significant difference was observed between groups regarding bleeding (5.3% vs 6.3%, $p = 0.380$).

After PSM, a new dataset including 315 non-OMT and 315 OMT patients with similar baseline demographics and clinical and procedural characteristics was generated (Table 1). Standardized differences $\leqslant 0.1$ for all covariates in propensity score matching indicated balance between treatment and control groups. The advantages of OMT over the one-year clinical outcomes were confirmed in this cohort. The outcomes included death (5.1% vs 14.0%, $p < 0.001$), re-AMI (4.9% vs 9.7%, $p = 0.021$), and MACE (9.8% vs 18.9%, $p = 0.001$) (Figure 2). No difference was observed regarding bleeding (5.7% vs 6.7%, $p = 0.469$).

Multivariable Cox regression analysis using all patients ($n = 765$) revealed that OMT was an independent protective factor of the one-year survival in the overall population (HR: 0.31, 95% CI: 0.18–0.53, $p < 0.001$) and the STEMI subset (HR: 0.23, 95% CI: 0.11–0.46, $p < 0.001$).
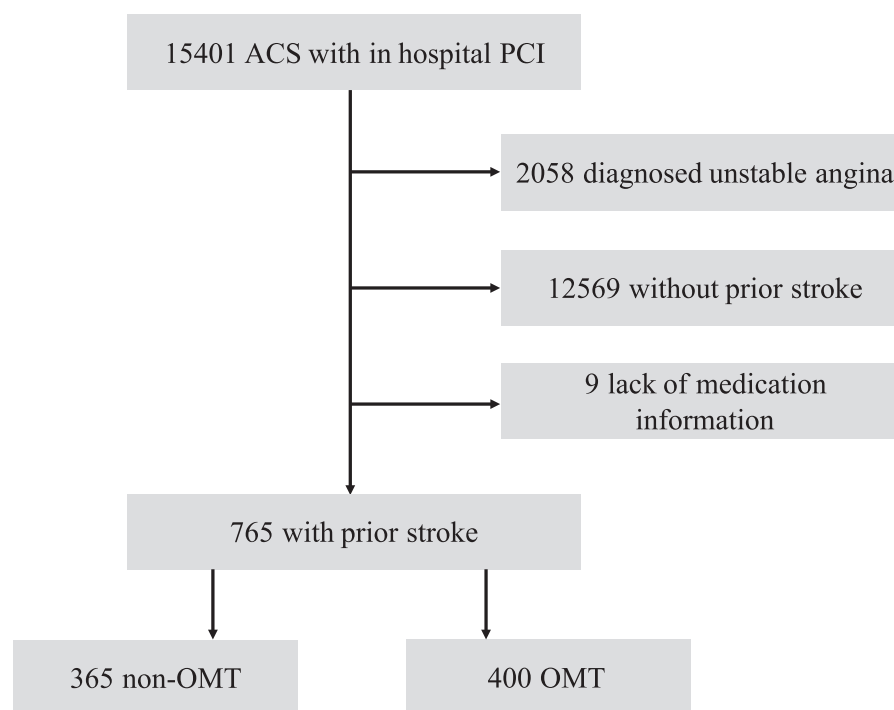
Figure 1. The flow chart of patient selection process.
ACS, acute coronary syndrome; OMT, optimal medical therapy; PCI, percutaneous coronary intervention.

Hence, OMT at discharge could produce a 69% reduction of all-cause mortality risk in AMI patients with prior stroke. Age was a risk factor in the overall population (HR: 3.04, 95% CI: 1.46–6.36, $p = 0.003$) and the STEMI subset (HR: 2.36, 95% CI: 1.09–5.07, $p = 0.029$), as shown in Table 2. Creatinine over 2.5 mg/dl was a risk factor for NSTEMI patients (HR: 3.46, 95% CI: 1.01–11.92, $p = 0.049$).

The subgroup analysis of the primary endpoint of all-cause death across various patient populations was consistent across most subgroups (Table 3).

Discussion

The present study, based on the international BleeMACS registry, assessed the application of OMT and its impact on the 1-year outcomes in patients with AMI and prior stroke. A certain proportion of AMI patients were admitted to the hospital for ischemic stroke (5%). OMT was associated with improvements in the one-year outcomes, including mortality, re-AMI, and MACE in this patient population, without bleeding risk. Even though the prescription rate of each

OMT medication was reasonably high (73.3%–97.3%), 47.7% of AMI patients lacked at least one OMT medication.

