Association of multiple preventive therapies postdischarge and long-term health outcomes after acute myocardial infarction

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Abstract

Background: Statins, beta-blockers, and angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers have been advocated by guidelines as secondary prevention medications to improve the long-term outcomes of post-acute myocardial infarction (AMI) patients. However, adequate drug adherence has always been challenging, and different treatment regimens may lead to divergent outcomes that remain unclear under current myocardial infarction (MI) care standards. This study investigated the association between use of different preventive regimens post-AMI and patients' long-term outcomes.

Methods: This cohort study used data files from the Taiwan National Health Insurance Research Database. A total of 77 520 people who were hospitalized with AMI between 2002 and 2015 were assessed. On the basis of medication possession ratio (MPR) to individual medications, eight treatment groups were examined in this study. Receiving therapy was defined as MPR ≥40%. We investigated the association between different treatment groups and all-cause mortality in 24 months.

Results: Overall, 51 322 patients with ST-elevation MI and 26 198 with non-ST-elevation MI were included in the study. Patients received all three preventive medications show the lowest mortality in 24 months follow-up periods among all treatment groups. Patients who did not usage of any of these three preventive medications had the highest mortality in 24 months (adjusted hazard ratio, 1.78; 95% CI, 1.64-1.93). This mortality rate had the same pattern across the three cohort generations (2002-2005, 2006-2010, and 2011-2015).

Conclusion: In this large population-based real-world study, usage of three preventive therapies post-MI was associated with the lowest rate of all-cause mortality.

Keywords: Acute myocardial infarction; Guideline-directed medical therapy; Mortality

1. INTRODUCTION

Long- and short-term mortality in patients with acute myocardial infarction (AMI) has declined for decades because of the extensive application of early reperfusion and revascularization therapy, the progress of antiplatelet agents and devices for vascular interventions, and the implementation of secondary prevention medications, such as angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin II receptor blockers (ARBs), beta-blockers, and statins.[1–3] Current guidelines for the treatment of AMI are derived from evidence that shows the benefit of several single-drug therapies.[1,2] However, evidence of the health outcomes of various drug-combination therapies and patients' characteristics in determining medication adherence remains scarce.[4–8] In addition, the majority of studies have supported using beta-blockers and ACEIs post-AMI before the extensive use of statins and timely percutaneous coronary intervention (PCI) became the standard protocol for AMI. Reevaluating the effectiveness of ACEIs/ARBs, beta-blockers, statins, and their combinations, for treating AMI in the modern era is necessary.

Landmark beta-blocker and ACEI/ARB studies have not presented data regarding ethnicity.[4–6] Knowledge of guideline-directed medical therapy (GDMT) in post-AMI Asian populations remains scarce, including the rate of adherence to GDMT; the benefits of ACEIs/ARBs, beta-blockers, statins, and their combinations. We conducted this study to investigate the

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association between 3-month usage of different preventive regimens after discharge and long-term outcomes in a comprehensive real-world Asian population.

2. METHODS

2.1. Ethical statement

This study was approved by the Joint Institutional Review Board of Taipei Medical University (TMU-JIRB No. 201911004).

2.2. Study design and data source

We conducted a retrospective cohort study and used data files from the National Health Insurance (NHI) Research Database (NHIRD), which is a nationwide claim-based database that contains reimbursement claims that are covered by the NHI programme in Taiwan. The NHI programme is a single-payer health insurance programme that was initiated in 1995. It provides comprehensive medical services, including inpatient and outpatient care, prescription drugs, treatment with traditional Chinese medicine, dental services, childbirth services, rehabilitation therapy, and home health care. Under legislation, all legal residents of Taiwan are eligible for NHI benefits and must enroll in the programme; as such, NHI coverage reached 99.9% of the Taiwanese population by the end of 2017.

2.3. Patient and public involvement

This research was done without patient involvement.

2.4. Study cohort

Patients who had a discharge record of AMI between 2002 and 2015 were first selected, and their date of first AMI admission was treated as their index date of AMI. To increase the validity of the AMI diagnosis, only patients who received heparin or antiplatelet agents during admission were included.

Of these patients, the following were excluded: (1) those younger than 20 years, with missing sex information, or who were not a Taiwanese citizen; (2) those who had underwent coronary artery bypass surgery during the follow-up period; (3) those with a history of AMI; (4) those with a length of hospital stay of more than 1 month; and (5) those who died or had a discharge record of AMI or stroke within 3 months after the AMI index date. The last two criteria were designed to exclude patients with severe and complicated status. Finally, we excluded patients who did not undergo dual antiplatelet therapy, which is a combination of aspirin and clopidogrel or ticagrelor, within 3 months after the AMI index date because their therapeutic strategy did not follow the guidelines for managing AMI. The detailed patient selection process is displayed in Fig. 1.

2.5. Treatment regimen

Usage of three preventive therapies (ACEIs/ARBs, beta-blockers, and statins) within 3 months after the patients were discharged was considered in this study. The medication possession ratio (MPR) is used as surrogate marker of adherence of drugs according to literature.[9] However, in this current study, we used a MPR that is the total number of days covered by filled prescriptions divided by a predefined period (a 3-month period in this case) to determine whether a patient was under a specific medication therapy. We chose a cut-off point of 40% because patients were often regarded as not adherence to treatment when a MPR <40%.[10,11] Therefore, eight treatment regimens were measured in this study, namely adherence to (1) all three therapies; (2) ACEIs/ARBs and beta-blockers only; (3) ACEIs/ARBs and statins only; (4) beta-blockers and statins only; (5) ACEIs/ARBs only; (6) beta-blockers only; (7) statins only; and (8) none of the three therapies.

