Passive Prescription of Secondary Prevention Medical Therapy During Index Hospitalization for Acute Myocardial Infarction is Prevalent and Associated with Adverse Clinical Outcomes

Nancy Xu-Rui Huang (✉ xuruinancy@126.com)  
hangzhou first hopital  https://orcid.org/0000-0002-6944-844X
Fang Fang  
Capital Medical University Affiliated Anzhen Hospital
Yizhou Xu  
Zhejiang University School of Medicine
Jinyu Huang  
Zhejiang University School of Medicine
John E. Sanderson  
Chinese University of Hong Kong
Bryan P. Yan  
Chinese University of Hong Kong

Research article

Keywords: Secondary Prevention, Acute Myocardial Infarction, Quality of Care

DOI: https://doi.org/10.21203/rs.3.rs-59605/v1

License: © This work is licensed under a Creative Commons Attribution 4.0 International License.  Read Full License
Abstract

Background: Secondary prevention therapy reduces death and re-infarction after acute myocardial infarction (AMI) but is under-utilized in clinical practice. Mechanisms for this therapeutic gap are not well established. We aimed to evaluate the impact of passive continuation compared to active initiation of secondary prevention therapy for AMI patients during index hospitalization.

Methods: We analyzed 1083 consecutive patients with AMI to a tertiary referral hospital in Hong Kong and assessed discharge prescription rates of secondary prevention therapies (aspirin, clopidogrel, beta-blockers, statins, angiotensin-converting enzyme inhibitor or angiotensin II receptor blockers (ACEI/ARBs)). Multivariate analysis was used to identify independent predictors of discharge and 6-month medication, Kaplan-Meier survival curve was used to evaluate 12-month survival.

Results: Overall prescription rates of aspirin, clopidogrel, beta-blockers, statins, ACEI/ARBs on discharge was 94.8%, 54.2%, 64.5%, 83.5% and 61.4%, respectively. Multivariate analysis showed that prior use of each therapy, except clopidogrel, was an independent predictor of prescription of the same therapy on discharge: aspirin [Odds ratio (OR) = 4.8, 95% CI = 1.9-12.3, P<0.01]; beta-blockers (OR=2.5, 95%CI = 1.8-3.4, P<0.01); statins (OR=8.3, 95%CI = 4.1-15.7, P<0.01) and ACEI/ARBs (OR=2.9, 95%CI = 2.0-4.3, P<0.01). Passive continuation of prior medication was associated with higher 1-year mortality rates than active initiation in treatment naïve patient [aspirin (13.7% vs. 5.7%), beta-blockers (12.9% vs. 5.6%), statins (11.0% vs. 4.6%), all P<0.01]. Active prescription was more common in lower risk patients (who were younger, with less co-morbidity, and with higher left ventricular ejection fraction) who were treated more aggressively with secondary prevention medication on discharge. Also patients who were not on a given medication before admission were less likely to be prescribed it on discharge.

Conclusions: Overall use of secondary prevention medication for AMI was suboptimal compared to guideline recommendations. Our findings suggested the practice of passive continuation of prior medication was prevalent and associated with adverse clinical outcomes compared to those who received secondary preventive medication for the first time during index hospitalization. Failure to start additional medication and possible inadequate dose titration in the passive continuation group may be in part the reason for the poorer clinical outcome in this group.

1. Introduction

AMI has become one of the most common causes for hospital admission and is associated with significant risk of mortality and morbidity in the world [1], especially in China [2]. Despite that guideline recommendations are well-established, many AMI patients still do not receive optimal care resulting in suboptimal clinical outcomes[3–5]. Multiple studies have been performed to explore the factors associated with non-adherence in order to improve quality of care. Many factors have been reported to be associated with this gap including patient’s risk status[6], age[7], relevant medical history [8], ethnicity [9], the type of institution and clinician [10]. However, the reasons for this treatment gap in Asia especially the Chinese population still remain unknown. Moreover, most of the investigations were mainly focused on the inpatient quality of care during the acute period of disease and discharge time point, while the potential factors related to 6-month prescriptions are still unclear.

In this study, we mainly sought to 1) analyze the potential reasons for the therapeutic gap by discharge and 6-month physician adherence, 2) estimate the clinical impact of these gaps for patients with AMI, in particular of the comparison between passive prescription and active prescription.

2. Methods

2.1 Study population and definition

We analyzed consecutive patients presenting with AMI to a tertiary referral hospital in Hong Kong from February 2006 to March 2012. Besides unstable angina (UA), our registry consecutively recruited 1083 patients with AMI (ST-elevation and non ST-elevation myocardial infarction (STEMI/NSTEMI)), involving all causes of AMI in our health institution. And UA patients were excluded from analysis because of the AMI performance measures we used. The study protocol was approved by the ethics committee of the joint Chinese University of Hong Kong-New Territories East Cluster and was performed in accordance with the Declaration of Helsinki and Good Clinical Practice. All subjects provided written informed consent to participate.

