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ORIGINAL INVESTIGATIONS

Adherence Tradeoff to Multiple Preventive Therapies and All-Cause Mortality After Acute Myocardial Infarction

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ABSTRACT

BACKGROUND Angiotensin-converting enzyme (ACE) inhibitors/angiotensin II receptor blockers (ARB), beta-blockers and statins are recommended after acute myocardial infarction (AMI). Patients may adhere to some, but not all, therapies.

OBJECTIVES The authors investigated the effect of tradeoffs in adherence to ACE inhibitors/ARBs, beta-blockers, and statins on survival among older people after AMI.

METHODS The authors identified 90,869 Medicare beneficiaries ≥65 years of age who had prescriptions for ACE inhibitors/ARBs, beta-blockers, and statins, and survived ≥180 days after AMI hospitalization in 2008 to 2010. Adherence was measured by proportion of days covered (PDC) during 180 days following hospital discharge. Mortality follow-up extended up to 18 months after this period. The authors used Cox proportional hazards models to estimate hazard ratios of mortality for groups adherent to 2, 1, or none of the therapies versus group adherent to all 3 therapies.

RESULTS Only 49% of the patients adhered (PDC ≥80%) to all 3 therapies. Compared with being adherent to all 3 therapies, multivariable-adjusted hazard ratios (95% confidence intervals [CIs]) for mortality were 1.12 (95% CI: 1.04 to 1.21) for being adherent to ACE inhibitors/ARBs and beta-blockers only, 0.98 (95% CI: 0.91 to 1.07) for ACEI/ARBs and statins only, 1.17 (95% CI: 1.10 to 1.25) beta-blockers and statins only, 1.19 (95% CI: 1.07 to 1.32) for ACE inhibitors/ARBs only, 1.32 (95% CI: 1.21 to 1.44) for beta-blockers only, 1.26 (95% CI: 1.15 to 1.38) statins only, and 1.65 (95% CI: 1.54 to 1.76) for being nonadherent (PDC <80%) to all 3 therapies.

CONCLUSIONS Patients adherent to ACE inhibitors/ARBs and statins only had similar mortality rates as those adherent to all 3 therapies, suggesting limited additional benefit for beta-blockers in patients who were adherent to statins and ACE inhibitors/ARBs. Nonadherence to ACE inhibitors/ARBs and/or statins was associated with higher mortality. (J Am Coll Cardiol 2017;70:1543-54) © 2017 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

AMI = acute myocardial infarction

ARB = angiotensin II receptor blocker

CI = confidence interval

CVD = cardiovascular disease

HR = hazard ratio

PDC = proportion of days covered

Clinical guidelines recommend prescribing angiotensin-converting enzyme (ACE) inhibitors/angiotensin II receptor blockers (ARB), beta-blockers, and statins after an acute myocardial infarction (AMI). The effectiveness of these guideline-recommended preventive therapies is dependent on patient adherence (1-4). However, a recent U.S. study reported that almost 40% of the patients who initiated use of ACE inhibitors/ARBs, beta-blockers or statins following hospitalization for AMI became nonadherent during the first treatment year (5). Many seem to do so already during the first 6 months (6). Studies from other countries also suggest sub-optimal adherence to preventive therapies for the secondary prevention of cardiovascular disease (CVD) (7-9).

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Adhering to multiple therapies can present considerable challenges for older adults with multiple comorbidities and medications. The proportion of adults 65 years of age and older who take 5 or more prescription medications tripled from 13% to 39% between 1988 and 2010 (10). Patients with multiple comorbidities and polypharmacy have an increased risk of drug-drug interactions and adverse drug events (11). Furthermore, therapeutic and medication regimen complexity may decrease medication adherence (12,13). Patients may have tradeoffs in adherence; in other words, they may choose to adhere to some post-AMI preventive therapies, but not to others. Studies have shown notable variation in adherence across post-AMI preventive therapies (1,5,9,14,15). Clinicians who manage patients with complex treatment regimens are required to balance benefits and risks of preventive therapies, because evidence from randomized clinical trials mostly relates to the efficacy of a single preventive therapy on survival following AMI rather than combinations of therapies (16,17). Indeed, post-AMI beta-blocker trials were largely performed before statin use became widespread, and additive efficacy of beta-blockers in statin-treated patients remains undetermined.

If a patient is not able to adhere to all post-AMI preventive therapies long term, which therapies should clinicians emphasize for patient adherence? Little is known about the clinical impact of the tradeoffs in adherence made among the preventive therapies after AMI. Thus, the objective of this study was to investigate the effects of tradeoffs in adherence to ACE inhibitors/ARBs, beta-blockers, and statins on all-cause mortality after AMI in a large cohort of Medicare beneficiaries.

METHODS

DATA SOURCES AND STUDY COHORT. Data were sourced from the Center for Medicare & Medicaid Services Medicare Chronic Condition Data Warehouse 2007 to 2011 files that include enrollment summaries and inpatient, outpatient, skilled-nursing facility, physician office visits, and prescription claims. We first identified all Medicare beneficiaries meeting the following eligibility criteria: 1) age 65 years or older; 2) continuous enrollment for ≥365 days before and ≥180 days after the index AMI hospitalization in the Medicare fee-for-service and Part D prescription benefits; 3) index AMI hospitalization between January 1, 2008, and December 31, 2010; 4) discharge to home, and 5) survival for >180 days after the index hospitalization (**Figure 1**). Patients hospitalized for AMI were identified using an International Classification of Diseases, Ninth Revision, code of 410.x1 recorded either in the primary or secondary discharge diagnosis field in the inpatient files (5). The index AMI hospitalization was defined as each patient's first hospitalization for AMI between 2008 and 2010. The final study population comprised patients who had all 3 preventive therapies (ACE inhibitors/ARBs, beta-blockers, and statins) within 30 days of the index hospital discharge (**Figure 1**). Having a preventive therapy was defined as either having filled a prescription during the 30-day period, or having enough medication supply from a prescription filled before the AMI hospitalization to cover the 30-day period after discharge.