2.6. Study outcomes

The primary outcome of this study was all-cause mortality, which was derived from the National Death Registry. The secondary outcomes were major adverse cardiovascular events (MACEs), which included cardiovascular (CV) deaths, hospitalizations for nonfatal myocardial infarction (MI), and hospitalization for

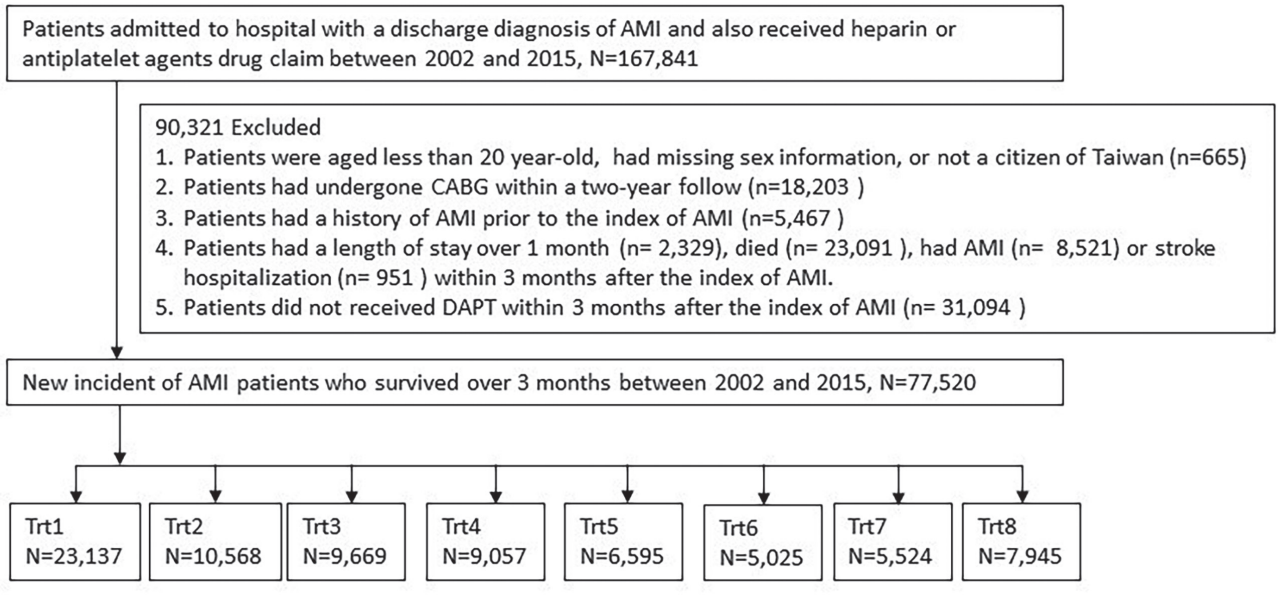

Fig. 1 Patient selection process. Adherence to ACEI treatment: 49969 (64.5%). Adherence to beta-blocker treatment: 47787 (61.6%). Adherence to statin treatment: 47387 (61.1%). ACEI = angiotensin-converting enzyme inhibitor; AMI = acute myocardial infarction; ARB = angiotensin receptor blocker; CABG = coronary artery bypass surgery; DAPT = dual antiplatelet therapy; trt = treatment; Trt1 = ACEI/ARB + beta-blocker + statin; Trt2 = ACEI/ARB + beta-blocker only; Trt3 = ACEI/ARB + statin only; Trt4 = beta-blocker + statin only; Trt5 = ACEI/ARB only; Trt6 = beta-blocker only; Trt7 = statin only; Trt8 = none.

nonfatal strokes. Each patient was followed up for the events of interest from the end of the 3-month treatment regimen assessment for up to 24 months.

2.7. Covariates

Patient demographics, AMI type (ST-elevation MI [STEMI] or non-STEMI [NSTEMI]), treatment procedures, and underlying comorbidities and medication use were included in this study. Underlying comorbidities included vascular comorbidities such as coronary artery disease, hypertension, diabetes, hyperlipidemia, peripheral arterial occlusive disease, heart failure, stroke, atrial fibrillation, ventricle diseases, kidney diseases such as hyperuricemia and chronic kidney disease, and bleeding history. A specific disease was defined only if the patients had at least two diagnostic claims within a year before the index AMI. Preadmission medication included aspirin, clopidogrel, ticlopidine, calcium channel blocker, insulin, proton pump inhibitors, warfarin, nonvitamin K antagonist oral anticoagulants, ACEIs/ARBs, statins, and hyperuricemia medication. Only patients who used these medications over 90 days within a year before the AMI index date were considered. Finally, intra-aortic balloon pump and extracorporeal membrane oxygenation use during and before the AMI index date were used to adjust the severity of the index AMI. Data on International Classification of Diseases, Ninth Revision, Clinical Modification and the Tenth Revision for disease diagnostic codes and Anatomical Therapeutic Chemical Classification codes for medications are listed in Appendix 1.

2.8. Statistical analysis

Descriptive statistics were used to present the baseline characteristics of treatment regimens. This study adopted an intention-to-treat analysis that ignored treatment switching or withdrawal after enrolment. We believed that this approach could provide a favorable estimate of the efficiency of therapeutic strategies when patients have a moderate level of adherence. Survival analysis was adopted in this study. The follow-up periods were set at 12, 18, and 24 months. The cumulative event rates of interest were estimated based on the Kaplan-Meier method. The incidence of events with a 95% CI were computed. A Cox proportional hazard regression was used to compare the risk of events among treatment groups. The analyses satisfied the assumption of proportional hazards. All analyses were performed using SAS/STAT 9.4 (SAS Institute Inc., Cary, NC, USA) and STATA 14 (Stata Corp LP, College Station, TX, USA). A p value of <0.05 was considered significant.

