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The impact of optimal medical therapy at discharge on mortality in patients with coronary artery disease

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Abstract

Objective To analyze the current usage of optimal medical therapy (OMT), influencing factors, and the predictive value of OMT for all-cause mortality in coronary artery disease (CAD) patients with different subgroups. **Methods** A total of 3176 CAD patients confirmed by coronary angiography were included. OMT was defined as the combination of anti-platelet drugs, statins, beta blockers, and angiotensin converting enzyme inhibitors or angiotensin receptor blockers. Factors for OMT and its prognostic value were analyzed in CAD patients across different subgroups. **Results** Out of 3176 patients, only 39.8% (n = 1265) were on OMT at discharge. Factors associated with OMT at discharge were pre-admission OMT and discharge department. All-cause mortality occurred in 6.8% (n = 217) of patients. Multivariate analyses indicated that OMT was significantly associated with reduced all-cause mortality (HR: 0.65, 95% CI: 0.45–0.95; P = 0.025). Sub-group analyses indicate that male acute coronary syndrome (ACS) patients were more likely to receive survival benefits with OMT at discharge. The positive impact of OMT at discharge was more apparent after 24 months, regardless of revascularization therapy. Four-drug combination of OMT was superior to 3-drug combination therapy in ACS patients but not in stable patients. **Conclusions** OMT was associated with significant improvement in survival in patients with CAD. The positive impact of OMT was distinct in the CAD patients with different characteristics.

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Keywords: Coronary artery disease; Optimal medical therapy; Prognosis

1 Introduction

Drug therapy plays a critical role in the prevention of further adverse cardiovascular events in patients with established coronary artery disease (CAD).[1–3] COURAGE trial[4] showed that optimal medical therapy (OMT) was not inferior to concomitant OMT with percutaneous coronary intervention (PCI) with respect to the clinical endpoints of death, myocardial infarction, or other major cardiovascular events in patients with stable CAD. In the secondary prevention of patients with acute coronary syndrome, ACC/AHA guidelines recommended that antiplatelet drugs, statins and beta-receptor antagonists should be given, and angiotensin-converting enzyme inhibitors (ACEI) might be given to all patients without contraindication.[2,3,5] Nevertheless, some literatures reported serious under-usage of OMT in appropriate candidates after hospital discharge.[6,7]

Most of existing evidence about secondary prevention drugs was examined single drug effect but not combined effect and was from pre-reperfusion era. In contemporary era of increasing implementation of reperfusion therapies and aspirin or statin use, it is currently unclear whether if all CAD patients could receive similar benefits from OMT at discharge. In addition, it is not clear whether each of evidence-based drugs is indispensable in OMT, or that the effect of individual drug would be modified by the combination of other secondary prevention drugs. Therefore, the aim of this study was to investigate the usage rate and influential factors of OMT at discharge, as well as its impact on survival in CAD patients with different subgroups.

2 Methods

2.1 Patients inclusion

This study included patients from CAD database of West

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China Hospital, Sichuan University from July 2008 to October 2012. The inclusion criteria was CAD patients with an angiographically confirmed stenosis ≥ 50% in at least one major coronary artery, including those with stable CAD and those who were stabilized after 15 days after an acute coronary syndrome (ACS). The exclusion criteria are as follows: (1) in-hospital mortality; (2) history of gastrointestinal or cerebral hemorrhage; (3) malignant tumor, connective tissue disease, creatinine ≥ 225 μmol/L or acute bronchial asthma patients; and (4) incomplete follow-up.

2.2 Consent and ethics

Current study is adopted with the principles of the Helsinki declaration on human experiments. All subjects signed an informed consent prior to the inclusion in the CAD database, and this study was approved by the ethics committee from our institute's ethics review board.

2.3 Data collection

Drugs at discharge were validated against the hospital's medical records. OMT was defined as combination of antiplatelet [dual antiplatelet therapy (DAPT) for PCI or ACS patients, and one for stable angina patients without PCI], statins, beta blockers (BBs), and angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), which was in line with the definition of OMT in previous published studies.[6,8,9] Follow-up of patients was conducted primarily by telephone, and if necessary, hospital-visits. The primary end-point of the study was death from any cause (all-cause mortality).