ASSESSMENT OF ADHERENCE AND ADHERENCE TRADEOFF. A timeline for measurement of patient

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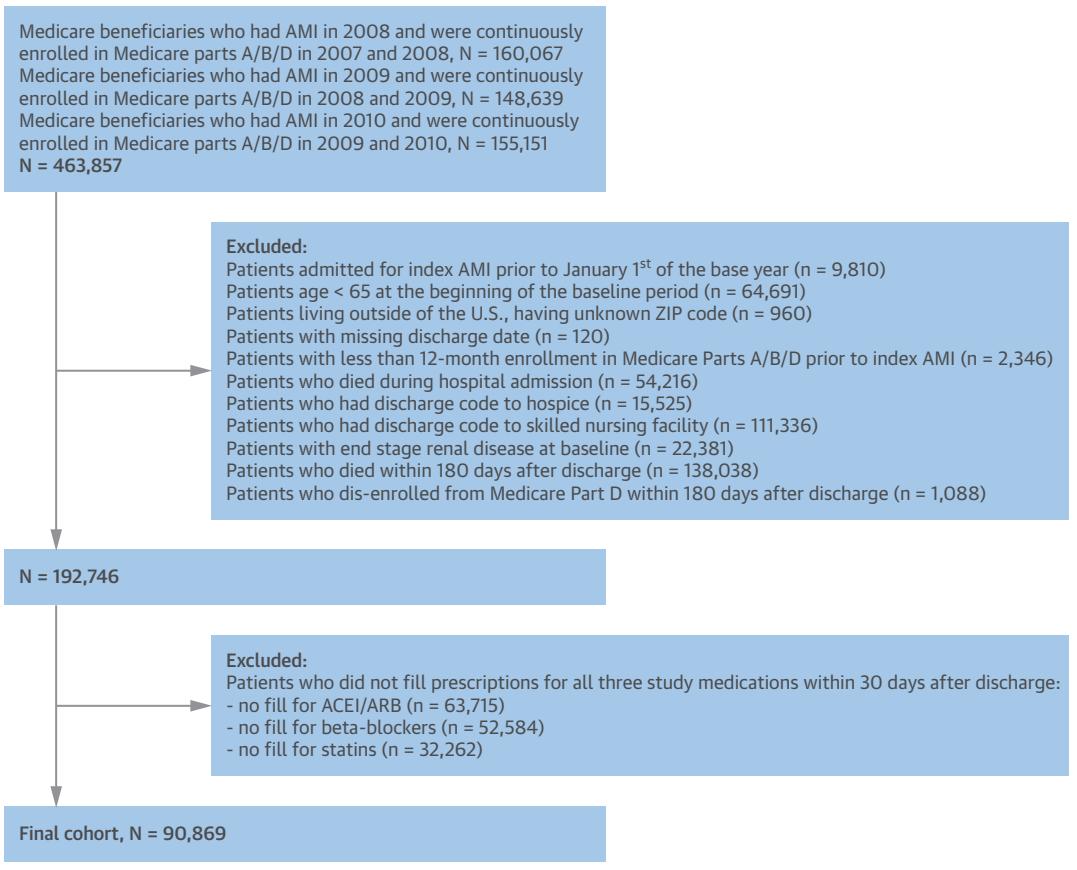
FIGURE 1 Flowchart of the Study Population



ACEI/ARB = angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers; AMI = acute myocardial infarction.

characteristics, adherence and outcomes is shown in Online Figure 1. We measured adherence for 180 days following hospital discharge. We calculated the proportion of days covered (PDC) over the entire 180 days using Medicare Part D prescription claims files to measure patient adherence to a therapy (5). The PDC was calculated using dates and days of supply of the prescriptions filled. We classified patients as adherent (PDC ≥80%) or nonadherent (<80%) separately to each of the 3 preventive therapies. Previous research has shown that post-AMI patients benefit from use of preventive therapies at the adherence levels of ≥80% (2). Tradeoffs in medication adherence were assessed by adherence categories to the 3 therapies. We had the following 8 categories: 1) adherent to all 3 therapies; 2) adherent to ACE inhibitors/ARBs and beta-blockers only; 3) adherent to ACE inhibitors/ARBs and statins only; 4) adherent to beta-blockers and statins only; 5) adherent to ACE inhibitors/ARBs only; 6) adherent to beta-blockers only; 7) adherent to statins only; and 8) adherent to none of the 3 therapies.

ASSESSMENT OF OUTCOME. Mortality was measured using the verified date of death from the Medicare enrollment file. Patients were followed-up for death from the end of the 180-day adherence assessment period up to 18 months (Online Figure 1).

PATIENT CHARACTERISTICS. All covariates were measured prior to the adherence assessment period (Online Figure 1). Clinical characteristics included the Charlson Comorbidity Index, diagnoses of any CVD and other risk factors for mortality in the 365-day baseline period before index AMI hospitalization. The baseline CVD diagnoses and risk factors included AMI, coronary artery bypass graft surgery, percutaneous coronary intervention, stroke/transient ischemic attack, unstable angina, angina pectoris, ischemic heart disease, heart failure, atrial fibrillation, peripheral vascular disease, hypertension,

diabetes mellitus, hyperlipidemia, cancer, depression and dementia/Alzheimer's disease, and baseline potential intolerant conditions/contraindications to the preventive therapies including chronic kidney disease, liver disease, chronic obstructive pulmonary disease, and asthma. In addition, dispensations of ACE inhibitors/ARBs, beta-blockers, and statins within the 180 days before the index AMI hospitalization were included as were AMI type (ST-segment elevation versus non-ST-segment elevation myocardial infarction), revascularization procedures (angiography, coronary artery bypass graft surgery, percutaneous coronary intervention, cardiac catheterization, infusion of thrombolytic and/or platelet inhibitors), complications (heart failure, cardiogenic shock, acute renal failure, hypotension, cardiac dysrhythmias), total intensive care unit and inpatient days measured during the index hospitalization, and sociodemographic variables (sex, age, median household income of U.S. Census block groups, state of residence, and insurance status) measured before the index AMI hospitalization.