3. RESULTS

3.1. Baseline patient characteristics

In total, 77 520 patients with AMI were included in the study, 51 322 (66.2%) of which had STEMI and 26 198 (33.8%) of which had NSTEMI. The mean age of these patients was 62.6 ± 13.6 years. In total, 50 730 (65.5%) patients had a history of hypertension, 28 383 (36.6%) had diabetes, and 42 288 (54.6%) had dyslipidemia. Baseline characteristics among the eight treatment regimens differed. In particular, the patients who received ACEIs/ARBs only, beta-blockers only, and none of the three types of medications were older and less likely to receive PCI treatment during the index AMI admission. In terms of time trends, the proportion of patients who received a full regimen of these three medications increased from 19.5% of patients in 2002-2005 to 34.0% of patients in 2011-2015. Other baseline characteristics, underlying comorbidities, medication histories, and inhospital treatment characteristics are presented in Table 1.

3.2. MPR in each treatment group

Receiving specific preventive therapy was defined as an MPR greater than 40% within 3 months after the index date. Of all patients, 23 137 (29.8%) received all three GDMTs during the 3-month assessment period, 29 294 (37.8%) received two of

Table 1

Baseline characteristics of patients after AMI

	Treatment regimens within 3 mo after the index AMI discharge								
	All patients	Trt1: ACEI/ARB + beta-blocker + statin	Trt2: ACEI/ARB + beta-blocker only	Trt3: ACEI/ARB + statin only	Trt4: beta-blocker + statin only	Trt5: ACEI/ARB only	Trt6: beta-blocker only	Trt7: statin only	Trt8: none
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Sample size	77 520	23 137	10 568	9669	9057	6595	5025	5524	7945
Adherence to therapies (MPR), mean (SD)									
ACEI/ARB	0.58 (0.42)	0.86 (0.21)	0.87 (0.22)	0.86 (0.21)	0.05 (0.11)	0.86 (0.22)	0.07 (0.12)	0.05 (0.12)	0.13 (0.15)
Beta-blockers	0.55 (0.43)	0.86 (0.21)	0.86 (0.22)	0.04 (0.10)	0.85 (0.21)	0.05 (0.11)	0.84 (0.22)	0.05 (0.11)	0.11 (0.15)
Statins	0.54 (0.43)	0.86 (0.21)	0.04 (0.10)	0.86 (0.21)	0.86 (0.21)	0.03 (0.09)	0.05 (0.11)	0.83 (0.21)	0.11 (0.15)
Demographics									
Age, y									
Mean (SD)	62.6 (13.6)	59.9 (12.8)	63.6 (13.4)	63.7 (13.4)	59.9 (13.0)	68.5 (13.3)	64.1 (13.8)	62.2 (13.8)	65.5 (14.7)
20-44	7149 (9.2)	2676 (11.6)	820 (7.8)	744 (7.7)	1002 (11.1)	281 (4.3)	430 (8.6)	538 (9.7)	658 (8.3)
45-64	36 327 (46.9)	12 307 (53.2)	4733 (44.8)	4340 (44.9)	4950 (54.7)	2156 (32.7)	2112 (42.0)	2665 (48.2)	3064 (38.6)
65-74	16 566 (21.4)	4673 (20.2)	2466 (23.3)	2212 (22.9)	1691 (18.7)	1604 (24.3)	1187 (23.6)	1097 (19.9)	1636 (20.6)
75+	17 478 (22.5)	3481 (15.0)	2549 (24.1)	2373 (24.5)	1414 (15.6)	2554 (38.7)	1296 (25.8)	1224 (22.2)	2587 (32.6)
Male	61 133 (78.9)	18 572 (80.3)	8164 (77.3)	7640 (79.0)	7323 (80.9)	4911 (74.5)	3868 (77.0)	4476 (81.0)	6179 (77.8)
DX year									
2002-2005	10 349 (13.4)	2031 (8.8)	2371 (22.4)	1016 (10.5)	876 (9.7)	1532 (23.2)	1005 (20.0)	428 (7.7)	1090 (13.7)
2006-2010	26 896 (34.7)	7428 (32.1)	4229 (40.0)	3650 (37.7)	2685 (29.6)	2771 (42.0)	1779 (35.4)	1620 (29.3)	2734 (34.4)
2011-2015	40 275 (52.0)	13 678 (59.1)	3968 (37.5)	5003 (51.7)	5496 (60.7)	2292 (34.8)	2241 (44.6)	3476 (62.9)	4121 (51.9)

(*Continued next page*)

Table 1 (Continued)