2.2 Adherence to clinical guidelines

We selected five of secondary prevention therapies recommended by American College of Cardiology (ACC) and American Heart Association (AHA), and classified as performance measures by ACC/AHA (aspirin, clopidogrel, beta-blockers, and ACEI/ARBs for patients with left ventricular systolic dysfunction (LVSD) is defined as chart documentation of an left ventricular ejection fraction (LVEF) less than 40% or narrative description of LVEF consistent with moderate or severe systolic dysfunction), and statins (if serum LDL-cholesterol > 100 mg/dL)). In order to measure the physician adherence rate more accurately, we analyzed their use in patients without known contra-indications that was clearly defined in ACC/AHA 2008 performance measures for AMI [11]. Thus, those patients with contra-indications and who were not prescribed according to the guideline recommendations, we did not regard it as non-adherence and these patients were excluded.

The prescription of evidence-based therapies at two time points, discharge and six-month, was assessed. The use of medications on discharge was examined in patients who survived to hospital discharge, and the rate of 6-month prescription was assessed among patients who had survived up to 6-month post discharge.

Two prescription patterns emerged in our preliminary analysis, active and passive prescription patterns. Active prescription was defined as patients who received the prescription on discharge and but were not taking any of the same medications before admission (active prescription pattern). And the passive
pattern was the patients who received guideline recommended treatment but were already treated with the same therapy before admission to hospital (passive prescription pattern).

2.3 Follow-up (outcomes)

The clinical impact was calculated at two time-points: six-month post discharge, and one-year post discharge. Clinical outcome was defined as event (including death, recurrent myocardial infarction, cardiac hospitalization, bleeding). Mortality involved the death caused by all reasons. Outside-hospital clinical events of 6-month and 1-year were obtained from the record of patient’s primary care system or through phone call follow-up.

2.4 Statistical analysis

Baseline information were summarized using continuous or categorical data depending the characteristics of the variables. Shapiro–Wilks test was done to test the normality of the data. Continuous data with normal distributions were presented as mean ± standard deviation (SD), otherwise they were showed as median with interquartile range (IQR). For categorical data, they were showed as frequency and percentage (%). Patients who received complete guidelines recommended secondary prevention treatments were compared with those who received partial guideline recommended treatments. Further comparisons were also done between the two-prescription pattern groups (i.e. active and passive prescription) for each evidence-based medical therapy. Independent t-test and Chi-square test (fisher exact test if one cell has the count below 5) were performed to establish the difference of baseline informal between the two-prescription pattern groups. Logistic regression was conducted to explore the potential mechanism of adherence and influence of adherence on clinical outcomes. Univariate regression model including the following variables (baseline characteristics, medical histories, medication before admission, presentation of AMI, laboratory results during hospitalization, and procedures during index admission). And variables with P values of < 0.05 on univariate analysis were entered into multivariate logistic regression model. A multivariate regression model was performed to determine the predictors of adherence. The effect of prescription patterns of all five drugs on the clinical outcomes including 6-month mortality and 1-year mortality rate were explored after controlling for the following variables: age, gender, cardiovascular medical histories, diabetes, hypertension, hyperlipidemia, smoking status, and discharge diagnosis. Survival was evaluated by Kaplan–Meier survival curve, and differences in survival between two prescription patterns (active prescription and passive prescription) were calculated by the log-rank test. A two-sided p-value below 0.05 were considered statistically significant. Statistical analysis was performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1 Patient population and Performance measure (Quality of care)

During the whole study period, a total of 1083 AMI patients with 459 of STEMI (42.4%) or 624 of NSTEMI (57.6%) were enrolled. 54 patients died before discharge, therefore, the analysis of prescription of discharge guideline recommended medications were estimated with 1029 patients. 108 AMI patients died within six months after admission, so 975 patients were taken into account for 6-month physician adherence assessment. Finally, totally 149 patients cumulatively died during the one-year period post admission as AMI in our registry.

Overall, physician adherence rates for the key performance measures (discharge medication) were: 94.8% for aspirin, 54.2% for clopidogrel, 64.5% for beta-blockers, 61.4% for ACEI/ARBs use in patients with LVSD, 83.5% for statins.

For secondary prevention adherence at 6-month: calculated by the type of AMI, the STEMI population had a significantly higher usage than NSTEMI of aspirin (94.8% vs. 91.4%, P = 0.042), ACEI/ARBs (67.6% vs. 58.8%, P = 0.006), statins (90.3% vs. 81.5%, P < 0.001) and all 5 medications (21.1% vs.14.4%, P = 0.012).