Haraguchi *et al.* enrolled 457 AMI patients, and 77.6% received OMT. They demonstrated advanced age, impaired renal function, vasospastic angina, bradycardia, asthma, non-PCI revascularization, and NSTEMI that were significantly associated with non-OMT.[11] Yan *et al.* examined the use of medications at discharge among 5833 patients from the Canadian ACS I and ACS II Registries. Advanced age, female sex, prior heart failure, renal function, and coronary bypass surgery were shown to be negative independent predictors of OMT.[12] Similar to the above studies, we demonstrated in this study that patients receiving OMT were likely to be much younger, with less bleeding history, lower creatinine levels and more DES implantations. After adjusting for confounding factors, OMT was an independent protective factor of 1-year mortality, while age was risk factors.

Age is an important determinant of outcomes for AMI patients. After accounting for other factors,

Table 1. Baseline demographic, clinical and procedural characteristics.

	Overall (n=765)	Before propensity				After propensity			
		Non-OMT (n=365)	OMT (n=400)	pValue	SMD	Non-OMT (n=315)	OMT (n=315)	pValue	SMD
Age, y	72.7 (64.0–79.4)	75.0 (65.0–80.7)	70.0 (63.3–78.0)	<0.001	−0.27	72.1 (65.0–80.0)	71.3 (65.0–79.5)	0.376	−0.07
Male, n (%)	549 (71.8)	259 (71.0)	290 (72.5)	0.636	−0.02	217 (68.9)	226 (71.7)	0.433	−0.07
Type of AMI									
STEMI, n (%)	503 (65.8)	233 (63.8)	270 (67.5)	0.286	0.09	205 (65.1)	199 (63.2)	0.618	−0.04
NSTEMI, n (%)	262 (34.2)	132 (36.2)	130 (32.5)	0.286	−0.09	110 (34.9)	116 (36.8)	0.618	0.04
Concomitant risk factors									
Hypertension, n (%)	552 (72.2)	259 (71.0)	293 (73.3)	0.480	0.05	219 (69.5)	230 (73.0)	0.333	0.07
DM, n (%)	257 (33.6)	122 (33.4)	135 (33.8)	0.924	0.02	103 (32.7)	110 (34.9)	0.556	0.04
Dyslipidemia, n (%)	423 (55.3)	194 (53.2)	229 (57.3)	0.255	0.08	170 (54.0)	179 (56.8)	0.471	0.06
Concomitant disease									
Previous AMI, n (%)	116 (15.2)	57 (15.6)	59 (14.8)	0.739	−0.03	50 (15.9)	48 (15.2)	0.826	−0.03
Previous PCI, n (%)	97 (12.7)	44 (12.1)	53 (13.3)	0.620	0.03	37 (11.7)	43 (13.7)	0.473	0.06
Previous CABG, n (%)	32 (4.2)	12 (3.3)	20 (5.0)	0.237	0.09	9 (2.9)	17 (5.4)	0.109	0.09
CHF, n (%)	50 (7.6)	29 (9.4)	21 (5.9)	0.093	−0.13	22 (8.3)	16 (5.8)	0.255	−0.09
PAD, n (%)	117 (15.3)	57 (15.6)	60 (15.0)	0.813	−0.03	48 (15.2)	53 (16.8)	0.587	0.05
CKD, n (%)	17 (6.6)	9 (6.3)	8 (7.0)	1.000	0.04	8 (6.5)	8 (8.2)	0.621	0.04
Malignancy, n (%)	74 (9.7)	41 (11.2)	33 (8.3)	0.163	−0.11	35 (11.1)	28 (8.9)	0.353	−0.07
Previous bleeding, n (%)	80 (10.6)	47 (13.0)	33 (8.3)	0.035	−0.18	31 (9.8)	30 (9.5)	0.893	0.00

(Continued)

Table 1. (Continued)