2.4 Statistical analyses

Patients were divided into OMT group and non-OMT group according to medication at discharge. Continuous variables, if were normal distribution, were expressed as mean ± SD; otherwise, they were expressed as median and interquartile range. Categorical variables were expressed as percentage. Initially, Shapiro-Wilk test was used to examine the normal distribution and homogeneity of variance of continuous data. If both of above were met, Student's *t*-test or analysis of variance (ANOVA) was conducted to compare baseline characteristics between two groups or multiple groups, respectively. Multiple comparisons were performed with S-N-K method. In the condition of non-normal distribution or unequal variances, Wilcoxon rank sum test were performed. Pearson χ^2 or Fisher test were performed to compared the variables with categorical variables between groups. Kaplan-Meier method was used to constructed survival curve, and the differences between curves were examined using log-rank test. Multivariate logistic regression was conducted to detect the possible influential factors of OMT at discharge. Multivariate Cox regression was performed to examine the predictive factors of long-term outcome. Both of traditional cardiovascular risk factors, such as age, sex, smoking history, pre-hypertension and pre-diabetes, and variables with $P < 0.2$ in the baseline comparison were included into multivariate analysis. Besides, subgroup analyses were conducted between following groups: (1) ACS and stable CAD; (2) men and women; (3) revascularization or not; (4) follow-up duration of < 24 months or ≥ 24 months; and (5) medication with OMT, 3 types of drugs and ≤ 2 types of drugs.

Two-sided P value < 0.05 indicated statistical significance. All the statistical analysis was performed with SPSS 20.0 (SPSS, Inc., Chicago, Illinois).

3 Results

From July 2008 to October 2012, a total of 3714 patients were included into our center's CAD database, of which, 347 patients were lost during follow-up. After exclusion according to aforementioned study criteria, 3176 patients were finally included in current study. (Figure 1)

A total of 1265 (39.8%) patients were discharged with OMT. The baseline characteristics of the included patients are shown in Table 1. Patients with OMT at discharge were more likely to have hypertension, diabetes mellitus, or prior myocardial infarction compared with non-OMT group; furthermore, they had higher heart rate, blood pressure at admission, and shorter hospital stay duration. Although usage

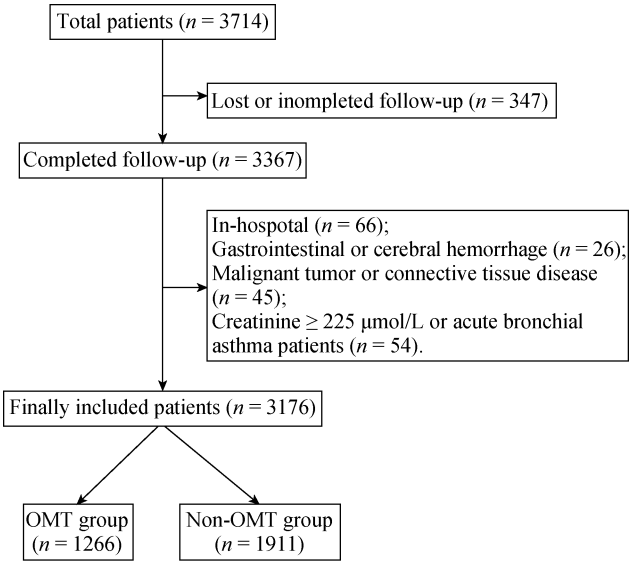

Figure 1. The study flow chart of patients included. OMT: optimal medical therapy.

Table 1. Baseline characteristics of OMT and Non-OMT groups.

