Kidney Function and Long-Term Medication Adherence after Myocardial Infarction in the Elderly

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Summary

Background and objectives The association of kidney function with long-term outpatient medication adherence in the elderly remains understudied.

Design, setting, participants, & measurements A cohort of 2103 patients over the age of 65 years enrolled in a pharmacy benefits program after hospital discharge for myocardial infarction was studied. Using linear mixed effects models, the association of baseline kidney function with long-term adherence to recommended medications after myocardial infarction was examined, including angiotensin converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs), β-blockers, and statins. The primary outcome measure was the percentage of days covered as calculated by pharmacy refill data for 12 serial 3-month intervals (totaling 36 months of follow-up).

Results Overall long-term adherence to ACEIs/ARBs, β-blockers, and statins was poor. The mean percentage of days covered by 36 months was only 50% to 60% for all three medication classes. Patients with baseline kidney dysfunction had significantly lower long-term ACEI/ARB and β-blocker adherence compared with patients with higher baseline kidney function. Long-term statin adherence did not vary by baseline level of kidney function.

Conclusions Long-term medication adherence after myocardial infarction in the elderly is low, especially in patients with kidney dysfunction. Future strategies to improve medication adherence should pay special attention to the elderly with kidney dysfunction because they may be especially vulnerable to its adverse clinical consequences.

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Introduction

The World Health Organization estimates that only half of people with chronic diseases take their medications consistently as prescribed (*i.e.*, are medication adherent) (1). Hypertension and hyperlipidemia are examples of two such chronic diseases, with antihypertensive medication and statin adherence rates of only 30% to 40% 1 year after initiation (2–4). Inadequate BP and lipid control, two major cardiovascular disease risk factors, are exacerbated by poor adherence to medications and contribute to increased healthcare costs, hospitalizations, and death (5–7). Older age and kidney dysfunction confer additional cardiovascular risk compared with the general population risk (8,9). Moreover, elderly persons with kidney dysfunction may be at higher risk for medication nonadherence because they often have a greater pill burden and other contributing conditions such as functional status limitations, cognitive impairment, or depression (3,10–12). However, long-term medication adherence in elderly patients with kidney dysfunction has yet to be extensively studied.

We previously reported that outpatient use of angiotensin converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) within 90 days after hospitalization for myocardial infarction (MI) was lower for patients with more severe kidney dysfunction compared with patients with higher kidney function (13). The analysis presented here extends our previous study to examine long-term medication adherence after hospitalization for MI in the elderly. Specifically, we hypothesized that patients with more severe baseline kidney dysfunction would have lower long-term medication adherence compared with patients with higher kidney function.

Materials and Methods

Study Population

We conducted this study using data from patients who were >65 years old and hospitalized for MI in Pennsylvania in 1999 and 2000. This data set was originally collected to validate various claims-based algorithms for the identification of MI patients from large insurance databases (14) and has been used for a validation study of claims-based algorithms to identify patients with chronic kidney disease (CKD) (15).

The source population included all Medicare beneficiaries in Pennsylvania who were also enrolled in that state's Pharmaceutical Assistance Contract for the Elderly (PACE) in 1999 and 2000. PACE and the embedded PACE Needs Enhancement Tier (PACENET; from here on both are referred to as PACE) are state-run pharmacy benefits programs that pay for medications for low- and middle-income elderly (annual gross income ≤$23,500 if single, ≤$31,500 if married in the study year). All hospitalization episodes with the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 410.xx ("acute myocardial infarction") as a discharge diagnosis in the primary or secondary position or diagnosis-related group codes of 121, 122, or 123 during 1999 or 2000 were selected for hospital record review.

From the claims information, we first created an initial data set that contained the patient's date of birth, gender, dates of admission and discharge for the index hospitalizations, and the American Hospital Association provider number for the treating hospitals. This information was supplied to a Peer Review Organization in Pennsylvania, which then sent requests for hospital records to the respective hospitals. The protocol was approved by the Centers for Medicare and Medicaid Services and the Institutional Review Board of Brigham and Women's Hospital. Copies of both approval letters were made available to all treating facilities.