Baseline characteristics of patients after AMI

	Treatment regimens within 3 mo after the index AMI discharge								
	All patients	Trt1: ACEI/ARB + beta-blocker + statin	Trt2: ACEI/ARB + beta-blocker only	Trt3: ACEI/ARB + statin only	Trt4: beta-blocker + statin only	Trt5: ACEI/ARB only	Trt6: beta-blocker only	Trt7: statin only	Trt8: none
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Characteristics of the index AMI admission									
STEMI	51 322 (66.2)	15 503 (67.0)	7384 (69.9)	6316 (65.3)	6064 (67.0)	4450 (67.5)	3366 (67.0)	3424 (62.0)	4815 (60.6)
Heart failure	36 251 (46.8)	9509 (41.1)	5181 (49.0)	4485 (46.4)	3995 (44.1)	3834 (58.1)	2604 (51.8)	2608 (47.2)	4035 (50.8)
PCI	63 780 (82.3)	20 453 (88.4)	8061 (76.3)	8331 (86.2)	7926 (87.5)	4762 (72.2)	3735 (74.3)	4757 (86.1)	5755 (72.4)
IABP	3330 (4.3)	1025 (4.4)	424 (4.0)	411 (4.3)	445 (4.9)	245 (3.7)	228 (4.5)	272 (4.9)	280 (3.5)
ECMO	155 (0.2)	41 (0.2)	33 (0.3)	12 (0.1)	16 (0.2)	7 (0.1)	17 (0.3)	15 (0.3)	14 (0.2)
Aspirin	77 520 (100)								
Clopidogrel	70 799 (91.3)	20 206 (87.3)	10 168 (96.2)	8832 (91.3)	8033 (88.7)	6426 (97.4)	4804 (95.6)	4937 (89.4)	7393 (93.1)
Ticagrelor	8089 (10.4)	3421 (14.8)	505 (4.8)	1024 (10.6)	1238 (13.7)	233 (3.5)	283 (5.6)	746 (13.5)	639 (8.0)
Ticlopidine	729 (0.9)	120 (0.5)	112 (1.1)	86 (0.9)	52 (0.6)	123 (1.9)	69 (1.4)	46 (0.8)	121 (1.5)
Preadmission medication use (≥90 d within 12 mo before the index AMI admission)									
Aspirin	14 828 (19.1)	4034 (17.4)	2288 (21.7)	1895 (19.6)	1396 (15.4)	1649 (25.0)	994 (19.8)	858 (15.5)	1714 (21.6)
Clopidogrel	2498 (3.2)	552 (2.4)	347 (3.3)	308 (3.2)	255 (2.8)	252 (3.8)	202 (4.0)	210 (3.8)	372 (4.7)
Ticlopidine	614 (0.8)	135 (0.6)	104 (1.0)	81 (0.8)	51 (0.6)	80 (1.2)	50 (1.0)	49 (0.9)	64 (0.8)
CCB	20 688 (26.7)	6423 (27.8)	3453 (32.7)	2745 (28.4)	1818 (20.1)	2084 (31.6)	1280 (25.5)	981 (17.8)	1904 (24.0)
ACEI	6799 (8.8)	2024 (8.7)	1274 (12.1)	965 (10.0)	451 (5.0)	885 (13.4)	386 (7.7)	266 (4.8)	548 (6.9)
ARB	16 483 (21.3)	5518 (23.8)	2619 (24.8)	2253 (23.3)	1373 (15.2)	1591 (24.1)	871 (17.3)	780 (14.1)	1478 (18.6)
Beta-blocker	16 741 (21.6)	5726 (24.7)	3113 (29.5)	1492 (15.4)	1864 (20.6)	1153 (17.5)	1313 (26.1)	661 (12.0)	1419 (17.9)
Statin	12 178 (15.7)	4353 (18.8)	1119 (10.6)	1825 (18.9)	1597 (17.6)	665 (10.1)	595 (11.8)	942 (17.1)	1082 (13.6)
Insulin	3964 (5.1)	1013 (4.4)	576 (5.5)	430 (4.4)	444 (4.9)	379 (5.7)	324 (6.4)	281 (5.1)	517 (6.5)
PPI	2219 (2.9)	520 (2.2)	304 (2.9)	241 (2.5)	269 (3.0)	249 (3.8)	185 (3.7)	161 (2.9)	290 (3.7)
Warfarin	592 (0.8)	138 (0.6)	99 (0.9)	70 (0.7)	57 (0.6)	66 (1.0)	54 (1.1)	42 (0.8)	66 (0.8)
NSAID	27 648 (35.7)	8021 (34.7)	3901 (36.9)	3540 (36.6)	3081 (34.0)	2569 (39.0)	1858 (37.0)	1881 (34.1)	2797 (35.2)
Hyperuricemia agent	7406 (9.6)	2217 (9.6)	1053 (10.0)	966 (10.0)	837 (9.2)	681 (10.3)	516 (10.3)	429 (7.8)	707 (8.9)
Underlying comorbidities (within 12 mo before the index AMI admission)									
HTN	50 739 (65.5)	16 404 (70.9)	7890 (74.7)	6484 (67.1)	4859 (53.6)	4726 (71.7)	3092 (61.5)	2600 (47.1)	4684 (59.0)
DM	28 383 (36.6)	8531 (36.9)	4265 (40.4)	3455 (35.7)	3004 (33.2)	2540 (38.5)	1927 (38.3)	1778 (32.2)	2883 (36.3)
Hyperlipidaemia	42 288 (54.6)	16 020 (69.2)	3565 (33.7)	6336 (65.5)	6230 (68.8)	1853 (28.1)	1691 (33.7)	3570 (64.6)	3023 (38.0)
PAOD	2225 (2.9)	529 (2.3)	322 (3.0)	289 (3.0)	217 (2.4)	259 (3.9)	181 (3.6)	142 (2.6)	286 (3.6)
Stroke	4876 (6.3)	1145 (4.9)	760 (7.2)	603 (6.2)	442 (4.9)	618 (9.4)	383 (7.6)	309 (5.6)	616 (7.8)
AF and flutter	4509 (5.8)	910 (3.9)	758 (7.2)	559 (5.8)	409 (4.5)	610 (9.2)	360 (7.2)	308 (5.6)	595 (7.5)
Ventricular tachycardia	1815 (2.3)	542 (2.3)	253 (2.4)	196 (2.0)	238 (2.6)	158 (2.4)	131 (2.6)	127 (2.3)	170 (2.1)
VF or flutter	1160 (1.5)	405 (1.8)	149 (1.4)	112 (1.2)	154 (1.7)	85 (1.3)	86 (1.7)	78 (1.4)	91 (1.1)
Hyperuricemia	8847 (11.4)	2689 (11.6)	1258 (11.9)	1136 (11.7)	1038 (11.5)	808 (12.3)	578 (11.5)	501 (9.1)	839 (10.6)
ICH	450 (0.6)	101 (0.4)	73 (0.7)	51 (0.5)	41 (0.5)	51 (0.8)	38 (0.8)	24 (0.4)	71 (0.9)
GI bleeding	3371 (4.3)	736 (3.2)	515 (4.9)	361 (3.7)	372 (4.1)	388 (5.9)	282 (5.6)	235 (4.3)	482 (6.1)
Other noncritical site bleeding	1450 (1.9)	395 (1.7)	209 (2.0)	168 (1.7)	162 (1.8)	127 (1.9)	106 (2.1)	109 (2.0)	174 (2.2)
CKD	4704 (6.1)	1033 (4.5)	570 (5.4)	454 (4.7)	683 (7.5)	460 (7.0)	508 (10.1)	374 (6.8)	622 (7.8)
CLD	9087 (11.7)	1699 (7.3)	1088 (10.3)	1510 (15.6)	711 (7.9)	1425 (21.6)	574 (11.4)	767 (13.9)	1313 (16.5)
Cancer	2916 (3.8)	665 (2.9)	430 (4.1)	316 (3.3)	314 (3.5)	304 (4.6)	249 (5.0)	213 (3.9)	425 (5.3)
PCI	1859 (2.4)	569 (2.5)	239 (2.3)	177 (1.8)	231 (2.6)	140 (2.1)	134 (2.7)	137 (2.5)	232 (2.9)
Follow-up period, mo, mean (SD)	22.7 (4.4)	23.2 (3.4)	22.7 (4.5)	23.0 (4.0)	23.1 (3.8)	21.8 (5.7)	22.2 (5.3)	22.7 (4.5)	21.6 (6.0)