Table 1 showed the baseline clinical characteristics of two different discharge prescription patterns (active vs. passive). Additionally, this pattern of active prescription was seen in those lower risk patients (who were younger, with less comorbidities, had better LVEF value) and who were treated more aggressively with secondary prevention on discharge. However, for clopidogrel, the discharge medication pattern was highly associated with the patients’ vascular histories and in-hospital percutaneous coronary intervention (PCI) treatment.
| Prescription Pattern | Aspirin | Clopidogrel | Beta-blocker | ACEI/ARBs | Statins |
|----------------------|---------|------------|-------------|----------|---------|
| Number               | 652     | 307        | 542         | 16       | 392     |
|                      | 215     | 545        | 219         |          |         |
| Demographics         |         |            |             |          |         |
| Age, mean(SD)        | 66.2 ± 12.7 | 73.4 ± 1.3 | < 0.001     | 64.7 ± 11.8 | 66.0 ± 14.4 | 0.657 |
| Male, no.%           | 71.9    | 61.6       | 0.001       | 75.5     | 87.5    | 0.268 |
| Smoker, no.%         | 51.7    | 42.0       | 0.005       | 54.1     | 56.2    | 0.862 |
| Medical histories, no.% |      |            |             |          |         |
| MI                   | 2.5     | 29.0       | < 0.001     | 7.9      | 43.8    | < 0.001 |
| PVD                  | 0.9     | 3.3        | 0.008       | 0.6      | 12.5    | < 0.001 |
| Stroke               | 2.0     | 22.5       | < 0.001     | 5.0      | 25.0-   | 0.001  |
| Diabetes mellitus    | 26.8    | 49.8       | < 0.001     | 28.2     | 43.8    | 0.176  |
| Hypertension         | 52.0    | 73.3       | < 0.001     | 54.6     | 43.8    | 0.390  |
| Hyperlipidemia       | 21.9    | 34.5       | < 0.001     | 25.3     | 18.8    | 0.553  |
| CRF                  | 4.3     | 20.2       | < 0.001     | 5.4      | 6.2     | 0.875  |
| CHF                  | 2.8     | 19.5       | < 0.001     | 3.9      | 25.0    | < 0.001 |
| Physical characteristics at admission |         |            |             |          |         |
| Heart rate (bpm), mean(SD) | 79.7 ± 20.9 | 85.6 ± 21.6 | < 0.001     | 79.1 ± 19.0 | 96.2 ± 23.9 | 0.002 |
| SBP (mmHg), mean(SD)  | 141.6 ± 30.1 | 148.5 ± 33.0 | 0.003       | 29.2 ± 1.3 | 30.7 ± 8.5 | 0.580 |
| LVEF(%), mean(SD)     | 51.6 ± 12.1 | 49.2 ± 13.9 | 0.039       | 11.7 ± 0.6 | 17.8 ± 6.7 | 0.224 |
| Killip class III–IV, no.% | 8.1     | 11.7       | 0.073       | 5.7      | 6.2     | 0.928  |
| STEMI, no.%           | 50.6    | 22.8       | < 0.001     | 51.7     | 25.0    | 0.036  |
| Laboratory results, mean (SD) |         |            |             |          |         |
| Serum LDL (mmol/L)    | 3.1 ± 1.0 | 2.4 ± 1.0  | < 0.001     | 3.0 ± 1.0 | 1.8 ± 0.8 | < 0.001 |
| eGFR, mL/min/1.73 m²  | 65.2 ± 25.3 | 49.6 ± 13.9 | < 0.001     | 64.9 ± 21.8 | 72.5 ± 35.3 | 0.408 |
| In-hospital Treatment |         |            |             |          |         |
| PCI, no.%             | 63.3    | 38.8       | < 0.001     | 89.1     | 56.2    | < 0.001 |
| ACEI/ARBs, angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blockers (ARB); CI, confidence interval; OR, Odds ratio; STEMI, ST elevate myocardial infarction; eGFR, estimated glomerular filtration rate; CHF, congestive heart failure; CRF, chronic renal failure; MI, myocardial infarction; PVD, perip vascular disease; PCI, percutaneous coronary intervention; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure

*All the data were analyzed after adjusting with excluding the patients who have contraindications.
3.2 Predictors of adherence to guideline therapy