Hospital chart review was performed by ten trained hospital records abstractors at the Peer Review Organization using a structured chart abstraction program. The chart abstraction data were entered directly into an electronic database. Data elements included sex, date of birth, detailed information relevant to the diagnosis of acute MI, and other data that are relevant for the study presented here such as first serum creatinine at admission. The inter-rater agreement (κ) of the structured chart abstraction, defined as the agreement between two independent reviewers for all data elements in a 20-chart sample, was 0.931.

Baseline Variables

For each patient, we used the first serum creatinine measurement after admission for MI as well as age, sex, and race to calculate the estimated GFR (eGFR) using the four-variable version of the Modification of Diet in Renal Disease formula (16). We then separated all patients into three categories of baseline kidney function (in ml/min per 1.73 m^2): eGFR ≥60, 30 to 59, and <30. Individuals with a physiologically implausibly high eGFR were assigned a maximum of 200 ml/min per 1.73 m^2 (17).

From PACE eligibility files, we ascertained each patient's age on the day of admission for MI, sex, and race. Medicare claims from the 365 days before MI admission were used for the definition of several diagnosed comorbid conditions (coronary artery disease, congestive heart failure, cerebrovascular disease, peripheral artery disease, diabetes, hypertension, depression, chronic obstructive pulmonary disease, and malignancy; all dichotomous), as well as to describe prior healthcare utilization (number of hospital days). We included these variables in all multivariable-adjusted models.

Outcome Measures

We used PACE claims to ascertain filled prescriptions for ACEIs and ARBs (combined into one group, ACEIs/ARBs), β-blockers, and statins for each patient. These include the identifier of the prescriber, the specific drug dispensed (the National Drug Code, a unique indicator of the specific compound, strength or concentration, manufacturer, and other information), and the number of days of medication supplied. For patients who filled a prescription for one of these three medication classes between dis-

Table 1. Baseline characteristics of study patients by level of kidney function

Characteristics	All Patients (n = 1380)	eGFR ≥ 60 ml/min per 1.73 m^2 (n = 503)	eGFR 30 to 59 ml/min per 1.73 m^2 (n = 693)	eGFR < 30 ml/min per 1.73 m^2 (n = 184)	P
Age (years)	80.8 (±6.6)	79.2 (±6.4)	81.7 (±6.4)	81.8 (±7.2)	<0.001
Male gender	259 (18.8)	120 (23.9)	107 (15.4)	32 (17.4)	0.004
Race					0.38
white	1306 (94.6)	470 (93.4)	663 (95.7)	173 (94.0)	
non-white	74 (5.4)	33 (6.6)	30 (4.3)	11 (6.0)	
Length of stay (days)	7.7 (±4.4)	7.2 (±4.2)	7.7 (±4.4)	8.8 (±5.0)	<0.001
Hospital days (prior year)	5.4 (±11.0)	3.9 (±9.3)	5.8 (±11.5)	8.2 (±12.8)	<0.001
Previous diagnosis of					
coronary artery disease	1163 (84.3)	417 (82.9)	590 (85.1)	156 (84.8)	0.38
congestive heart failure	575 (41.7)	155 (30.8)	305 (44.0)	115 (62.5)	<0.001
COPD	426 (30.8)	148 (29.4)	223 (32.2)	55 (29.9)	0.63
cerebrovascular disease	390 (28.3)	129 (25.7)	202 (29.2)	59 (32.1)	0.07
depression	227 (16.5)	94 (18.7)	104 (15.0)	29 (15.8)	0.17
diabetes mellitus	585 (42.4)	178 (35.4)	315 (45.5)	92 (50.0)	<0.001
hypertension	871 (63.1)	292 (58.1)	448 (64.7)	131 (71.2)	<0.001
malignancy	241 (17.5)	89 (17.7)	117 (16.9)	35 (19.0)	0.86
peripheral artery disease	360 (26.1)	113 (22.5)	195 (28.1)	52 (28.3)	0.04

Descriptors include number (n) and percentage (%) or mean (±SD). P value for trend across categories of eGFR. COPD, chronic obstructive pulmonary disease.