	OMT group	Non-OMT group	*P* value
Sample size (n = 3176)	1265 (39.8%)	1911 (60.2%)	
Age, yrs	64.4 (10.6%)	64.4 (10.7%)	0.920
Male	1002 (79.2%)	1524 (79.7%)	0.712
BMI, kg/m^2	24.2 (2.92%)	24.0 (2.89%)	0.003
Ethnicity			
Han people	1220 (96.4%)	1858 (97.2%)	0.211
People of ethnic minorities	45 (3.6%)	53 (2.8%)	
Marital status			0.338
Married	1241 (98.1%)	1865 (97.6%)	
Single or spouse died	24 (1.9%)	46 (2.4%)	
Prior MI	393 (31.3%)	478 (25.0%)	< 0.001
Prior PCI	148 (11.7%)	230 (12.0%)	0.775
Pre-hypertension	929 (73.4%)	1026 (53.7%)	< 0.001
Pre-diabetes	376 (29.7%)	444 (23.2%)	< 0.001
Smoking	355 (28.1%)	570 (29.8%)	0.284
Length of hospital days	8 (6–11)	9 (6–13)	< 0.001
ACS	912 (72.1%)	1357 (71.0%)	0.508
Heart rate at admission, beats/min	73 (66–80)	72 (63–80)	0.002
Serum creatinine, mmol/L	85.5 (74.1–99.5)	85.1 (74–98.6)	0.571
Blood glucose, mmol/L	6.01 (5.1–7.8)	6.02 (5.1–7.8)	0.753
TC, mmol/L	3.95 (3.3–4.7)	3.94 (3.3–4.7)	0.677
TG, mmol/L	1.49 (1.08–2.18)	1.44 (1.0–1.9)	0.005
HDL-c, mmol/L	1.11 (0.9–1.3)	1.11 (0.9–1.3)	0.610
LDL-c, mmol/L	2.27 (1.7–2.90)	2.24 (1.7–2.9)	0.946
WBC, 109/L	6.62 (5.4–8.2)	6.65 (5.4–8.6)	0.307
PLT, 109/L	154 (121–194)	153 (119–193)	0.793
LVEF, %			< 0.001
< 40%	67 (5.3%)	106 (5.5%)	
40%–55%	170 (13.4%)	251 (13.1%)	0.201
≥ 55%	651 (51.5%)	1157 (60.5%)	
Not recorded	377 (29.8%)	397 (20.8%)	
CCS classes of angina			
1	210 (21.4%)	297 (19.3%)	
≥ 2	771 (78.6%)	1241 (80.7%)	
SBP, mmHg	135.3 (20.3%)	127.6 (21.2%)	< 0.001
DBP, mmHg	78.4 (12.4%)	75.4 (12.3%)	< 0.001
Discharge department			
Cardiology	1194 (94.4%)	1669 (87.3%)	< 0.001
Other department	71 (5.6%)	242 (12.7%)	
OMT before admission	143 (11.3%)	77 (4.0%)	< 0.001
PCI or CABG	965 (76.3%)	1466 (76.7%)	0.780

Data were presented as n (%) or mean (range). ACS: acute coronary syndrome; BMI: body mass index; CABG: coronary artery bypass grafting; CCS: Canadian Cardiovascular Society; DBP: diastolic blood pressure; HDL-c: high density lipoprotein cholesterol; LDL-c: low density lipoprotein cholesterol; LVEF: left ventricular ejection fraction; OMT: optimal medical therapy; PCI: percutaneous coronary intervention; PLT: platelets; SBP: systolic blood pressure; TC: total cholesterol; TG: triglyceride; WBC: white blood cell.

rate of OMT was low in both groups before admission, it was higher in OMT groups than non-OMT groups (11.3% *vs*. 4.0%, $P < 0.001$). Patients receiving OMT were more likely to be discharged from department of Cardiology than those not receiving OMT (94.4% *vs*. 87.3%) ($P < 0.001$). Non-OMT group has a higher percentage of left ventricular ejection fraction (LVEF) in the normal range (≥ 55%), while OMT group has a higher proportion of patients without LVEF examination during hospitalization. There was no significant difference in age, gender, smoking, ethnicity, marriage status, laboratory values, Canadian Cardiovascular Society (CCS) classes of angina and revascularization therapies. The types of medications used before and after admission are shown in Figure 2 and Figure 3.

Multiple Logistics regression analyses indicated that pre-

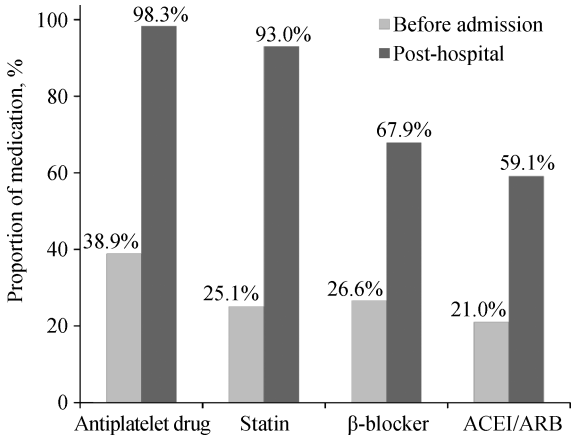

Figure 2. Proportion of each drug used before admission and after discharge. Beta blockers and angiotensin converting enzyme inhibitor/angiotensin receptor blockers were significantly lesser compared with antiplatelet drug or statins. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker.