	Overall (n = 765)	Before propensity				After propensity			
		Non-OMT (n = 365)	OMT (n = 400)	pValue	SMD	Non-OMT (n = 315)	OMT (n = 315)	pValue	SMD
LVEF (%)	51.0 (40.0–60.0)	51.5 (40.0–60.0)	50.5 (42.0–60.0)	0.947	0.01	50.7 (40.0–60.0)	50.3 (42.0–60.0)	0.732	-0.03
Hemoglobin at admission, mg/dl	13.5 (12.1–14.7)	13.5 (12.0–14.6)	13.6 (12.2–14.8)	0.293	0.08	13.1 (11.8–14.4)	13.3 (12.0–14.7)	0.291	0.09
Creatinine at admission, mg/dl	1.0 (0.8–1.1)	1.0 (0.8–1.2)	0.9 (0.8–1.1)	0.001	-0.40	1.1 (0.8–1.2)	1.0 (0.8–1.1)	0.680	-0.03
Procedural features									
Thrombolysis, n (%)	8 (1.0)	1 (0.3)	7 (1.8)	0.099	0.10	0 (0)	5 (1.6)	0.072	0.10
Femoral access, n (%)	472 (67.3)	228 (66.7)	244 (68.0)	0.714	0.02	198 (66.4)	186 (66.2)	0.949	0.00
Multi-vessel disease, n (%)	352 (58.8)	169 (60.6)	183 (57.2)	0.401	-0.08	143 (59.1)	152 (60.3)	0.781	0.02
DES, n (%)	284 (37.1)	111 (30.4)	173 (43.3)	<0.001	0.26	106 (33.7)	116 (36.8)	0.404	0.06
Complete revascularization, n (%)	285 (46.8)	115 (42.8)	170 (50.0)	0.075	0.14	100 (44.2)	127 (47.4)	0.485	0.06

AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; CHF, congestive heart failure; CKD, chronic kidney disease; DES, drug eluting stents; DM, diabetes mellitus; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-elevation myocardial infarction; OMT, optimal medical therapy; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; SMD, standardized mean difference; STEMI, ST-elevation myocardial infarction.
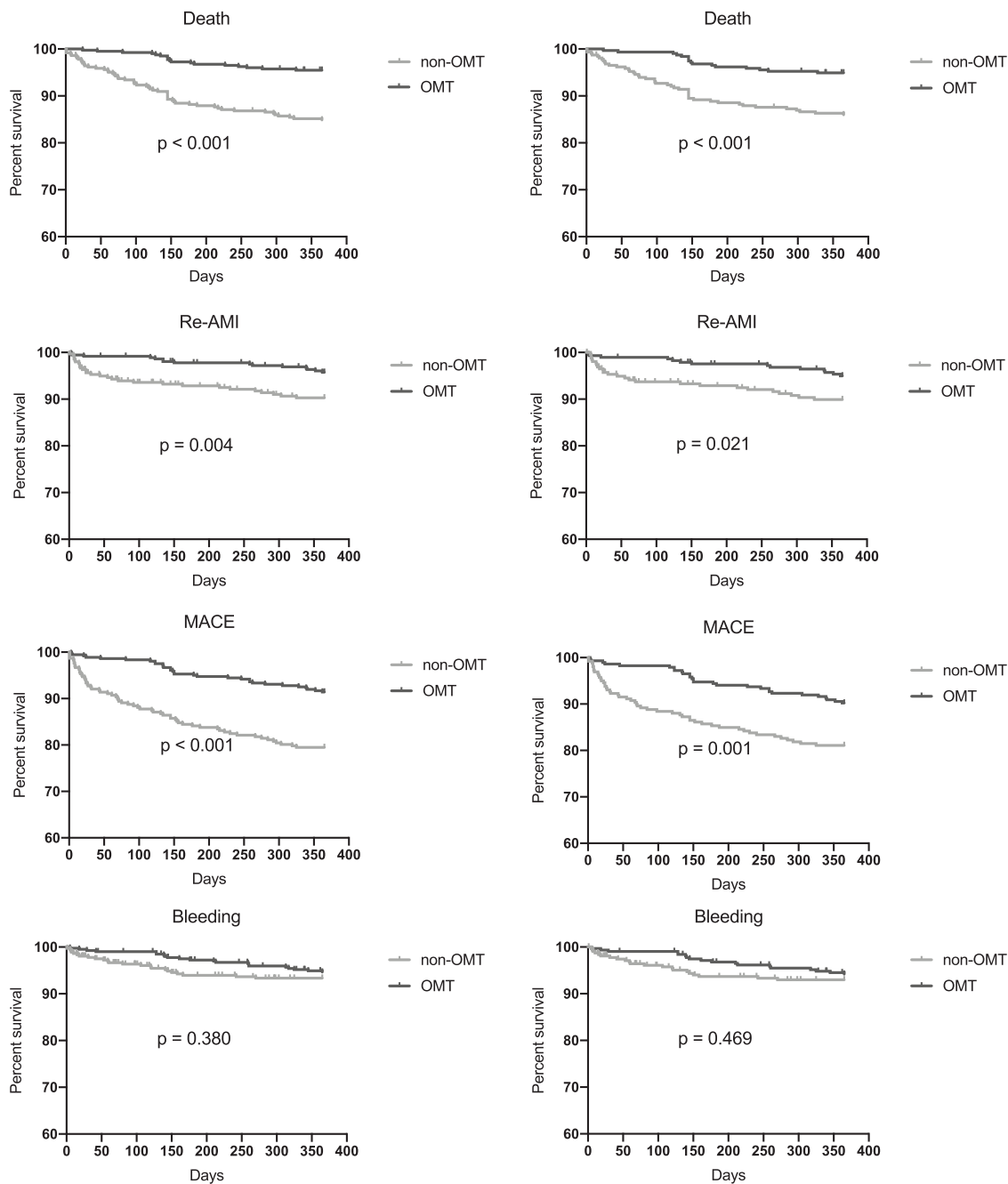
Figure 2. Kaplan-Meier curve of 1-year outcomes of death, re-AMI, MACE, and bleeding in patients with or without OMT before (left) and after (right) PSM.
AMI, acute myocardial infarction; MACE, major adverse cardiovascular event; OMT, optimal medical therapy; PSM, propensity score matching.