3.2.1 Discharge prescription

As shown in Table 2 increasing age was related to the lower prescription rates of aspirin (OR = 0.94; 95% CI = 0.91–0.97; P = 0.001, per year), beta-blockers (OR = 0.97; 95% CI = 0.96–0.99; P < 0.001, per year) and statins (OR = 0.95; 95% CI = 0.94–0.97; P < 0.001, per year) on discharge. Traditional risk features (corresponding medical histories and comorbidities) were correlated with lower usage of beta-blockers and ACEI/ARBs, but did not significantly influence the prescription rate of aspirin and statins on discharge.
| Predictor                          | Adjusted OR | 95% CI        | P value |
|----------------------------------|-------------|---------------|---------|
| Aspirin on discharge             |             |               |         |
| Age (per year)                   | 0.94        | 0.91–0.97     | 0.001   |
| Index revascularization          | 2.77        | 1.13–6.82     | 0.026   |
| Aspirin before admission         | 4.84        | 1.90–12.30    | 0.001   |
| Clopidogrel on discharge         |             |               |         |
| eGFR (mL/min/1.73 m²)            | 1.01        | 1.00–1.02     | 0.037   |
| Hemoglobin (g/dL)                | 1.17        | 1.05–1.29     | 0.004   |
| Killip class (II-IV)             | 0.45        | 0.23–0.86     | 0.016   |
| Index revascularization          | 34.28       | 22.94–51.22   | < 0.001 |
| Beta-blockers on discharge       |             |               |         |
| Age (per year)                   | 0.97        | 0.96–0.99     | < 0.001 |
| NSTEMI                           | 1.54        | 1.18–2.02     | 0.002   |
| History of Hypertension          | 1.75        | 1.31–2.32     | < 0.001 |
| Heart Failure on admission       | 0.58        | 0.35–0.95     | 0.032   |
| Beta-blockers before admission   | 2.50        | 1.83–3.42     | < 0.001 |
| ACEI/ARBs on discharge           |             |               |         |
| Systolic Blood Pressure          | 1.01        | 1.00–1.02     | < 0.001 |
| (per mmHg)                       |             |               |         |
| Diabetes mellitus                | 1.43        | 1.03–1.98     | 0.033   |
| ACEI/ARBs before admission       | 2.93        | 1.97–4.34     | < 0.001 |
| Statins on discharge             |             |               |         |
| Age (per year)                   | 0.95        | 0.94–0.97     | < 0.001 |
| STEMI                            | 1.94        | 1.32–2.87     | 0.001   |
| Albumin (per g/l)                | 1.08        | 1.04–1.12     | < 0.001 |
| Peak Creatinine (per µmol/l)     | 0.99        | 0.98–1.01     | 0.018   |
| Statins before admission         | 8.27        | 0.35–15.71    | < 0.001 |
| Combined medication use on discharge |       |               |         |
| Diastolic Blood Pressure         | 1.01        | 1.00–1.03     | 0.005   |
| (per mmHg)                       |             |               |         |
| Index revascularization          | 9.6         | 5.60–16.5     | < 0.001 |
| ACEI/ARBs before admission       | 1.92        | 1.26–2.92     | 0.003   |
| Aspirin at 6-month               |             |               |         |
| Index revascularization          | 1.97        | 1.08–3.58     | 0.027   |
| Aspirin on discharge             | 15.13       | 7.13–32.13    | < 0.001 |
| Clopidogrel at 6-month           |             |               |         |
| Albumin during hospitalization   | 1.05        | 1.01–1.09     | 0.018   |

*All the data used in analyzing were after adjusted with excluding the patients who have contraindications.

+Analysis performed using multivariable logistic regression, variables in the model including baseline characteristics, medical histories, medication before admission, presentation of AMI, laboratory results during hospitalization, and procedures during index admission.

ACEI/ARBs, angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blockers (ARB); CI, confidence interval; OR, Odds ratio; STEMI, ST elevated myocardial infarction; NSTEMI, non-ST elevated myocardial infarction; eGFR, estimated glomerular filtration rate; CHF: congestive heart failure; AF: atrial fibrillation; Combined medication: combined using five medication including aspirin, Clopidogrel, Beta-blockers, ACEI/ARBs, and Statins
|                               | Adjusted OR | 95% CI      | P value |
|-------------------------------|-------------|-------------|---------|
| History of revascularization  | 2.04        | 1.15–3.63   | 0.015   |
| Index revascularization       | 2.51        | 1.45–4.35   | 0.001   |
| Clopidogrel on discharge      | 6.02        | 3.42–10.60  | < 0.001 |
| Beta-blockers at 6-month      |             |             |         |
| Current smoker                | 0.54        | 0.34–0.85   | 0.008   |
| Heart rate during hospitalization (bpm) | 1.01        | 1.00–1.02   | 0.029   |
| Albumin during hospitalization (g/L) | 1.04        | 1.01–1.08   | 0.047   |
| Beta-blockers on discharge    | 19.70       | 13.00–29.85 | < 0.001 |
| ACEI/ARBs at 6-month          |             |             |         |
| Hypertension                  | 1.51        | 1.01–2.26   | 0.044   |
| CHF                           | 2.27        | 1.32–3.91   | 0.003   |
| AF                            | 0.274       | 0.09–0.87   | 0.029   |
| Presented with STEMI          | 1.92        | 1.28–2.89   | 0.002   |
| ACEI/ARBs on discharge        | 15.43       | 10.36–22.98 | < 0.001 |
| Statins at 6-month            |             |             |         |
| Statins on discharge          | 26.30       | 15.90–43.51 | < 0.001 |
| Combined medication use       |             |             |         |
| History of revascularization  | 1.97        | 1.09–3.53   | 0.024   |
| Index revascularization       | 2.80        | 1.59–4.93   | < 0.001 |
| Statins on discharge          | 8.24        | 5.35–12.70  | < 0.001 |

*All the data used in analyzing were after adjusted with excluding the patients who have contraindications.