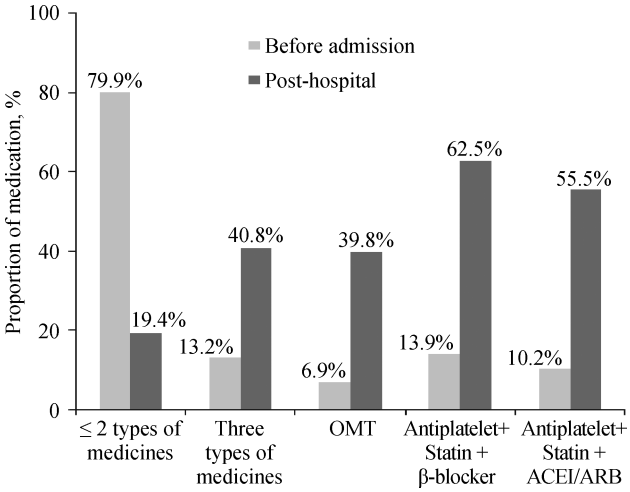

Figure 3. Proportion of drug combination used before admission and after discharge. ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; OMT: optimal medical therapy.

hypertension, pre-diabetes, faster heart rate, higher SBP, discharge form department of cardiology (OR: 1.82, 95% CI: 1.29–2.59, P = 0.001), and OMT before admission (OR: 3.21, 95% CI: 2.32–4.44, P < 0.001) were associated with OMT at discharge, while older age and longer length of hospital stay were associated with a lower likelihood to receive OMT (Table 2).

After a median follow-up of 27.1 months, all-cause mortality occurred in 217/3176 (6.8%) patients [OMT: 69 (5.5%), non-OMT: 148 (7.7%), log-rank test: P = 0.01] (Figure 4). Multiple Cox regression analyses indicates OMT at discharge was associated with a 35% reduced risk of all-cause mortality [(HR: 0.65, 0.45–0.95), P = 0.025]. Other factors associated with all-cause mortality included age, ethnic minorities, LVEF, creatinine, white blood cell count, and revascularization therapy (Table 3). Further analysis adjusting for LVEF (categorical variable) and prior myocardial infarction (MI) did not change the results (data were not shown). A further analysis indicates OMT at discharge on the outcomes of survival differs across subgroups, especially in consideration of follow-up duration (Figure 5). At follow-up ≥ 24 months, the benefit of OMT at discharge was most apparent, while there was no statistical significance below 24 months of follow-up. Both in ACS patients and in men, OMT at discharge were associated with reduced risk of all-cause mortality (HR: 0.65, 95% CI: 0.46–0.90 and 0.63, 95% CI: 0.45–0.88, respectively). Both patients with or without revascularization therapies were able to receive benefit with OMT at discharge, and the benefits were more evident at ≥ 24 months follow-up.

Efficacy of types of secondary prevention drugs at discharge differs between ACS and stable angina patients. In ACS patients, a trend towards reduced risk of all-cause mortality was observed with 3-drug therapy in comparison with ≤ 2 drug therapy, while OMT maximized the clinical benefits of evidence-based drugs (Table 4). For stable angina patients however, the survival benefits of OMT and 3-drug therapy were similar compared to those with ≤ 2-drug therapy.

Table 2. Multivariate logistic regression analysis of factors associated with OMT at discharge.

	P value	OR, 95% CI
Age (every increase in 10 years)	0.021	0.90 (0.82–0.98)
Pre-hypertension	< 0.001	2.24 (1.80–2.80)
Pre-diabetes	0.015	1.34 (1.09–1.65)
Length of hospital stay	< 0.001	0.96 (0.95–0.98)
Heart rate at admission (every increase in 10 beats/min)	0.001	1.08 (1.01–1.16)
SBP (every increase in 10 mmHg)	< 0.001	1.15 (1.09–1.20)
Discharge department (Cardiology *vs*. others)	0.001	1.82 (1.29–2.59)
OMT before admission	< 0.001	3.21 (2.32–4.44)

Adjusted for five traditional cardiovascular risk factors (age, sex, pre-hypertension, pre-diabetes, current smoker) and variables with P < 0.2 at baseline between OMT and Non-OMT groups. OMT: optimal medical therapy; SBP: systolic blood pressure.