We included an additional set of covariates to reduce potential confounding bias by frailty. Frailty is a strong risk factor for mortality in older people (18,19) and may affect adherence. This additional set included the following variables previously found to predict dependency in activities of daily living in Medicare population: use of ambulance transport, wheelchair, podiatric care, rehabilitation services, and screening tests, treatment for coagulation deficiency and lipid abnormality, as well as diagnoses for decubitus ulcer, falls/difficulty walking, obesity, bladder dysfunction, infection/sepsis, neurological disorder, osteoarthritis, paralysis, Parkinson disease, pulmonary circulation disorder, vertigo, weakness, and weight loss (19).

STATISTICAL ANALYSES. The distributions of patient characteristics, adherence, and outcome events were assessed by the categories of adherence to the therapies. Categorical variables were expressed as numbers and percentages, and continuous variables as mean ± SD. Kaplan-Meier estimators were applied to estimate the crude mortality rate at 1-year follow-up. We used Cox proportional hazards models to estimate hazard ratios (HRs) and their 95% confidence intervals (CIs) for all-cause mortality associated with other adherence groups in comparison with the group adherent to all 3 therapies. The model adjusted for all patient characteristics measured. The adjusted survival curves of the adherence groups were also plotted (20). The adjusted mortality rates at 1-year follow-up were estimated from the model. We assessed the proportional hazards assumption using 2 methods: Schoenfeld residuals test (Online Table 1) and graphical examination for crossover of Kaplan-Meier curves (**Central Illustration**). The Schoenfeld residuals test only showed very weak correlation between the Schoenfeld residuals for the groups adherent to ACE inhibitors/ARBs only and adherent to none of the therapies and time, and there was no crossover between their curves and the curve of the reference group (adherent to all 3 therapies). The assessment suggests that although the HRs may not be constant over time for the 2 adherence groups, inference on their HRs as average effects over time will still be valid.

Given the compelling indication of ACE inhibitors/ARBs for managing heart failure and diabetes, and polypharmacy burden for cognitively impaired patients, we additionally conducted subgroup analyses stratified by heart failure (either pre-admission or during admission), diabetes, and dementia, as well as age group (65 to 74 years, 75 to 84 years, 85+ years) and sex. We tested for statistical significance of the heterogeneity of the association between adherence group and mortality across the subgroups defined by presence of heart failure by including a product term "heart failure*adherence group" in the model, and similarly for presence of diabetes and dementia, and finally for age group and sex.

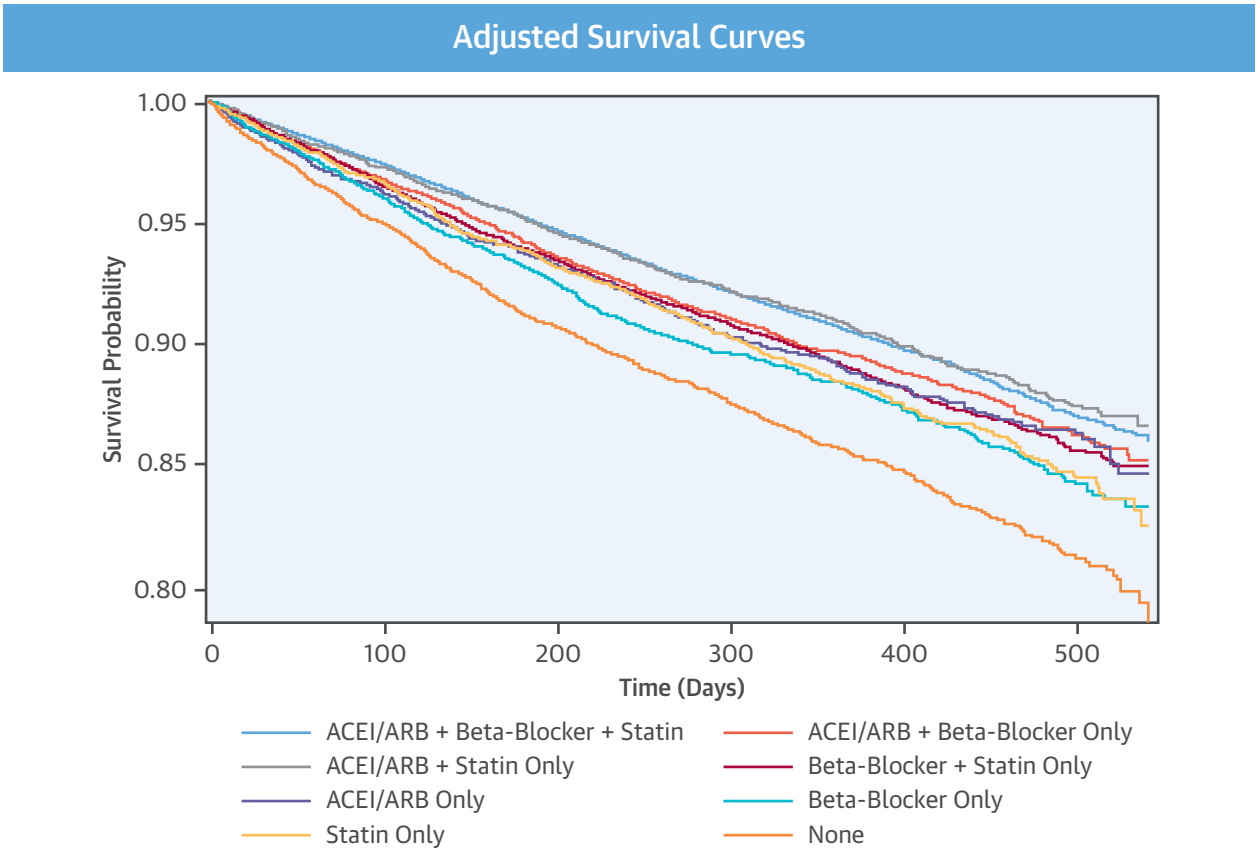
In the sensitivity analysis, we additionally adjusted for polypharmacy (total number of unique medication classes with prescriptions filled in the 30 days after hospital discharge) and average daily dose of the last prescription for each of the 3 therapies filled in the 30 days after hospital discharge from Part D prescription files. All statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