+Analysis performed using multivariable logistic regression, variables in the model including baseline characteristics, medical histories, medication before admission, presentation of AMI, laboratory results during hospitalization, and procedures during index admission.

ACEI/ARBs, angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blockers (ARB); CI, confidence interval; OR, Odds ratio; STEMI, ST-elevated myocardial infarction; NSTEMI, non-ST elevated myocardial infarction; eGFR, estimated glomerular filtration rate; CHF: congestive heart failure; AF: atrial fibrillation; Combined medication: combined using five medication including aspirin, Clopidogrel, Beta-blockers, ACEI/ARBs, and Statins

Invasive procedures during hospitalization including PCI or coronary artery bypass grafting (CABG) were strongly associated with discharged prescription of aspirin. In-hospital revascularization was strongly associated with clopidogrel discharge prescription, as well as higher level of estimated glomerular filtration rate (eGFR) and hemoglobin during hospitalization and lower standard Killip-class (I or II). Presenting with NSTEMI and having a medical history of hypertension (HT) were associated with a higher likelihood to be discharged on beta-blockers, whereas having congestive heart failure (CHF) on admission was surprisingly a block to its use. Presenting with higher systolic blood pressure and diabetes mellitus (DM) were predictors of ACEI/ARBs prescription in eligible patients. In those diagnosed as STEMI, higher albumin level during hospitalization predicted use of statins on discharge, while lower peak creatinine level during index hospitalization was more likely to be prescribed with statins. Patients who underwent revascularization during index hospitalization were more likely to be prescribed with combined therapy on discharge (Table 2).

Patients who were not on a given medication before admission were less likely to be prescribed it on discharge and this was consistent through the four medications, except clopidogrel. Clopidogrel was highly influenced by invasive interventions like PCI or CABG. Taking a specific medication before admission was still the strongest independent predictor for it to be taken on discharge of other four drugs; aspirin before admission (OR = 4.84; 95% CI = 1.90–12.30; P = 0.001) for aspirin on discharge; beta-blockers before admission (OR = 2.50; 95% CI = 1.83–3.42; P < 0.001) for beta-blockers on discharge; ACE/ARBs before admission (OR = 2.93; 95% CI = 1.97–4.34; P < 0.001) for ACE/ARBs on discharge; statins before admission (OR = 8.27; 95% CI = 0.35–15.71; P < 0.001) for statins on discharge. And for combination guideline prescription, ACEI/ARBs used before admission played a non-ignorable role in the medical part (OR = 1.92; 95% CI = 1.26–2.92; P = 0.003) (Table 2).

### 3.2.2 Six-month prescription

Table 2 shows the attributes of the disparate 6-month utilization of individual recommendation and composited treatment pattern and adherence in a multivariable model.
Predictors of losing prescription at 6-month were different for each drug. For aspirin, less in-hospital revascularization including PCI or CABG and not prescribed with aspirin on discharge were found to be independent predictors. For clopidogrel, the strongest predictors associated with lower continuous use were no history of revascularization, decreasing level of albumin, no index procedure of PCI or CABG, and without clopidogrel prescription on discharge. As for beta-blockers, current smoker, less heart rate beats, lower in-hospital laboratory level of albumin, and no prescription of beta-blockers contributed to inconstant use. In terms of ACEI/ARBs, independent predictors of withheld prescription were presence of AF, absence of CHF and hypertension, presentation with NSTEMI, and not prescribed ACEI/ARBs on discharge. Inconsistent use of statins was the result of no prescription on discharge. No revascularization before admission or during hospitalization and no statin therapy on discharge were considered to be two independent factors for low prescription rate of combined medication (Table 2).

### 3.3 Impact of passive prescription

According to Table 3, the patients who received the prescription on discharge and did not get the same medication before admission (active prescription pattern) had the lower risk in 6-month and 1-year mortality compared with the patients who adhered to discharge guideline recommendation and already treated with the same therapy before admitted to hospital (passive prescription pattern). Specifically, for 6-month mortality post discharge, active prescription compared with passive prescription of aspirin (2.9% vs. 7.5%, P < 0.001), beta-blockers (2.3% vs. 6.8%, P = 0.005), statins (2.4% vs. 5.9%, P = 0.014); for one-year mortality post discharge, active prescription compared with passive prescription of aspirin (5.7% vs. 13.7%, P < 0.001), beta-blockers (5.6% vs. 12.9%, P = 0.001), statins (4.6% vs. 11.0%, P = 0.001). Even after adjustment for age, gender, smoking status, cardiovascular disease histories, diabetes, hypertension, hyperlipidemia, and discharge diagnosis, active prescription still demonstrated survival benefit compared to passive prescription: for 6-month mortality, aspirin (OR = 0.436, 95% CI = 0.225–0.845, P = 0.014), beta-blockers (OR = 0.374, 95% CI = 0.163–0.861, P = 0.021); for 1-year mortality, aspirin (OR = 0.538, 95% CI = 0.326–0.887, P = 0.015), beta-blockers (OR = 0.481, 95% CI = 0.260–0.892, P = 0.020), statins (OR = 0.514, 95% CI = 0.277–0.956, P = 0.036).