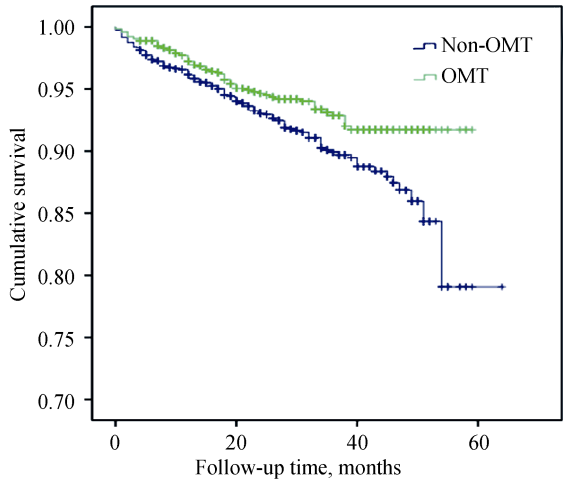

Figure 4. Kaplan Meier survivor curve between OMT and non-OMT group. OMT: optimal medical therapy.

Table 3. Multivariate Cox proportional hazard regression of factors associated with all-cause mortality.

	P value	HR, 95% CI
People of ethnic minorities	0.021	2.50 (1.15–5.44)
Age (every increase in 10 years)	< 0.001	1.87 (1.54–2.27)
LVEF (every increase in 1%)	< 0.001	0.96 (0.95–0.97)
Creatinine (each rise in 10 mmol/L)	< 0.001	1.05 (1.03–1.06)
WBC (each rise in 1×10^9/L)	0.011	1.07 (1.02–1.13)
OMT at discharge	0.025	0.65 (0.45–0.95)
PCI or CABG	< 0.001	0.46 (0.32–0.66)

Adjusted for five traditional risk factors (age, sex, pre-hypertension, pre-diabetes, current smoker) and variables with P < 0.2 in the baseline comparison between patients who were survival and who were dead. CABG: coronary artery bypass grafting; LVEF: left ventricular ejection fraction; OMT: indicates optimal medical therapy; PCI: percutaneous coronary intervention; WBC: white blood cell.

4 Discussion

The principle findings of this study suggests: (1) there is a serious under-usage of OMT in CAD patients, only 39.8% received OMT at discharge; (2) OMT at discharge was associated with decreased risk of mortality, and subgroup analyses indicates this positive impact is more apparent at ≥ 24 months follow-up; (3) patients with or without revascularization therapies were both able to receive benefit from

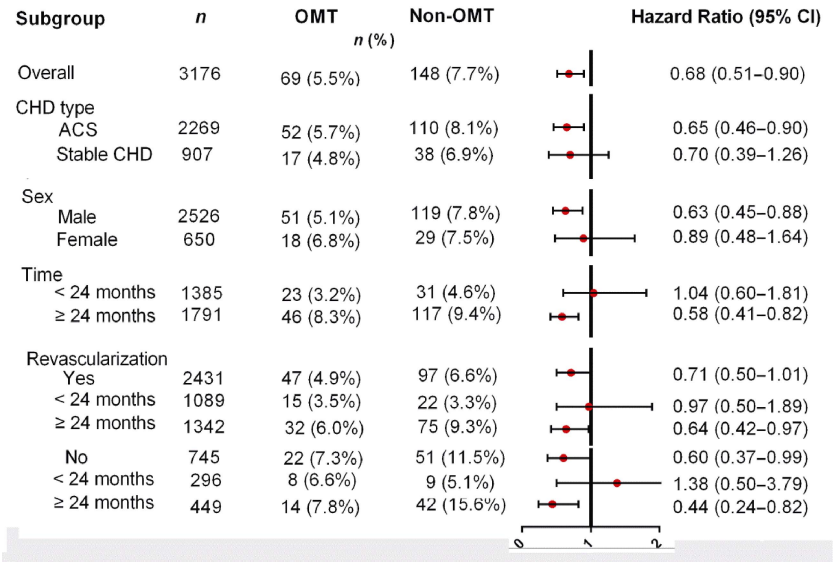

Figure 5. Subgroup analyses across different characteristics. ACS: acute coronary syndrome; CHD: coronary heart disease; OMT: optimal medical therapy.

OMT at discharge; and for those with revascularization therapies, the positive impact was more apparent at longer-term follow-up; and (4) ACS patients were able to receive maximal survival benefit from OMT at discharge compared to ≤ 2-drug therapy. For stable CAD patients however, the survival benefits of OMT and 3-drug therapy were similar.