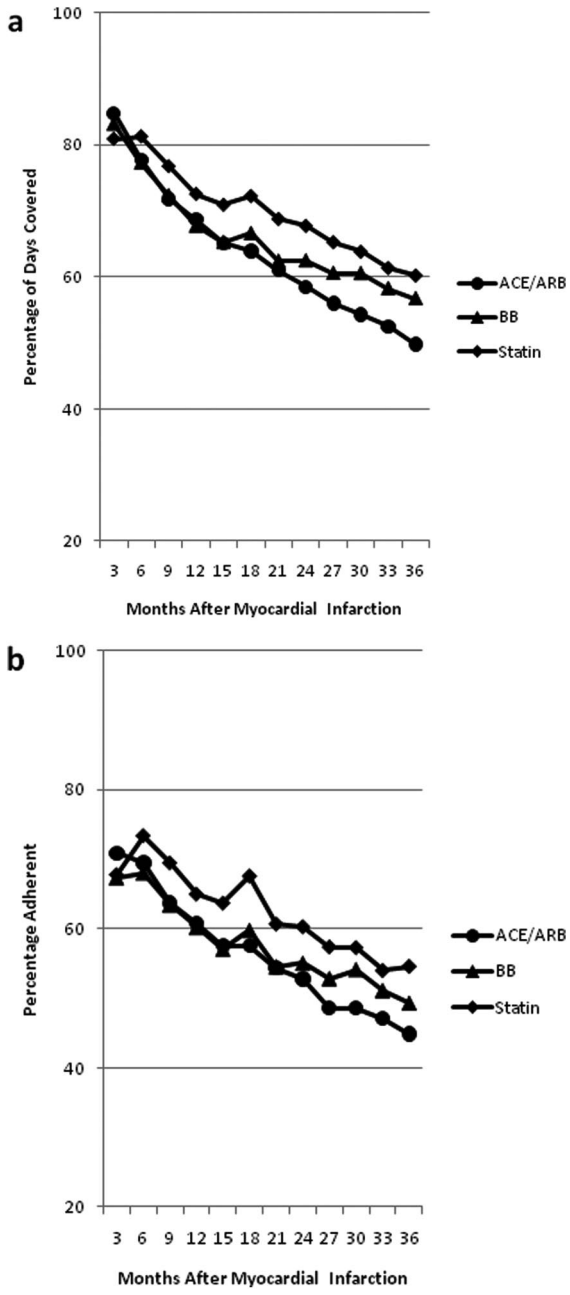

Figure 1. | **(a) Mean PDC and (b) proportion of the cohort that was medication adherent (PDC ≥ 80%) for each medication category over 36 months after MI. BB, β-blocker.**

charge from their MI hospitalization and 3 months (90 days) after admission, we calculated the percentage of days covered (PDC) (2). We calculated the PDC for 12 serial 3-month (90-day) intervals by adding the days of medication supplied to each patient from all filled prescriptions for these medications during the interval and describe this as long-term medication adherence. If the days supplied at the most recent encounter exceeded the remaining days of the interval, the excess days were carried over to the subsequent time interval. Using the same logic, patients who used the medication before their index admission were credited with their excess supply in the first 3 months. Days spent in a hospital or nursing home were deducted from the denominator because these institutions supply patients with these drugs at their discretion and from their supplies and such information is not billed to the drug benefit program. Patients with a PDC ≥80% were classified as adherent, and patients with a PDC <80% were considered nonadherent (2,3,18). Patients continued to be included in the analysis after periods of nonadherence.