ACEIs = angiotensin-converting enzyme inhibitors; AF = atrial fibrillation; AMI = acute myocardial infarction; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; CKD = chronic kidney disease; CLD = chronic lung disease; DM = diabetes mellitus; Dx = diagnosis; ECMO = extracorporeal membrane oxygenation; GI = gastrointestinal; HTN = hypertension; IABP = intra-aortic balloon pump; ICH = intracerebral hemorrhage; MPR = medication possession ratio; NSAIDs = nonsteroidal anti-inflammatory drugs; PAOD = peripheral arterial occlusive disease; PCI = percutaneous coronary intervention; PPIs = proton pump inhibitors; STEMI = ST-elevation myocardial infarction; VF = ventricular fibrillation.

three preventive therapies, 16 844 (21.7%) received only one of three preventive therapies, and 7945 (10.2%) did not receive any of the three preventive therapies (MPR <40%) during the first 3 months after the AMI date. The MPR of the group with all three GDMTs was over 85%.

3.3. Mortality and MACE outcome

For the entire cohort, the mean follow-up period was 22.7 months. Overall, 4243 deaths (5.5%) occurred in 12 months, 5743 deaths (7.4%) occurred in 18 months, and 7178 (9.3%) deaths occurred in 24 months. For all-cause mortality at

24-month follow-up, all treatment groups had significant differences during the study period. The differences among all groups in terms of mortality rate shared the same pattern across the three cohort generations (2002-2005, 2006-2010, and 2011-2015 cohorts; Fig. 2B–D). Fig. 3A presents the mortality rate within 12 and 24 months among the different treatment groups. Compared with the patients who received all three preventive therapies (Trt1), patients who did not receive to any medication (Trt8) had the highest 12-month mortality (adjusted hazard ratio [HR], 1.90; 95% CI, 1.72-2.11), followed by those who received to ACEIs/ARBs only (Trt5: adjusted HR, 1.47; 95% CI, 1.31-1.65), and beta-blockers only (Trt6: adjusted HR, 1.53; 95% CI, 1.34-1.73); however, we did not observed a significant difference in patients who received to ACEIs/ARBs + statins only (Trt3: adjusted HR, 1.07; 95% CI, 0.95-1.21). The results were similar to those after a 24-month follow-up period in which the mortality rate was significantly higher than that for Trt 1 to Trt3. For MACE outcomes at the 24-month follow-up, all treatment groups were significantly different from Trt1, except for the ACEI/ARB + statin only group (Trt3: HR, 1.06; 95% CI, 0.98-1.16) and beta-blocker + statin only group (Trt4: HR, 1.05; 95% CI, 0.96-1.15; Fig. 3B). For CV deaths, all treatment groups exhibited significant differences with Trt1 except for the ACEI/ARB + statin only group (Trt3: HR, 1.09; 95% CI, 0.90-1.31) and beta-blocker + statin only group (Trt4: HR, 1.02; 95% CI, 0.83-1.26; Supplementary Table 4, http://links.lww.com/JCMA/A107). For nonfatal MI, the beta-blocker only group (Trt6: HR, 1.17; 95% CI, 1.03-1.33) and nonadherence to all three medications groups (Trt8: HR, 1.24; 95% CI, 1.11-1.38) had significantly higher mortality rates than patients with Trt1 (Supplementary Table 5, http://links.lww.com/JCMA/A107). Full multivariate regression models of all-cause mortality and MACE in 12- and 24-month follow-ups are present in Supplementary Table 7 (http://links.lww.com/JCMA/A107).

3.4. Mortality and MACE in patient subgroups

The association between treatment groups and mortality in patients with distinct subgroups was similar to those in the entire study population according to our subgroup analysis (Fig. 4). Patients with all three preventive therapies had the lowest mortality compared with other treatment groups, particularly patients with heart failure, those who had STEMI, those aged 65 years or over, and those who were male. Mortality in patients who adhered to ACEI/ARB-base two combined therapies (Trt2 and Trt3) had significant differences from those who adhered with all three preventive therapies in patients with heart failure. For patients with diabetes, the ACEI/ARB + statin treatment group (Trt3) had a similar mortality rate compared with patients with all three preventive therapies (Trt1) at 12 months. The statin-base dual therapies groups exhibited similar mortality with that of the three preventive therapies group in patients with NSTEMI and who were female.