**Table 3**

| Variables | Prescription Pattern | 6-month mortality | Adjusted* OR of 6-month mortality | 1-year mortality | Adjusted* OR of 1-year mortality |
|-----------|----------------------|-------------------|----------------------------------|------------------|----------------------------------|
| Aspirin   | Active               | 2.9%              | < 0.001                          | 0.436            | 0.225–0.845                     | 0.014                           |
|           | Passive              | 7.5%              | 1.000                            | Reference        | 13.7%                           | Reference                       |
| Clopidogrel| Active              | 0.0%              | 0.730                            | 0.0%             | 0.547                           | Reference                       |
|           | Passive              | 0.7%              | 0.0%                            | 2.2%             | 0.0%                            | Reference                       |
| Beta-Blockers| Active         | 2.3%              | 0.005                            | 0.374            | 0.163–0.861                     | 0.021                           |
|           | Passive              | 6.8%              | 1.000                            | Reference        | 12.9%                           | Reference                       |
| ACEI/ ARBs| Active              | 4.8%              | 0.919                            | 6.9%             | 0.283                           | Reference                       |
|           | Passive              | 4.7%              | 0.0%                            | 9.3%             | 0.0%                            | Reference                       |
| Statins   | Active              | 2.4%              | 0.014                            | 0.538            | 0.326–0.887                     | 0.125                           |
|           | Passive              | 5.9%              | 1.000                            | Reference        | 11.0%                           | Reference                       |

*All the data used in analyzing were after adjusted for age, gender, cardiovascular medical histories, diabetes, hypertension, hyperlipidemia, smoking status, discharge diagnosis.

In Kaplan–Meier survival analysis, active prescription of aspirin had the better one year survival rate (Log-rank χ² = 17.8, P < 0.001), active prescription of beta-blockers also gave significant benefit in one year survival rate (Log-rank χ² = 10.3, P = 0.001), as well as the active use of statins (Log-rank χ² = 10.7, P = 0.001) (Fig. 1). After adjustment with age, gender, smoking status, cardiovascular disease histories, diabetes, hypertension, hyperlipidemia and, discharge diagnosis, the hazard ratio (HR) of active prescription of aspirin was [HR = 1.750, 95% CI = 1.091–2.805, P = 0.020], of beta-blockers was [HR = 1.955, 95% CI = 1.099–3.477, P = 0.022], of statins was [HR = 1.891, 95% CI = 1.056–3.388, P = 0.032].

### 4. Discussion

With the increasing realization of the treatment gap, more attention has been paid to the possible reasons of withholding such important medications[7, 12–14]. Our study results are consistent with other publications, which have identified that elder group[7], and traditional high-risk group with relevant medical histories and comorbidities were the significant negative predictors of physician adherence to the various performance measures after AMI[14].

However, we have found a novel reason that in our regression model prior medication is a strong independent predictor for prescription of the same discharge drug so that patients who were taking some standard medication were less likely to receive any new additional medication on discharge. This pattern was persistent for all four medications (aspirin, beta-blockers, ACEI/ARBs and statins). And for 6-month prescription, the pattern was similar to the discharge prescription’s predictors. Six-month prescription was also highly dependent on the previous medications (discharge time point). However, those patients who
are not on any therapy before admission, the pattern of active prescription, who tended to be younger and lower risk patients were treated more aggressively with PCI and secondary prevention on discharge and therefore had better outcomes.

Another potential explanation for this phenomenon could be human behavior. The physician may have assumed that the doctor before him/her already had prescribed the right medications and no further dose titration was necessary, or it may be due to the lack of awareness of the guidelines and the importance of adequate dosage of preventive medications post discharge to reduce later mortality. Another plausible reason is that the patients on previous medication were generally older and sicker and perhaps the doctors were unwilling to use the standard recommended doses. Relevant to this was the interesting finding in our study that low albumin level is a strong predictor of withheld discharge prescription and non-continuous use of secondary prevention. This may relate worse general health condition and more comorbidities. Albumin is one of the hepatic proteins, and its plasma concentration is usually affected by several factors, like the rate of albumin synthesis, exogenous albumin loss, and dilution. Synthesis of albumin is highly influenced by nutritional intake, colloid oncotic pressure variations, and liver function[15]. Some papers published have indicated that albumin is a bio-marker of chronic illness, including heart failure, renal failure and so on[16]. Liu et al. found that Hypoalbuminemia is common in HF patients and is associated with increased risk of death[17]. Prenner et al. also found that serum albumin is associated with myocardial fibrosis, adverse pulsatile aortic hemodynamics, and prognosis in HF[18]. Hirata et al. pointed out low albumin is associated with high mortality[19]. These previous studies have linked low serum albumin to general ill health of patients and worse clinical outcomes. Based on that, it probably reflects the reason why treatment is not optimally used in these patients with Hypoalbuminemia. This may explain continuation of insufficient doses from admission to discharge and follow-up with passive prescription.