STUDY COHORT AND ADHERENCE GROUPS. Overall, 466,385 beneficiaries suffered an index AMI during the study period. Among these beneficiaries 192,746 patients met all the eligibility criteria. Of these patients 63,715 (33.1%) did not fill any prescriptions for ACE inhibitors/ARBs; 52,584 (27.3%) filled no prescriptions for beta-blockers, and 32,262 (16.7%) filled no prescriptions for statins within 30 days after the index discharge. The final study populations consisted of 90,869 patients who had all 3 therapies within the 30 days.

More than one-half of the patients (51.5%) were nonadherent to 1 or more of the 3 preventive therapies during the 180-day adherence assessment

CENTRAL ILLUSTRATION **Adherence Tradeoff to Preventive Therapies and Survival**



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Adjusted survival curves of all-cause mortality by adherence categories to preventive therapies. Adjusted for patient characteristics shown in Online Table 2 and total intensive care unit and inpatient days. ACEI/ARB = angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers.

period. Overall, 27,911 patients (30.7%) were nonadherent to ACE inhibitors/ARBs, 21,589 (23.8%) were nonadherent to beta-blockers, and 20,861 (23.0%) were nonadherent to statins. **Table 1** shows selected baseline characteristics of the final study population according to the adherence category (see Online Table 2 for the distributions of all covariates).

MORTALITY IN THE WHOLE COHORT. Of the final study population, 9,617 (10.6%) died during the mean follow-up of 347 days. Crude and adjusted mortality rates among patients who were adherent to all 3 therapies were 8.9% and 9.3% at 1-year follow-up, respectively (**Figure 2**). The 1-year crude and adjusted mortality rates for patients who were nonadherent to all 3 therapies were 16.1% and 14.3%, respectively. **Figure 2** shows that those who were adherent to ACE inhibitors/ARBs and statins only had similar mortality as those adhering to all 3 therapies (adjusted HR: 0.98; 95% CI: 0.91 to 1.07). Those who were nonadherent to all 3 therapies had highest mortality (HR: 1.65; 95% CI: 1.54 to 1.76), followed by those who were adherent to beta-blockers only (HR: 1.32; 95% CI: 1.21 to 1.44), to statins only (HR: 1.26; 95% CI: 1.15 to 1.38), to ACE inhibitors/ARBs only (HR: 1.19; 95% CI: 1.07 to 1.32), to beta-blockers and statins only (HR: 1.17; 95% CI: 1.10 to 1.25), and to ACE inhibitors/ARBs and beta-blockers only (HR: 1.12; 95% CI: 1.04 to 1.21). The adjusted survival curves are presented in the **Central Illustration**. Adjustment for additional variables suggestive of pre-admission frailty did not appreciably change the HRs already adjusted for conventional sociodemographic and clinical variables (Online Table 3). The sensitivity analysis by additionally adjusting for polypharmacy

TABLE 1 Selected Baseline Characteristics of the Study Population Stratified by Adherence to the 3 Classes of Preventive Therapies