We required that patients survive at least 90 days from the day of admission for MI and that their hospitalization length of stay not exceed 30 days to be eligible for study. These steps were chosen so that each patient had at least 2 months to fill prescriptions for the study medications after discharge. Patients were censored at time at death or if they spent >100 consecutive days in a nursing home, the maximum number of nursing home days covered by Medicare.

Statistical Analyses

We described the characteristics of the study cohort by baseline kidney function using univariate logistic regression with eGFR category (≥60, 30 to 59, or <30 ml/min per 1.73 m^2) as an ordinal variable. We plotted the crude observed adherence metrics for each 3-month interval and drug class overall and by stratum of baseline kidney function. To quantify relations, we used linear mixed effects models including a random intercept and random slope for each patient to account for the correlation of observations within a patient and variability in PDC over time, respectively. We provided point estimates that describe associations that are unadjusted and adjusted for potential confounders. Follow-up time in 3-month intervals was analyzed as a continuous variable. We included a multiplicative interaction term to test for effect modification by baseline eGFR category and time on PDC.

We used SAS Enterprise Guide 4.2 (Cary, NC) for all calculations. All tests were two-sided and used a statistical significance threshold of 0.05.

Results

Of the 2103 patients eligible for study, we excluded 227 (10.8%) patients missing serum creatinine. Of the remaining 1876 patients, 492 (26.2%) died during the first 90 days after admission. Additionally, four patients whose length of stay exceeded 30 days were excluded, leaving 1380 patients in the analytic data set. Table 1 describes the baseline demographic and health-related characteristics of these patients, stratified by baseline kidney function. Patients with higher levels of kidney function tended to be younger, male, and had a lower prevalence of several comorbid conditions (*e.g.*, congestive heart failure, diabetes mellitus, hypertension, and peripheral artery disease) compared with patients with more severe baseline kidney dysfunction.

Long-Term Medication Adherence and éGFR

Overall, 675 patients (49%) filled a prescription for an ACEI/ARB, 619 (45%) filled a prescription for a β-blocker, and 406 (29%) filled a prescription for a statin after discharge but within 90 days after hospital admission for acute MI. The mean PDC for ACEIs/ARBs, β-blockers, and statins declined steadily over time (Figure 1a). At baseline, approximately 70% of patients were medication adherent

(PDC ≥ 80%) in each of the three medication classes, but only approximately half of patients were still medication adherent (PDC ≥ 80%) by the end of the 36 months of follow-up (Figure 1b). Category of eGFR had no significant association with baseline adherence for ACEIs/ARBs, β-blockers, or statins (Table 2). However, we found that long-term ACEI/ARB adherence over time differed by category of eGFR (*P* value for interaction between time and eGFR = 0.05; Figure 2a, Table 2). More specifically, patients in the lowest eGFR category (<30 ml/min per 1.73 m^2) had a steeper decline in ACEI/ARB adherence than patients in the higher eGFR categories. For example, using the information provided in Table 2, the expected PDC at 24 months after hospitalization for MI for an 80 year-old white woman with a history of coronary artery disease, congestive heart failure, diabetes mellitus, and hypertension would be 67.0% for eGFR ≥ 60 ml/min per 1.73 m^2 *versus* 55.2% for eGFR < 30 ml/min per 1.73 m^2. The same woman with an eGFR of 30 to 59 ml/min per 1.73 m^2 would have an expected PDC of 66.6% at 24 months, similar to the expected PDC if her eGFR were ≥60 ml/min per 1.73 m^2.