However, further studies of doctors' awareness of guidelines seem to be essential and urgent although this may have improved over the intervening years since our study. Another strategy to increase prescription rate and consequently improve the clinical outcome could be to set up a formal discharge checking system with the recommended discharge medications for all AMI patients before discharge. This reminder system could ensure that patients leave hospital on the most optimal medication for them. More importantly, given the incomplete physician adherence and the potential source we found from this study, relying on an informal educational system does not seem to be adequate.

In addition, our results also showed that patients who had the lower mortality at 6-month and 1-year were the ones who had the greater likelihood to be in active prescription group. In particular, the active prescription of medications of aspirin, beta-blockers and statins could account for the statically significant survival benefit to AMI patients after recovery although it was clear that this group had better general health and were younger. Therefore, our findings indicated that substantial support and encouragement of prescription of secondary prevention medications with dose titration if necessary needs to be highlighted to maximize the survival benefit and minimize the mortality risk especially in those who are older and in poorer general condition.

Our results support the hypothesis that discharge on secondary preventive medications alone may not be enough but that the discharge dosage or subsequent dose titration may have an important impact on clinical outcomes and should be assessed to improve the quality of care for acute myocardial infarction patients.

5. Conclusions

Despite advances in cardiovascular care and the establishment of management guidelines, there remained gaps in the application of the best treatments and strategies for AMI patients in Hong Kong. Our findings, that previous medication influenced discharged medication and discharge prescription highly affected 6-month prescription, indicated a potential reason for non-adherence that physicians or patients prefer the continuation of prior medication rather than initiating new secondary preventive therapies and that in these patients treatment was sub-optimal. Better understanding and narrowing these gaps between guideline and practice will contribute to improving quality of care and clinical outcomes of AMI patients.

Abbreviations

AMI: Acute myocardial infarction; ACEI/ARBs: Angiotensin-converting enzyme inhibitor or angiotensin II receptor blockers; UA: Unstable angina; STEMI: ST-elevation myocardial infarction; NSTEMI: Non ST-elevation myocardial infarction; ACC: American College of Cardiology; AHA: American Heart Association; LVSD: Left ventricular systolic dysfunction; LVEF: Left ventricular ejection fraction; SD: Standard deviation; IQR: Interquartile range; OR: Odds ratio; HR: Hazard ratio; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; eGFR: Estimated glomerular filtration rate; HT: Hypertension; CHF: Congestive heart failure; DM: Diabetes mellitus;

Declarations

Acknowledgments

Authors would like to acknowledge the Chinese University of Hong Kong and the patients who participated in this study.

Authors' contributions

Conceptualization: N.XR.H, B.PY, and CM.Y; Methodology: N.XR.H,J.E.S, and F.F; Statistical analysis: N.XR.H; Supervision: B.PY,YZ.X,JY.H; Writing - original draft: N.XR.H; Writing - review & editing: N.XR.H, J.E.S, F.F, and B.PY. All authors read and approved the final manuscript.

Funding

Not applicable.
Availability of data and materials

All data used and/or analyzed during this study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

The study protocol was approved by the ethics committee of the joint Chinese University of Hong Kong-New Territories East Cluster and was performed in accordance with the Declaration of Helsinki and Good Clinical Practice. All subjects provided written informed consent to participate.

Consent for publication

Not applicable.

Competing interests

All authors declare that they have no competing interests related to the submission of this manuscript.