		Adherent To							
	Cohort (N = 90,869) (100%)	All 3 Therapies (n = 44,051) (48.5%)	ACE Inhibitor/ ARB + Beta-Blocker Only (n = 8,269) (9.1%)	ACE Inhibitor/ ARB + Statin Only (n = 7,242) (8.0%)	Beta-Blocker + Statin Only (n = 12,401) (13.6%)	ACE Inhibitor/ ARB Only (n = 3,396) (3.7%)	Beta-Blocker Only (n = 4,559) (5.0%)	Statin Only (n = 4,304) (4.7%)	None (n = 6,647) (7.3%)
Sociodemographics									
Age, yrs									
65–74	43.6	44.6	43.3	43.1	41.2	43.1	41.8	43.5	43.7
75–84	39.7	39.2	40.1	43.7	41.3	39.7	40.3	40.4	38.4
85+	16.7	16.1	17.6	17.2	17.6	17.2	17.9	16.2	17.9
Sex, male	45.2	45.4	40.9	45.5	45.9	41.4	43.0	51.5	47.3
Race									
White	85.0	86.1	84.5	84.8	87.1	80.0	85.1	86.2	76.6
Black	8.0	7.1	8.7	7.9	6.6	11.4	8.7	7.0	14.0
Hispanic	2.9	2.7	3.2	3.2	2.4	4.3	2.9	2.5	4.4
Asian	2.2	2.2	1.7	2.1	2.3	2.4	1.5	2.4	2.4
Other	1.9	1.9	1.9	2.0	1.6	1.9	1.8	1.9	2.7
Income proxy*									
≤$30,000	47.2	46.9	47.7	46.4	45.6	51.4	46.0	44.5	52.1
$30,001–$60,000	41.4	41.7	41.2	42.3	42.4	37.9	42.1	42.5	37.5
$60,001–$100,000	9.2	9.2	9.1	9.1	9.7	8.3	9.9	10.4	8.3
$100,001–$150,000	1.7	1.7	1.6	1.7	1.6	1.9	1.5	2.0	1.7
≥$150,001	0.5	0.5	0.4	0.6	0.6	0.5	0.4	0.7	0.4
Having Part D prescription drug benefit gap ("doughnut hole")	12.7	13.5	12.0	13.1	13.4	11.6	11.3	12.0	9.3
Medicare & Medicaid dual eligibility	23.5	24.4	21.5	22.6	21.2	25.7	19.8	19.3	29.6
Clinical characteristics (within 12 months before index admission)									
AMI	2.8	2.7	3.0	2.6	2.8	2.5	3.6	3.0	3.1
CABG	0.7	0.7	0.6	0.8	0.9	0.6	0.8	0.9	0.6
PCI	4.8	4.8	4.8	4.8	4.7	4.7	5.7	4.6	4.6
Stroke/TIA	6.0	5.6	5.9	6.4	6.1	6.2	7.3	6.5	7.2
Unstable angina	3.8	3.7	3.8	3.9	4.2	4.5	4.2	3.5	3.5
Angina pectoris	6.2	6.2	6.1	6.5	6.5	6.3	7.2	5.9	5.4
IHD	44.0	43.0	45.2	44.8	45.4	43.5	47.9	43.8	43.0
CHF	20.7	19.8	21.7	19.6	22.5	21.4	22.8	19.5	22.8
Atrial fibrillation	9.7	9.3	10.4	9.9	10.9	9.3	10.9	9.9	8.1
Hypertension	75.6	75.2	78.2	76.7	76.6	77.9	78.7	71.4	71.1
PVD	17.3	16.6	17.6	17.3	18.6	16.8	19.5	17.3	17.8
Hyperlipidemia	59.3	59.5	60.0	60.2	61.5	56.4	60.7	60.5	51.2
Diabetes	40.0	40.0	40.7	39.8	40.3	41.0	42.0	38.0	38.3
CKD	11.4	10.2	10.5	10.4	15.1	10.6	14.8	12.5	11.9
COPD	21.3	19.8	21.7	21.8	22.5	23.5	21.2	23.9	24.7
Asthma	5.1	4.6	5.2	5.4	5.5	6.4	5.0	5.7	6.2
Liver disease	1.5	1.5	1.8	1.1	1.4	1.9	1.6	1.5	1.8
Cancer	10.4	9.9	10.8	10.4	11.2	9.8	12.1	11.6	9.76
Depression	13.0	12.1	13.1	13.3	13.7	14.2	14.6	14.5	15.3
Dementia/Alzheimer disease	9.5	7.2	7.0	8.4	7.4	9.8	8.7	8.7	11.8
Charlson Comorbidity Index									
0	30.7	32.2	29.7	30.4	28.8	29.0	27.0	30.4	30.0
1–2	39.8	40.1	40.3	40.8	38.5	41.4	39.2	39.0	39.1
3–5	23.4	22.2	24.3	23.3	25.3	24.1	25.5	23.9	24.3
6–8	5.0	4.6	4.7	4.5	6.3	4.4	6.7	5.4	5.4
9+	1.1	0.9	1.0	1.0	1.2	1.2	1.6	1.4	1.2

Continued on the next page

TABLE 1 Continued

		Adherent To							
	Cohort (N = 90,869) (100%)	All 3 Therapies (n = 44,051) (48.5%)	ACE Inhibitor/ ARB + Beta-Blocker Only (n = 8,269) (9.1%)	ACE Inhibitor/ ARB + Statin Only (n = 7,242) (8.0%)	Beta-Blocker + Statin Only (n = 12,401) (13.6%)	ACE Inhibitor/ ARB Only (n = 3,396) (3.7%)	Beta-Blocker Only (n = 4,559) (5.0%)	Statin Only (n = 4,304) (4.7%)	None (n = 6,647) (7.3%)
Pre-admission medication use (within 180 days before index admission)									
ACE inhibitor/ARB	69.5	70.8	73.5	73.0	69.1	73.9	66.7	60.5	58.9
Beta-blocker	56.6	58.8	61.6	51.1	58.2	48.3	62.9	48.6	44.3
Statin	61.2	63.7	55.5	67.0	64.5	52.0	54.3	63.9	47.7
Characteristics of index admission									
NSTEMI	71.9	70.7	72.7	73.8	72.4	74.3	73.8	71.4	73.7
CHF	35.3	34.7	35.1	31.8	38.4	34.5	37.6	35.0	37.0
Cardiogenic shock	2.7	2.7	2.4	2.0	3.6	2.2	2.8	3.4	2.3
Cardiac arrest	1.2	1.2	1.1	0.9	1.2	0.8	1.5	1.6	0.9
Acute renal failure	12.2	10.3	11.0	10.7	18.0	10.4	15.5	14.6	13.3
Cardiac dysrhythmias	30.2	29.9	31.6	31.0	31.2	29.3	31.0	30.7	27.3
Hypotension	5.0	4.8	4.5	5.1	5.6	4.7	5.0	6.1	4.6
Angiocardiography	67.4	69.1	66.3	67.5	66.3	65.6	64.2	67.9	62.0
CABG	7.7	7.0	6.7	7.2	11.0	6.5	8.6	10.0	6.4
PCI	48.6	51.6	47.0	48.4	46.0	46.4	42.9	46.8	41.6
Cardiac catheterization	67.7	69.3	66.7	67.9	66.7	66.3	65.2	67.7	62.5
Thrombolytic use for AMI	0.7	0.7	0.8	0.6	0.5	0.8	0.6	0.7	0.7
Antiplatelet use for AMI	5.4	5.6	5.3	5.6	5.4	4.8	4.9	5.3	4.9
Adherence (PDC), mean (during 180 days after the index discharge)									
ACE inhibitor/ARB	0.81	0.97	0.96	0.96	0.45	0.94	0.46	0.46	0.45
Beta-blocker	0.86	0.97	0.96	0.53	0.97	0.53	0.95	0.52	0.48
Statin	0.85	0.97	0.52	0.95	0.96	0.51	0.51	0.94	0.46
Follow-up days, mean	347	351	347	352	344	345	344	347	335

Values are % unless otherwise stated. *Average household income at Census block groups of residence among residents who were age 65 years and older.