The lack of OMT at discharge in CAD patients is a common dilemma nationwide. Several countries reported that OMT was achieved in < 50% of ACS patients,[7,8,9] and in current study, only 40.2% of ACS accepted OMT at discharge. For patients with stable angina, the United States national cardiovascular disease registry revealed that 65% of them were on 3-drug therapy (antiplatelet, statins and BB)[10] and only 38.9% received OMT, which is similar with present study (62.5%). The lack of OMT at discharge may be due to non-compliance of patients and inadequate patient education or counseling. Perhaps the value of OMT at discharge is underestimated due to the limited evidence of studies without robust conclusions on the prognostic implications of OMT with subgroups. The conceivable illusion that patients who had revascularization therapy don't necessitate OMT at discharge ensues.[11,12]

Antiplatelet and statin drugs are currently recommended for all CAD patients without contraindications;[2,3] thus, were commonly used (98.3% and 93.0%, respectively). BBs and ACE inhibitors or angiotensin receptor blockers (ARBs) however, are more strongly recommended for CAD patients with hypertension, diabetes mellitus and/or heart failure.[2] Axiomatically, their application was much lower (67.9% and 59.1%, respectively). It is worthy to note that higher percentage of patients in the OMT group had baseline comorbidities. However, OMT group was significantly associated with better survival. This suggests it may be appropriate to stringent future applications of OMT at discharge in non-contraindicated hypertensive and/or diabetic CAD patients.

Previous studies indicated that revascularized patients are less likely to fill prescriptions, thus, a lower secondary preventive medical care.[11,12] The results of the COURAGE trial showed that in patients who received optimal drug therapy. PCI therapy did not further decrease the risk of adverse cardiovascular events[13] SYNTAX trial showed that OMT in the long run reduced 36% relative risk of PCI or coronary artery bypass grafting (CABG) therapy and 27% risk of the composite end point of death, stroke and myocardial infarction.[14] A South Korean registered research showed that OMT in-hospital was associated with a 21% reduction of major adverse cardiovascular events in patients with acute coronary syndrome.[6] Furthermore, a Canadian registry study showed that compared with those taking either the 0 or 1 secondary prevention drug, OMT was associated with a 50% reduced risk of all-cause mortality reduction, in patients with ACS.[15]

In the subgroup analyses, OMT at discharge was associated with better survival in both patients with or without revascularization therapies. For revascularized patients, this survival benefit is revealed only after 24 months follow-up. Possible explanation for this trend is that, the benefit of OMT at short-term follow-up is diluted due to revascularization therapies. In patients without revascularization therapies, OMT at discharge was not associated with an obvious

Table 4. Subgroup analyses of the association between discharge medication types and outcome in different subtypes of patients with CAD.

	Subgroups	HR	95% CI	*P* value
Overall patients				
	≤ 2 types	Reference		
Model 1	3 types	0.67	0.48–0.92	0.015
	OMT	0.52	0.37–0.74	< 0.001
	≤ 2 types	Reference		
Model 2	3 types	0.73	0.53–1.02	0.065
	OMT	0.56	0.39–0.79	0.001
	≤ 2 types	Reference		
Model 3	3 types	0.76	0.54–1.08	0.131
	OMT	0.60	0.42–0.87	0.007
ACS				
	≤ 2 types	Reference		
Model 1	3 types	0.79	0.53–1.16	0.223
	OMT	0.54	0.36–0.82	0.004
	≤ 2 types	Reference		
Model 2	3 types	0.81	0.55–1.20	0.296
	OMT	0.54	0.35–0.81	0.003
	≤ 2 types	Reference		
Model 3	3 types	0.85	0.56–1.30	0.455
	OMT	0.62	0.40–0.96	0.032
Stable CHD				
	≤ 2 types	Reference		
Model 1	3 types	0.37	0.20–0.72	0.003
	OMT	0.39	0.20–0.75	0.005
	≤ 2 types	Reference		
Model 2	3 types	0.43	0.22–0.83	0.012
	OMT	0.41	0.21–0.80	0.009
	≤ 2 types	Reference		
Model 3	3 types	0.42	0.21–0.84	0.014
	OMT	0.45	0.22–0.91	0.026