the odds of in-hospital death increase by 70% for each 10-year increase in age (OR: 1.70, 95% CI: 1.52–1.82).[13] Among people who died of ischemic heart disease, 83% were > 65 years of age.[14] With lengthening of life expectancy, the older population will gradually expand.

However, elderly patients are known to have altered pharmacodynamic responses and vulnerability to drugs with hypotensive actions and cerebral effects. Drugs that are cleared by the kidney require dose adjustment more often in the elderly based on package labeling. Age-associated decreases in total and

Table 2. Independent predictors of death at the 1-year follow-up.

Variables	Overall			STEMI			NSTEMI		
	HR	95%CI	*p*-value	HR	95%CI	*p*-value	HR	95%CI	*p*-value
OMT	0.31	0.18–0.53	<0.001	0.23	0.11–0.46	<0.001	. . .	. . .	. . .
Age[a], y	3.04	1.46–6.36	0.003	2.36	1.09–5.07	0.029	. . .	. . .	. . .
Creatinine[b], mg/dl	. . .	. . .	. . .	. . .	. . .	. . .	3.46	1.01–11.92	0.049

CI, confidence interval; HR, hazard ratio; NSTEMI, non-ST-elevation myocardial infarction; OMT, optimal medical therapy; STEMI, ST-elevation myocardial infarction.
Data were analyzed by use of a Cox regression model.
[a]HR for age>65y and ≤65y.
[b]Creatinine for >2.5mg/dl and ≤2.5mg/dl.

Table 3. Survival benefit of OMT versus non-OMT across population subgroups.

Variable	Groups	HR	95%CI	*p* value
Age	≤ 65 y	0.71	0.18–2.84	0.627
	> 65 y	0.25	0.14–0.46	<0.001
Sex	Male	0.34	0.18–0.63	0.001
	Female	0.18	0.06–0.51	0.001
DM	Yes	0.38	0.18–0.80	0.011
	No	0.21	0.10–0.45	<0.001
Prior AMI	Yes	0.29	0.09–0.90	0.032
	No	0.28	0.15–0.50	<0.001
Malignancy	Yes	0.43	0.11–1.62	0.213
	No	0.26	0.15–0.47	<0.001
Killip class ≥ 2	Yes	0.22	0.09–0.55	0.001
	No	0.31	0.16–0.63	0.001
Creatinine	< 1.3	0.35	0.19–0.64	0.001
	≥ 1.3	0.18	0.05–0.60	0.005
Multivessel	Yes	0.39	0.20–0.74	0.004
	No	0.08	0.02–0.35	0.001

AMI, acute myocardial infarction; CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; OMT, optimal medical therapy.

lean body mass make weight an additional consideration for drug dosing. Thus, real-world practice reveals a disproportionately lower use of cardiovascular medications and invasive treatment even among elderly patients who would stand to benefit. Limited trial data to guide the care of older

adults is available because most trials exclude patients on the basis of age, particularly with newer medications or invasive treatments and in the setting of advanced age or complex health status. Physicians might hesitate to prescribe OMT for the very elderly population. In this study, we revealed that OMT was associated with an improved one-year mortality even in AMI patients with prior stroke, especially in patients greater than 65 years old.