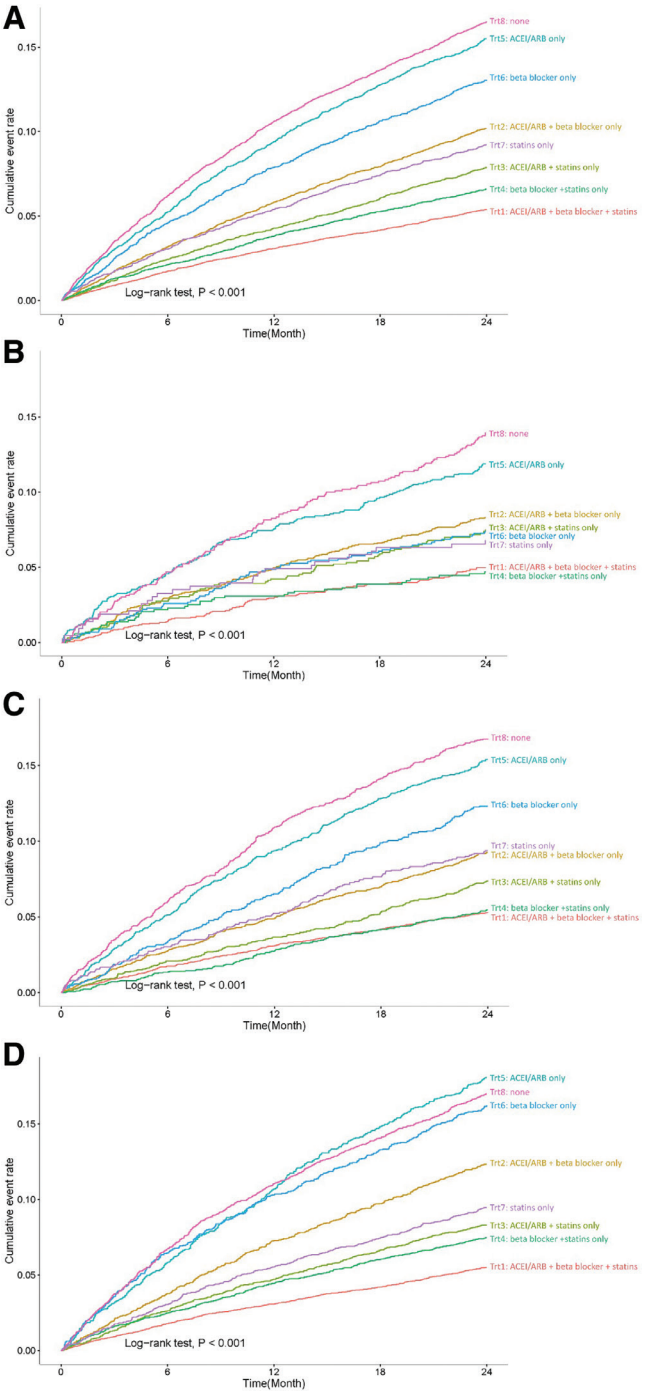

Fig. 2 Kaplan-Meier failure curve of all-cause mortality for the overall study period (A), 2002-2005 cohort (B), 2006-2010 cohort (C), and 2011-2015 cohort (D). ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; trt = treatment; Trt1 = ACEI/ARB + beta-blocker + statin; Trt2 = ACEI/ARB + beta-blocker only; Trt3 = ACEI/ARB + statin only; Trt4 = beta-blocker + statin only; Trt5 = ACEI/ARB only; Trt6 = beta-blocker only; Trt7 = statin only; Trt8 = none.

4. DISCUSSION

Our study provided several key findings: First, patients who received all three preventive therapies for at least 3 months after AMI had the lowest mortality and fewest MACEs within a 2-year follow-up compared with those of the other treatment groups. The findings had the same trend over all three cohort generations (2002-2005, 2006-2010, and 2011-2015). Second, only 29.8% of patients received all three preventive therapies in the first 3 months after being discharged after an MI; however, the three therapies' MPR continued improving over time (from 19.5% in 2002-2005 to 34.0% in 2011-2015). Third, statin-base dual therapy groups (Trt3: ACEI/ARB + statin and Trt4: beta-blocker + statin) had comparable outcome benefits in terms of MACEs and CV deaths at 1- and 2-year follow-up with the three preventives therapies group (Trt1). Fourth, after the three preventive therapies were used in all patient subgroups, lower mortality in patients was identified in patients, particularly those in old age, male sex, and those with heart failure or STEMI.