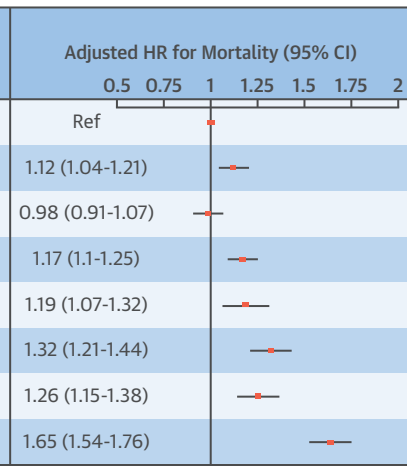
ACE inhibitor/ARB = angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; AMI = acute myocardial infarction; CABG = coronary artery bypass surgery; CHF = congestive heart failure; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; IHD = ischemic heart disease; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary interventions; PDC = proportion of days covered; PVD = peripheral vascular disease; TIA = transient ischemic attack.

and dose of the 3 therapies yielded very similar and consistent findings (Online Table 4).

MORTALITY IN PATIENT SUBGROUPS. We observed some variation in the associations across subgroups of patients with and without heart failure, diabetes, and dementia (p values for interactions heart failure*adherence group 0.176, diabetes*adherence group 0.002, and dementia*adherence group 0.032). The results of subgroup analyses comparing other adherence groups to the group adherent to all 3 therapies are presented in **Figure 3**. Overall, directions of all associations between adherence groups and mortality in patients with heart failure and diabetes were similar to those in the whole study population, with patients who were nonadherent to all 3 therapies having the highest mortality. Mortality in patients who were adherent to ACE inhibitors/ARBs and statins only was not significantly different to mortality in those who were adherent to all 3 therapies in any of the subgroups. Nonetheless, the HR of mortality for patients who were adherent to ACE inhibitors/ARBs only versus all 3 therapies was 1.38 (95% CI: 1.16 to 1.65) among patients without heart failure and 1.10 (95% CI: 0.96 to 1.26) with heart failure. The HR of mortality for patients who were adherent to ACE inhibitors/ARB only versus all 3 therapies was 1.14 (95% CI: 0.97 to 1.33) among patients without diabetes and 1.24 (95% CI: 1.07 to 1.43) with diabetes. The HR of mortality for patients who were adherent to beta-blockers only versus all 3 therapies was 1.18 (95% CI: 1.04 to 1.34) among patients without diabetes and 1.44 (95% CI: 1.28 to 1.62) with diabetes. The HR of mortality for patients who were adherent to statins only versus all 3 therapies was 1.38 (95% CI: 1.07 to 1.43) among patients without diabetes and 1.12 (95% CI: 0.98 to 1.29) with diabetes. Compared were patients without dementia, patients with dementia had higher mortality when adherent to ACE inhibitors/ARB and beta-blockers only (HR: 1.09; 95% CI: 1.01 to 1.18; and HR: 1.29; 95% CI: 1.06 to 1.55) and to beta-blockers only (HR: 1.29; 95% CI: 1.17 to 1.42; and HR: 1.58; 95% CI: 1.28 to 1.95) versus 3 therapies. The effects of adherence tradeoffs on

FIGURE 2 Crude and Adjusted Rates and HRs (95% CIs) of All-Cause Mortality by Adherence Categories to Preventive Therapies in the Whole Study Cohort

Adherence Group	Total No. of Mortality (Event Rate)	Crude K-M Mortality Rate at 1 Year	Crude HR for Mortality (95% CI)	Adjusted Mortality Rate at 1 Year	Adjusted HR for Mortality (95% CI)
ACEI/ARB + Beta-Blocker + Statin	3,995 (9.1%)	8.9%	Ref	9.3%	Ref
ACEI/ARB + Beta-Blocker Only	884 (10.7%)	10.5%	1.19 (1.11-1.28)	10.3%	1.12 (1.04-1.21)
ACEI/ARB + Statin Only	670 (9.3%)	8.9%	1.02 (0.94-1.10)	9.1%	0.98 (0.91-1.07)
Beta-Blocker + Statin Only	1,448 (11.7%)	11.6%	1.31 (1.23-1.40)	10.9%	1.17 (1.1-1.25)
ACEI/ARB Only	381 (11.2%)	11.1%	1.26 (1.13-1.40)	10.9%	1.19 (1.07-1.32)
Beta-Blocker Only	618 (13.6%)	12.8%	1.52 (1.40-1.66)	11.6%	1.32 (1.21-1.44)
Statin Only	530 (12.3%)	12.1%	1.37 (1.25-1.50)	11.5%	1.26 (1.15-1.38)
None	1,091 (16.4%)	16.1%	1.89 (1.77-2.02)	14.3%	1.65 (1.54-1.76)



Reference group: patients who were adherent to all 3 preventive therapies. Hazard ratios (HRs) are adjusted for patient characteristics shown in Online Table 2 and total intensive care unit and inpatient days. ACEI/ARB = angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers; CI = confidence interval; K-M = Kaplan-Meier.

mortality tended to be stronger in men than women (p value for sex*adherence group 0.031) and in younger age groups than the oldest one (P value for age group*adherence group = 0.097).