Model 1: Adjusted for age, sex, pre-hypertension, pre-diabetes and current smoker; Model 2: Adjusted for Model 1 + body mass index, ACS, nation and revascularization; Model 3: Adjusted for Model 2 + marital status,previous myocardial infarction, previous percutaneous coronary intervention, OMT before admission, serum creatinine, glucose, triglyceride, low density lipoprotein, white blood cell, platelet and systolic blood pressure. ACS: acute coronary syndrome; CHD: coronary heart disease; OMT: optimal medical therapy.

survival trend at short-term follow-up. Nevertheless, non-revascularized CAD patients might be frailer and accompanied with multiple adverse comorbidities; if a patient's general condition was promising, OMT at discharge could still reduce the risk of all-cause mortality at long-term follow-up. These results suggest that it is important for patients to be adamant with OMT at discharge, asthe survival benefit of OMT would maximize at long-term follow-up. Discharge medication was an important factor for the long-term outcomes of CAD patients as present database revealed that patients with OMT at discharge were 2.4 times more likely to continue OMT during follow-up compared with non-OMT group. Guideline also recommended physicians to initiate secondary preventive medical care prior to hospital discharge to improve patient compliances.[2,3,5]

There was a sex-related difference on the outcomes of OMT at discharge. Male CAD patients were more likely to receive substantial survival benefits, with a 37% reduction in all-cause mortality, while female patients with OMT on the other hand were not associated with an obvious survival trend. Possible explanation is the fact that female CAD patients are often more elderly, non-compliant, and complicated with multiple baseline adverse comorbidities, which might undermine the benefits of OMT.[16,17] Moreover, relative small percentage of female in our study might have no enough power to detect the significance.

The outcomes of drug combination therapies differs between ACS and stable CAD patients. Our results suggest OMT at discharge was associated with a 38% reduced risk of all-cause mortality in ACS patients. Further subgroup analyses showed that ACS patients with OMT at discharge had significantly better survival compared to those with ≤ 2-drug combination therapy, while 3-drug combination therapy did not. It is likely that the rennin angiotensin aldosterone system and sympathetic nervous system is more activated in ACS patients;[18,19] therefore, the positive impact of OMT was more apparent, and should be implemented in all ACS patients, if tolerated. For stable angina patients, OMT was not superior than the combination of the three types of the evidence-based drugs. (antiplatelet, statins, BB or ACE inhibitor/ARB). This result is in line with the PEACE study, which revealed that the presence of ACE inhibitors along with antiplatelet, statins and BBs in stable CAD patients was not associated with additional benefits.[20] Similarly, another study reported that BBs along with antiplatelet, statins and ACE inhibitors in stable CAD patients did not improve survival.[21] Nevertheless, due to the relatively small number of patients in our subgroup analyses, this result merits further study. In addition, we failed to identify superiority between BBs and ACE inhibitors on the basis of antiplatelet and statin therapy in stable CAD patients.

We also found several factors, including the discharged department and pre-admission OMT, were associated with OMT at discharge. It is likely that cardiologist have a more related and extensive knowledge on the management of secondary prevention. Besides, previous study showed that patients were more compliant with a drug they had ever

used in the past. Therefore, OMT at discharge was more acceptable in these patients, with less unfavorable drug-associated complications.[22]

4.1 Study limitations

There are several inherent limitations. Firstly, this was a single center observational study, therefore, the non-randomization and potential selection bias could have resulted in confounding. In addition, it is possible the rate of OMT at discharge were underestimated because OMT contraindication was not reported. Therefore, this study could have overstated the actual proportion of non-OMT group. Furthermore, the present study primarily focused on the hard endpoint, all-cause mortality, while other important endpoints, such as MI, HF and stroke, which has a significant impact on the quality of life were not reported; nevertheless, the present study might be underpowered to test the association between OMT and individual endpoints. Last but not least important, comprehensive treatment is as vital as secondary prevention for the long-term outcome of patients with CAD. In the present study, we focused on the effect of OMT on the prevention of further cardiovascular events in patients with CAD only while did not assess the impact of comprehensive treatment or rehabilitation on the outcome, which might result in bias and exaggerated the effect of OMT.

4.2 Conclusions

Lack of OMT at discharge is still a serious problem amongst CAD patients as OMT was associated significant reduced all-cause mortality. Patients with OMT should adhere to the evidence-based medication as the clinical benefit might be more apparent in the long-run. OMT of four-drug combination maximize the benefits in patients with ACS, while OMT of three-drug combination was sufficient to maximize the benefits in patients with stable CAD.

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