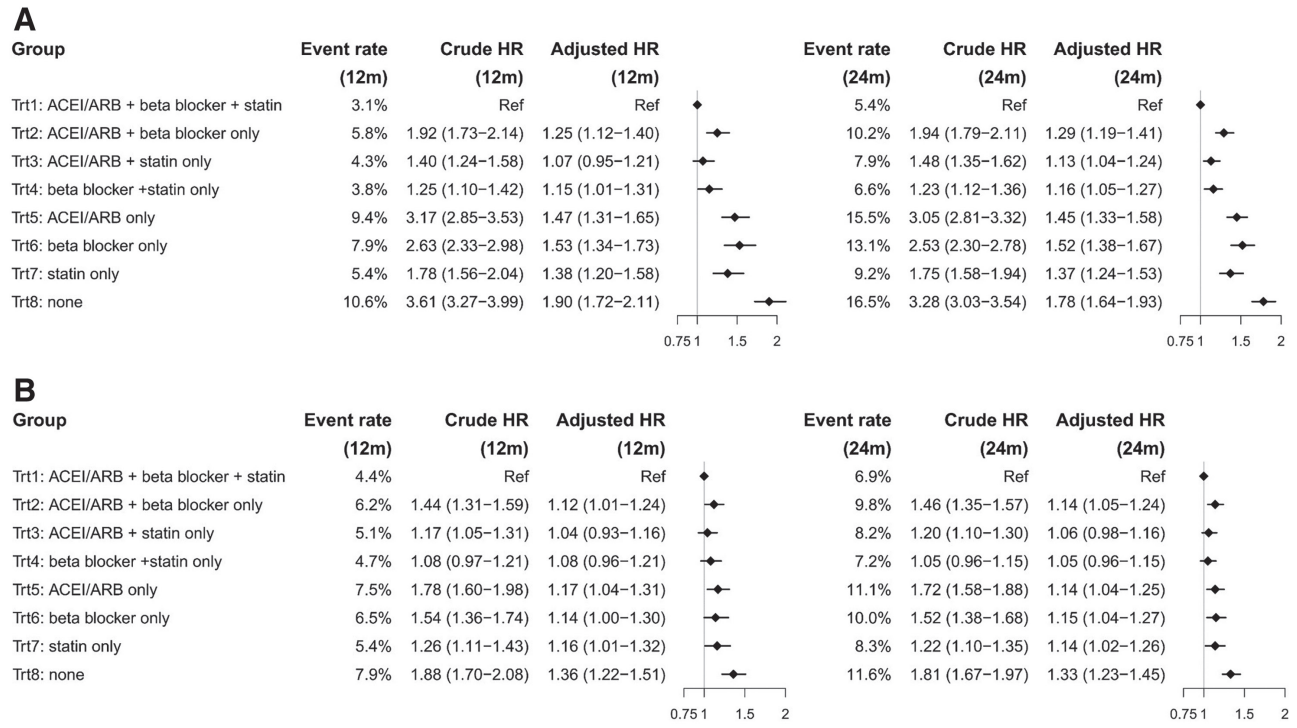

Fig. 3 Percentage of event rate (number of events/number of patients) and HR of all-cause mortality (A) and MACEs (B) in 12-mo and 24-mo follow-ups. *Adjusted HR was estimated through multivariable Cox regression after adjustment for the covariates listed in Table. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; HR = hazard risk; MACEs = major adverse cardiovascular events; Trt = treatment; Trt1 = ACEI/ARB + beta-blocker + statin; Trt2 = ACEI/ARB + beta-blocker only; Trt3 = ACEI/ARB + statin only; Trt4 = beta-blocker + statin only; Trt5 = ACEI/ARB only; Trt6 = beta-blocker only; Trt7 = statin only; Trt8 = none.

Most studies have reported mortality or MACE benefits as long-term outcomes, with preventive therapies after AMI based on the prescription during hospitalization or at discharge.[12,13] There were only few studies have explored postdischarge preventive therapies duration and long-term outcomes. A reduction in mortality risk from usage of these preventive therapies post-AMI discharge has been reported in two studies.[10,14] A large Canadian population-based observational study revealed that a high adherence rate with statin and beta-blocker use 1 year post-MI was associated with a significant improvement in long-term mortality.[10] Another cohort study analyzing older patients (≥65 years) that used the US Medicare database revealed that non-adherence (proportion of days covered <80%) to ACEI/ARB, statin, and beta-blocker use within 180 days after the index AMI discharge was associated with a 65% higher mortality compared with adherence to all three preventive therapies.[14] Furthermore, a later study indicated that patients who received ACEIs/ARBs and statins had no significant mortality difference from patients who received all three preventive therapies, and this difference may have been attributed to differences in the ethnicity between these two populations, the design of study, and the follow-up length (18 months in the US study). In our study, patients who received ACEIs/ARBs and statins (Trt3) had no significant mortality difference from the three preventive therapies group (Trt1) at 12-month follow-up but had a significant mortality difference at 18- and 24-month follow-up. (Supplementary Table 2, http://links.lww.com/JCMA/A107).

In our cohort, 64.5% of participants received ACEI, 61.6% received beta-blockers, and 61.1% received statin in first 3 months after the index AMI. The prescription rates were comparable with the Taiwan Post-acute Coronary Syndrome Registry.[15] The average MPR in Trt1 (three preventive therapies) of our study was higher than 80%, which suggested adequate adherence. A prior database study indicated that the MPR of GDMT of >80% was associated with fewer MACEs compared with partial adherence (MPR of ≥40% but ≤79%) and nonadherence to GDMT (MPR <40%) in the post-MI population.[11] The current study found that patients who received all three preventive therapies in the first 3 months post-MI were associated with a significantly lower rate of mortality compared with other treatment regimens. This implied that even short-term (3 months) usage of the three preventive therapies may have relative long-term survival benefits.

Our study revealed that the statin-base dual therapy groups were the only two treatment groups that shared comparable 12-to-24-month MACE and CV death outcomes among the three combined therapy groups. With growing evidence revealing that low-density lipoproteins (LDLs) the lower, the better, statin therapy should be the keystone of GDMTs for post-AMI. An early cohort study in Canada revealed a modest superiority in favor of statins over beta-blockers for reducing mortality after AMI.[10] Furthermore, an Israeli retrospective cohort study showed that statin was associated with a marked reduction in mortality risk compared with ACEIs/ARBs or beta-blockers.[16] As for ACEI/ARB or beta-blocker treatment only, several studies have indicated that these treatments may only benefit patients with left ventricular systolic dysfunction[4,13,17–20] or who belong to high-risk groups (diabetes or anterior infarction).[1,2] Thus, statin-base therapies may be associated with the lowest MACE outcome in our study compared with ACEI/ARB- and beta-blocker-based therapy. Although the statin-base dual therapy groups had a higher mortality rate than the three preventive therapy groups in our study, the statin-base dual therapy groups still exhibited the lowest adjusted HR compared with the other treatment groups.