Patients presenting with ACS frequently have abnormal renal function.[15] The Global Registry of Acute Coronary Events (GRACE) registry has shown that serum creatinine levels upon admission are among the most important markers of hospital mortality in patients with ACS.[13] Cakar *et al.*[16] demonstrated that the 1-year mortality rate of the elevated creatinine group was greater than that of the normal group. There are multiple possible explanations for higher mortality, such as specific vascular disease, combined calcified atherosclerosis and large vessel remodeling or the presence of left ventricular hypertrophy, the effect of chronic volume, or pressure overload.[17]

Moreover, the creatinine level upon admission is an important factor that physicians should consider during the treatment process. Patients with moderate renal insufficiency were found to be less likely to receive aspirin, beta-blocker, thrombolytic therapy, angiography, and angioplasty during hospitalization compared to those with no renal insufficiency.[18] The low use of secondary prevention medicine in patients with renal insufficiency may result from fear of adverse effects. The available data suggest that aspirin therapy is safe and effective in ACS patients with renal dysfunction and should be used in these patients to reduce the risk of death and vascular events. A consistent benefit was noticed with regard to a reduction in cardiovascular events with statin therapy in chronic kidney disease patients who presented with ACS.[19] Trials have also demonstrated that ACEI and beta-blockers are associated with greater benefit in patients with renal insufficiency than in patients with preserved renal function.[20] We further confirmed the benefit of OMT in patients with elevated and normal creatinine levels.

Recently, two major clinical trials demonstrated the efficacy of PCSK9 monoclonal antibody therapies in reducing low-density lipoprotein cholesterol (LDL-C) levels beyond those attained with intensive statin treatment, resulting in significant reduction in cardiovascular events in patients with established atherosclerotic cardiovascular disease and ACS.[21,22] ESC guidelines recommend a lower LDL-C target in patients from very-high-risk populations.[23] If patients experience a second vascular event within two years (not necessarily of the same type as the first event) on maximally tolerated statin therapy, an LDL-C goal of < 1.0 mmol/L may be considered. We assume that there would be many benefits of OMT in current clinical practice. On the other hand, other new drugs, such as ivabradine, an inhibitor of I_f channel in the sinoatrial node, might increase systemic blood pressure by improving sinus tachycardia and could be used in patients with hypotension following AMI.[24] With improvements in the concept and the emergence of new drugs, the advantages of medical therapy should be fully realized.

In summary, although the importance of evidence-based OMT after AMI has been recognized, the prescription rate of OMT is too low in real-world clinical settings, especially in patients with prior stroke who require intensive treatment. These findings highlight opportunities to improve the use and maintenance of appropriate combinations of evidence-based treatment among patients with AMI and prior stroke.

Limitations

There are several potential limitations of our study. First, the BleeMACS was a cohort of a retrospective registry, carrying the limitations inherent to these types of studies. Second, the pharmacotherapy was inevitably influenced by the period between the ischemic stroke and subsequent AMI. However, the exact time interval was not collected.

Conclusion

OMT upon discharge was associated with a significantly lower 1-year mortality of patients with AMI and prior stroke in clinical practice. However, OMT was provided to just half of the eligible patients, leaving room for substantial improvement.

Author contributions

Dongfeng Zhang was responsible for data curation, formal analysis, investigation, and manuscript drafting. Xiantao Song helped to conceive

the theme and revise the manuscript. Sergio Raposeiras-Roubín, Emad Abu-Assi, Jose Paulo Simao Henriques, Fabrizio D'Ascenzo, Jorge Saucedo, José Ramón González-Juanatey, Stephen B. Wilton, Wouter J. Kikkert, Iván Nuñez-Gil, Albert Ariza-Sole, Dimitrios Alexopoulos, Christoph Liebetrau, Tetsuma Kawaji, Claudio Moretti, Zenon Huczek, Shaoping Nie, Toshiharu Fujii, Luis Correia, Masa-aki Kawashiri, Danielle Southern, and Oliver Kalpak were responsible for project administration, investigation, and manuscript review.

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