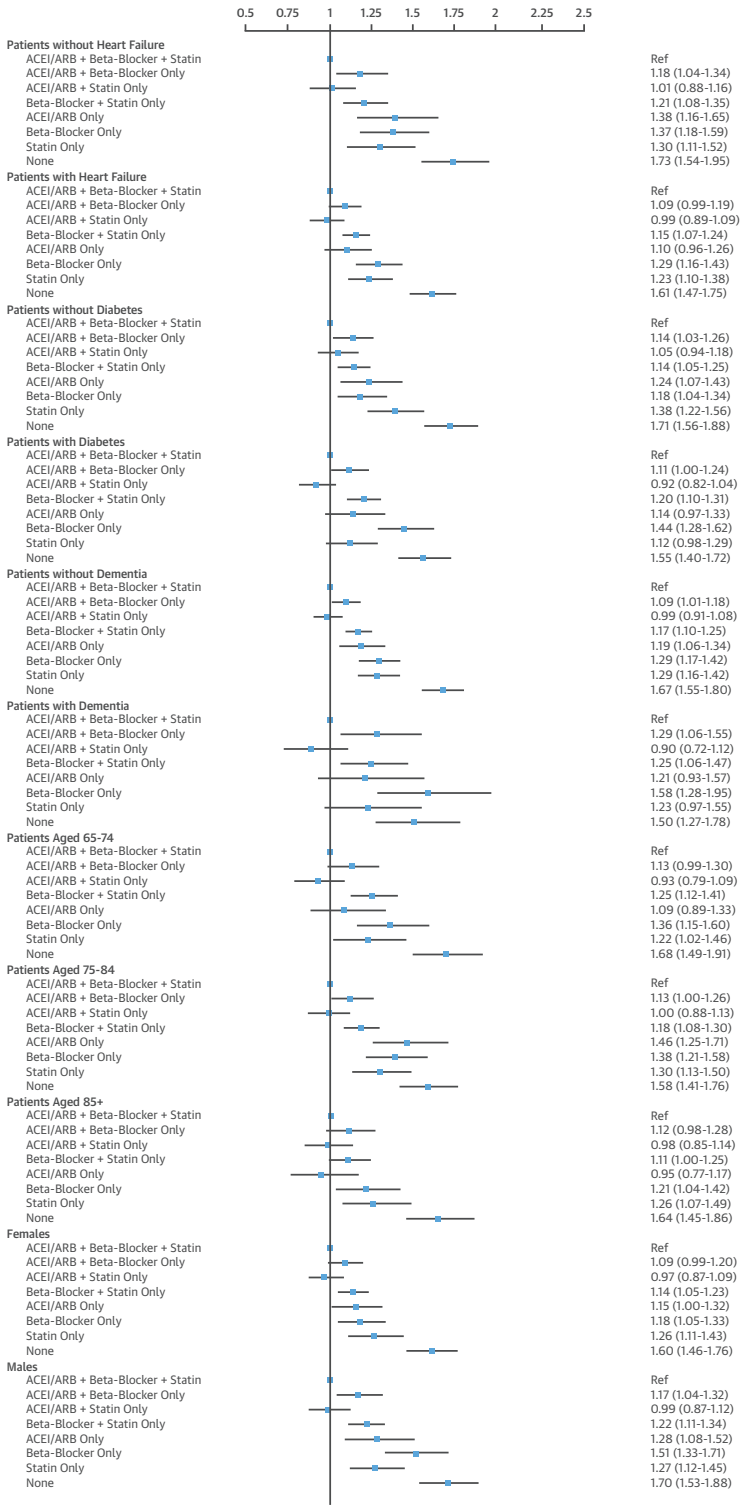
DISCUSSION

In our cohort of older Medicare beneficiaries, 30% were nonadherent to ACE inhibitors/ARBs, and almost 25% were nonadherent to beta-blockers and statins, respectively, at 6 months after discharge. These nonadherence rates are comparable to those reported recently among older post-AMI survivors in the United States (5). Among those who received ACE inhibitors/ARBs, beta-blockers, and statins within a month after AMI hospitalization, all-cause mortality rates among patients who were adherent to ACE inhibitors/ARBs and statins only did not differ from rates among those who were adherent to all 3 therapies. Nonadherence to ACE inhibitors/ARBs or statins in any combination and nonadherence to all 3 therapies in particular was associated with notably higher mortality. These associations were broadly similar in patient subgroups defined by sex, age, presence of heart failure, diabetes, and dementia.

Our findings are intriguing for long-term medical management of older patients after AMI. Clinical guidelines recommend all 3 therapies, ACE inhibitors/ARBs, statins, and beta-blockers, for long-term use as secondary prevention after AMI; however, their benefits were demonstrated in randomized controlled trials for a single therapy rather than combinations (16,17). Clinical uncertainties exist as to the clinical impact of adherence to some therapies versus all 3 in the long term. In clinical practice, this is a particularly challenging issue for older adults with multiple morbidities and polypharmacy. The high prevalence of comorbidities and polypharmacy may markedly increase the risk of adverse drug events and drug-drug interactions, which is further complicated by more prevalent cognitive impairment in older people. Occurrence of adverse drug events accompanied with the physical and cognitive burdens of taking many medications may render long-term adherence to all 3 AMI preventive therapies unrealistic, though desired.

We found that, among patients who had all 3 therapies after AMI hospitalization, being adherent to ACE inhibitors/ARBs and statins only was associated with equal survival as being adherent to all 3 therapies. Nonadherence to ACE inhibitors/ARBs or statins in any combination in particular was associated with notably higher mortality. Thus, our findings suggest that long-term adherence to ACE inhibitors/ARBs and statins may be more important than adherence to beta-blockers after AMI. Prior, smaller studies from the United States (1,21) and other countries (3,9,22) also showed larger reductions in all-cause mortality for adherence to statins and ACE inhibitors/ARBs than adherence to beta-blockers. Accordingly, in a large observational study (n = >44,000), beta-blockers were not associated with mortality benefit in patients with prior MI or those without a history of

FIGURE 3 **HRs (95% CIs) of All-Cause Mortality by Adherence to Various Combinations of Preventive Therapies in Subgroups Stratified by Presence of Heart Failure, Diabetes, and Dementia, and Age and Sex**



Reference group: patients who were adherent to all 3 preventive therapies. HRs are adjusted for the patient characteristics shown in Online Table 2 and total intensive care unit and inpatient days. Abbreviations as in **Figure 2**.