References

1. World Health Organization Cardiovascular disease: Fact sheet number 317 [http://www.who.int/mediacentre/factsheets/fs317/en/index.html]
2. Jiang He DG, Kristi Reynolds, Xiufang Duan, Chonghua Yao, Jialiang Wang, Chung-Shiuan Chen, Jing Chen, Rachel P. Wildman, Michael J. Klag, and Paul K. Whelton.: Major causes of death among men and women in China. N Engl J Med 2005; 353:1124-1134.
3. Solomon MD, Leong TK, Levin E, Rana JS, Jaffe MG, Sidney S, Sung SH, Lee C, DeMaria A, Go AS: Cumulative Adherence to Secondary Prevention Guidelines and Mortality After Acute Myocardial Infarction. J Am Heart Assoc 2020;9(6):e014415.
4. Kirsch F, Becker C, Schramm A, Maier W, Leidl R: Patients with coronary artery disease after acute myocardial infarction: effects of continuous enrollment in a structured Disease Management Program on adherence to guideline-recommended medication, health care expenditures, and survival. Eur J Health Econ 2020;21(4):607-619.
5. Makam RC, Erskine N, McManus DD, Lessard D, Gore JM, Yarzebski J, Goldberg RJ: Decade-Long Trends (2001 to 2011) in the Use of Evidence-Based Medical Therapies at the Time of Hospital Discharge for Patients Surviving Acute Myocardial Infarction. Am J Cardiol 2016;118(12):1792-1797.
6. Shore S, Jones PG, Maddox TM, Bradley SM, Stolker JM, Arnold SV, Parashar S, Peterson P Bhatt DL, Spertus J et al. Longitudinal persistence with secondary prevention therapies relative to patient risk after myocardial infarction. Heart 2015;101(10):800-807.
7. Al-Khadra S, Meisinger C, Amann U, Holle R, Kuch B, Seidl H, Kirchesberger I: Secondary prevention medication after myocardial infarction: persistence in elderly people over the course of 1 year. Drugs Aging 2014;31(7):513-525.
8. Brilakis ES, Hernandez AF, Dai D, Peterson ED, Banerjee S, Fonarow GC, Cannon CP, Bhatt DL: Quality of care for acute coronary syndrome patients with known atherosclerotic disease: results from the Get With The Guidelines Program. Circulation 2009;120(7):560-567.
9. Lai EJ, Grubisic M, Palepu A, Quan H, King KM, Khan NA: Cardiac medication prescribing and adherence after acute myocardial infarction in Chinese and South Asian Canadian patients. BMC Cardiovasc Disord 2011;11:56.
10. Huynh LT, Chew DPB, Sladek RM, Phillips PA, Brieger DB, Zeitz CJ: Unperceived treatment gaps in acute coronary syndromes. International Journal of Clinical Practice 2009;63(10):1456-1464.
11. Krumholz HM, Anderson JL, Bachelder BL, Fesmire FM, Fihn SD, Foody JM, Ho PM, Kosiborod MN, Masoudi FA, Nallamothu BK: ACC/AHA 2008 performance measures for adults with ST-elevation and non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures (Writing Committee to develop performance measures for ST-elevation and non-ST-elevation myocardial infarction): developed in collaboration with the American Academy of Family Physicians and the American College of Emergency Physicians: endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, Society for Cardiovascular Angiography and Interventions, and Society of Hospital Medicine. Circulation 2008;118(24):2596-2648.
12. Astley CM, Macdougall CJ, Davidson PM, Chew DP: Lost in translation: health resource variability in the achievement of optimal performance and clinical outcome. Circ Cardiovasc Qual Outcomes 2011;4(5):512-520.
13. Shang P, Liu GG, Zheng X, Ho PM, Hu S, Li J, Jiang Z, Li X, Bai X, Gao Y et al. Association Between Medication Adherence and 1-Year Major Cardiovascular Adverse Events After Acute Myocardial Infarction in China. J Am Heart Assoc 2019;8(9):e011793.
14. Yan AT, Yan RT, Tan M, Huynh T, Soghrati K, Brunner LJ, DeYoung P, Fitchett DH, Langer A, Goodman SG et al.: Optimal medical therapy at discharge in patients with acute coronary syndromes: temporal changes, characteristics, and 1-year outcome. Am Heart J 2007;154(6):1108-1115.
15. Fuhrman MP, Chaney P, Mueller CM: Hepatic proteins and nutrition assessment. J Am Diet Assoc 2004;104(8):1258-1264.
16. Arques S, Ambrosi P: Human serum albumin in the clinical syndrome of heart failure. J Card Fail 2011;17(6):451-458.
17. Liu M, Chan CP, Yan BP, Zhang Q, Lam YY, Li RJ, Sanderson JE, Coats AJ, Sun JP, Yip GW et al. Albumin levels predict survival in patients with heart failure and preserved ejection fraction. Eur J Heart Fail 2012;14(1):39-44.
18. Prenner SB, Pillutla R, Yenigalla S, Gaddam S, Lee J, Obeid MJ, Ans AH, Jehangir Q, Kim J, Zamani P et al.: Serum Albumin Is a Marker of Myocardial Fibrosis, Adverse Pulsatile Aortic Hemodynamics, and Prognosis in Heart Failure With Preserved Ejection Fraction. J Am Heart Assoc 2020;9(3):e014716.
19. Hirata T, Aray I, Yuasa S, Abe Y, Takayama M, Sasaki T, Kunitomi A, Inagaki H, Endo M, Morinaga J et al.: Associations of cardiovascular biomarkers and plasma albumin with exceptional survival to the highest ages. Nat Commun 2020;11(1):3820.
Figures

Figure 1
Kaplan–Meier survival curve: A) one-year mortality in 2 prescription patterns of aspirin; B) one-year mortality in 2 prescription patterns of beta-blockers; C) one-year mortality in the 2 prescription patterns of statins