Traditionally, given the complexity of comorbidities or comedications, patients with heart failure and in old age less

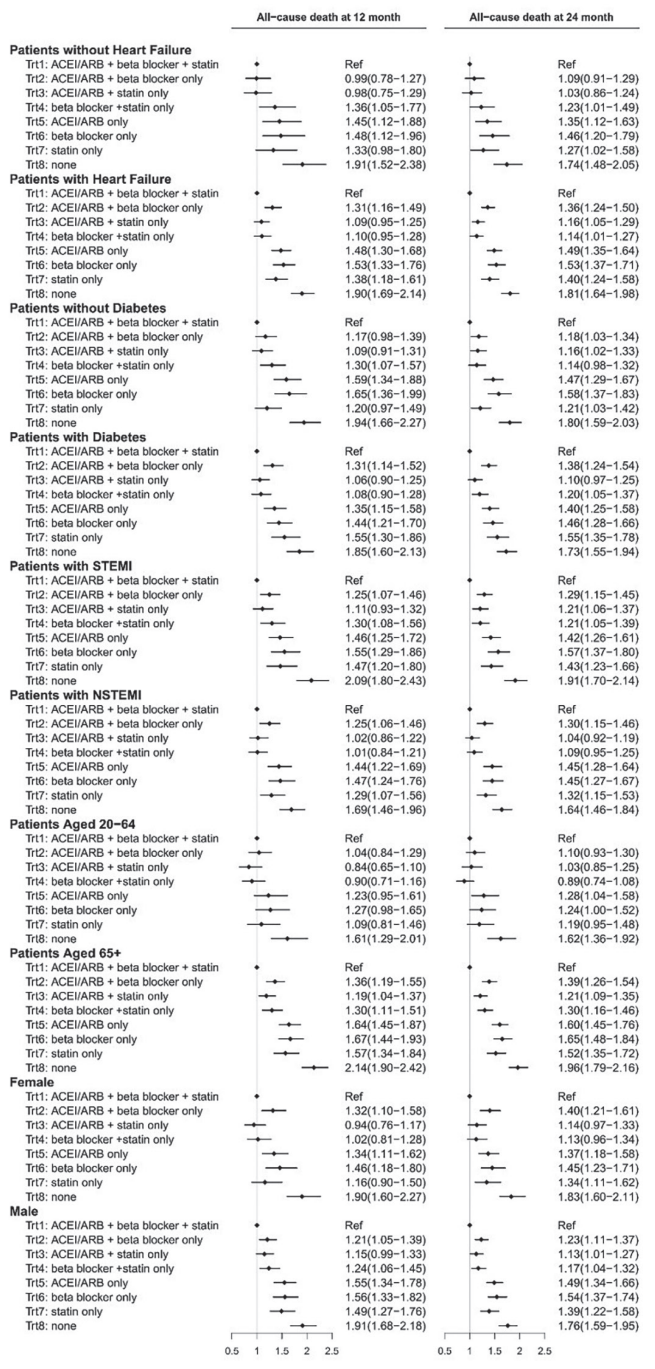

Fig. 4 HR of all-cause death for treatment efficiency in subgroups stratified by the presence of heart failure and diabetes, AMI type, age, and gender. *Adjusted HR was estimated through multivariable Cox regression after adjustment for the covariates listed in Table. ACEI = angiotensin-converting enzyme inhibitor; AMI = acute myocardial infarction; ARB = angiotensin receptor blocker; HR = hazard risk; NSTEMI = non-ST-elevation myocardial infarction; STEMI = ST-elevation myocardial infarction; Trt = treatment; Trt1 = ACEI/ARB + beta-blocker + statin; Trt2 = ACEI/ARB + beta-blocker only; Trt3 = ACEI/ARB + statin only; Trt4 = beta-blocker + statin only; Trt5 = ACEI/ARB only; Trt6 = beta-blocker only; Trt7 = statin only; Trt8 = none.

frequently receive evidence-based therapies.[21,22] In our study, older patients were also more likely to receive single or no preventive therapy. However, our subgroup analysis revealed that patients with heart failure, diabetes, and in old age appeared to benefit more in terms of survival and MACEs from adhering to all three preventive therapies, and this finding was similar to that of studies that revealed that GDMTs conferred a considerable benefit to these patients.[4,6,23] In addition, for patient with diabetes, Trt3 (ACEI/ARB + statin) was the only treatment group that did not confer a significant mortality difference compared with Trt1. The finding aligned with current evidence for ACEIs/ARBs and statin in reducing mortality in patients with diabetes.[24,25]

The current study has several limitations. First, in the observational studies, confounding by indication is an often-intractable threat to validity because patients with poor prognosis are more likely to be treated aggressively. We did observe the patients in the treatment group 1 received all three preventive medications had higher percent of hypertension and hyperlipidaemia but younger age (shown in Table); thus, the existence of confounding by indication was found. We used multivariable regression models and subgroup of patients to improve the validity of the findings in this current study; however, no adjustment methods fully resolve the issue of confounding by indication.[26] Therefore, the implementation and interpreting the results should be careful. Besides, in this study, we used intention to treat (IIT) approach to present the importance of the short-term preventive medication use associated with a lower risk of cardiac events. We recognized the patients might switch their treatment groups during the follow-up period. However, the effect of switch on the risk of outcomes was more likely to be smaller because the study using the Taiwan Acute Coronary Syndrome Full Spectrum Registry found that the prescription rate of preventive medications was not changed much after 3 months of index event except dual antiplatelet therapy.[15] Second, we used medical prescription claims to estimate adherence, and we had no information on patients' actual drug adherence. However, this measure of adherence has been shown to correlate with pill counts in other studies.[27] The misclassification among treatment groups should be nondifferential, which results in null bias. Third, in this study, only a small percentage of patients was classified into the treatment group 1 (received all three preventive therapies). The choice of treatment was often related to the characteristics of patients (eg, age, comorbidity, contraindication) as well as the preference of physicians (eg, age, sex, and specialty). It was very interesting if we could further investigate it; however, such data is not available due to the nature of the data from health insurance reimburse claims. Finally, we did not have information on actual left ventricular ejection fractions or the coronary anatomy of our study populations. Such information may be of particular importance in clinical practice for physicians to decide on prescribing medications such as ACEIs/ARBs or beta-blockers.

Our study may provide clinical and policy implications for post-MI patients from Asian populations. From this large population-based real-world study, the postdischarge adherence of all three secondary preventive medications after AMI was associated with significant long-term reductions in mortality.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://links.lww.com/JCMA/A107.

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