AMI (23). Our observations support the argument that in the current clinical practice, incremental survival benefits associated with use of beta-blockers may be smaller than benefits associated with use of the other 2 evidence-based preventive therapies (23–25).

Although the associations between adherence groups and mortality were generally similar among patients in subgroups as in the whole cohort, several variations are notable. The increase in mortality risk associated with being adherent to ACE inhibitors/ARBs only was considerably smaller among patients with heart failure than among patients without heart failure. Among patients with heart failure, there was no statistically significant difference in mortality risk between patients who were adherent to ACE inhibitors/ARBs only and those who were adherent to all 3 therapies. The findings are in line with the landmark clinical trials that have demonstrated ACE inhibitors/ARBs as cornerstone therapy in reducing mortality among patients with heart failure including those after AMI (26,27). In our heart failure subgroup, mortality in patients nonadherent to statins and those adherent patients did not differ. This is also consistent with 2 clinical trials that found no overall CVD risk reduction in Class II to IV heart failure patients treated with statins (28,29). The pivotal trials such as MERIT-HF (Metoprolol CR/XL Randomised Intervention Trial in-Congestive Heart Failure), COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival), and CIBIS-II (Cardiac Insufficiency Bisoprolol Study II), showed that beta-blockers are associated with lower all-cause mortality in heart failure (30–32). Our study suggests large relative benefit of beta-blocker adherence in reducing mortality in comparison to nonadherence to all 3 therapies among patients with heart failure. However, there was no benefit of beta-blocker adherence in reducing mortality in comparison to patients with heart failure and already adherent to ACE inhibitors/ARBs. This finding was a surprise to us. One possible explanation has to do with age. In the MERIT-HF, COPERNICUS, and CIBIS-II trials, the mean age of the patients was 61 to 64 years, whereas in our study, the patients were 77 years of age on average. In line with us, in the SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure) study in older heart failure patients (age >70 years), nebivolol, a beta-blocker, failed to reduce mortality (33). Further research on this is warranted.

By contrast, adherence to ACE inhibitors/ARBs and statins conferred a greater benefit in patients with diabetes than among patients without diabetes. These findings suggest that it may be most important to be adherent to ACE inhibitors/ARBs among patients with heart failure and to ACE inhibitors/ARBs and statins among patients with diabetes post-AMI. Meta-analyses of clinical trials have shown that ACE inhibitors/ARBs and statins reduce all-cause mortality among patients with diabetes (34,35). Current U.S. national guidelines recommend ACE inhibitors and statins as first-line therapy for patients with diabetes, hypertension, and CVD (36–38).

We found markedly higher mortality risk for being adherent to beta-blockers only among patients with diabetes or dementia than among patients without these conditions. This suggests that being adherent to beta-blockers in the long-term may not be as beneficial for patients with diabetes or dementia as among patients free of these conditions. Recently, a study conducted among ~16,000 U.S. nursing home residents found that among AMI survivors with moderate or severe cognitive impairment, the use of beta-blockers was associated with a 30% increased risk of experiencing functional decline over a 3-month period post-AMI (39). No such association was observed among survivors without cognitive impairment. Concerns have also been raised regarding the negative effects of beta-blockers on glycemic control, insulin sensitivity, masking of hypoglycemia, and dyslipidemia. Meta-analyses of clinical trials have shown that use of beta-blockers was associated with higher risk of new-onset diabetes than non-diuretic antihypertensive medications (40,41). The clinical implications of our findings need to be investigated in further studies.

STUDY LIMITATIONS. First, we restricted our study population to the patients who filled prescriptions for each of the 3 therapies shortly after hospital discharge. This feature of our study most likely enhances comparability of adherence groups; however, it precludes generalization of our results to situations where decisions are made to stop or not initiate preventive therapies among patients who are not eligible to all the 3 therapies at discharge. Second, due to our reliance on prescription refill data, we could not differentiate the tradeoff in adherence to multiple therapies as physicians' decision to discontinue medication or patient's/care taker's decision not to refill prescriptions. Third, although we adjusted our outcome models for a comprehensive list of baseline risk factors for potential adverse effects or intolerant conditions for therapies and mortality, including variables suggestive of pre-admission frailty, residual confounding by unmeasured factors such as use of aspirin may exist. However, the residual confounding may be limited in the comparisons between patients who were adherent to at least 1 therapy and those

adherent to all 3 therapies. By contrast, the estimates comparing patients who were adherent to none of the 3 therapies to those adherent to all therapies are likely to be affected by significant unmeasured confounding. Finally, due to relatively small numbers of patients in non-white subgroups of our study population, we did not conduct race-specific analyses. This important question should be addressed in future studies.

CONCLUSIONS

Those patients who were adherent to ACE inhibitors/ARBs and statins, but nonadherent to beta-blockers, had a similar mortality risk as those adherent to all 3 therapies, suggesting the role of post-MI beta-blockers in the statin and ACE/ARB era deserved further investigation. Nonadherence to ACEI/ARB or statins in any combination and nonadherence to all 3 therapies in particular was associated with higher mortality.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Nonadherence to statin and angiotensin inhibitor therapy among survivors of myocardial infarction (MI) may reduce survival, whereas adherence to beta-blockers may not be beneficial to patients with dementia or diabetes.

TRANSLATIONAL OUTLOOK: More research is needed to provide information on the risks and benefits of various combinations of guideline-recommended post-MI preventive therapies in patients with specific comorbidities, such as heart failure, diabetes, or dementia.

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KEY WORDS medication adherence, myocardial infarction, older adults, secondary prevention

APPENDIX For supplemental tables and a figure, please see the online version of this article.