We also found evidence that long-term β-blocker adherence over time differed by eGFR category (*P* value for interaction between time and eGFR = 0.005; Figure 2b, Table 2). In this case, the rate of decline in long-term β-blocker adherence over time was slower for those in the highest eGFR category (eGFR ≥ 60 ml/min per 1.73 m^2) than the other two eGFR categories. For example, using the information provided in Table 2, the expected PDC at 24 months after hospitalization for MI for an 80-year-old white woman with a history of coronary artery disease, congestive heart failure, diabetes mellitus, and hypertension would be 68.4% for an eGFR ≥ 60 ml/min per 1.73 m^2 *versus* 56.7% for an eGFR < 30 ml/min per 1.73 m^2. The same woman with an eGFR 30 to 59 ml/min per 1.73 m^2 would have an expected PDC of 58.3% at 24 months, similar to the expected PDC if her eGFR were <30 ml/min per 1.73 m^2.

We observed no significant differences by eGFR category on long-term statin adherence over time (*P* value for interaction between time and eGFR = 0.9; Figure 2c, Table 2). A previous diagnosis of depression was associated with significantly lower long-term β-blocker adherence but not ACEI/ARB or statin adherence (Table 2). Age, sex, and black race were not significantly associated with long-term adherence for any of the three medication classes.

Discussion

Despite an abundance of evidence supporting the use of ACEIs/ARBs, β-blockers, and statins for the secondary prevention of coronary artery disease, our analysis of elderly survivors of MI showed overall low rates of long-term adherence for these three medications classes. We found that by 12 months, 35% to 40% of the cohort was nonadherent for ACEIs/ARBs, β-blockers, and statins, and this percentage increased to 40% to 48% and 45% to 55% by 24 and 36 months, respectively. Our results differ from Benner *et al.* (2), who analyzed statin adherence in an elderly cohort of Medicaid enrollees and found adherence

Table 2. Expected PDC by medication class: Results from multivariable-adjusted linear mixed effects models

	ACEIs/ARBs			β-Blockers			Statins		
	β	SEM	*P*	β	SEM	*P*	β	SEM	*P*
Intercept	86.9	13.6	<0.0001	71.6	14.5	<0.0001	60.1	17.7	0.0007
Time (per 3 months)	−2.5	0.3	<0.0001	−2.1	0.3	<0.0001	−2.2	0.4	<0.0001
Baseline eGFR (ml/min per 1.73 m^2)									
30 to 59 *versus* ≥60	1.2	2.4	0.62	−1.9	2.5	0.44	−1.5	2.9	0.60
<30 *versus* ≥60	0.7	4.1	0.86	4.0	4.0	0.31	2.9	4.8	0.55
Interaction terms									
time × eGFR 30 to 59	−0.2	0.3	0.57	−1.0	0.4	0.02	−0.1	0.5	0.87
time × eGFR <30	−1.6	0.6	0.01	−2.1	0.7	0.005	−0.4	0.9	0.62
Age (per year)	−0.09	0.2	0.58	0.1	0.2	0.47	0.2	0.2	0.35
Male gender	1.4	2.8	0.61	−0.2	3.1	0.95	5.6	3.4	0.10
Race (*versus* white)	−5.3	5.2	0.31	−7.1	5.6	0.21	−6.9	6.7	0.30
black	14.4	10.2	0.16	5.14	7.2	0.48	−5.9	9.0	0.51
other									
Length of stay (days)	0.3	0.3	0.23	0.08	0.3	0.76	0.7	0.3	0.05
Hospital days in prior year	−0.3	0.1	0.03	0.04	0.1	0.79	−0.2	0.2	0.24
Previous diagnosis of									
coronary artery disease	2.0	3.1	0.52	−3.4	3.2	0.29	−1.7	4.0	0.68
congestive heart failure	2.3	2.3	0.32	−4.3	2.6	0.11	1.6	3.1	0.60
COPD	−2.2	2.4	0.35	−2.2	2.7	0.41	−2.0	3.0	0.51
cerebrovascular disease	−1.4	2.4	0.56	2.0	2.6	0.44	2.9	3.1	0.35
depression	0.5	3.0	0.86	−9.9	3.2	0.002	−7.0	3.8	0.07
diabetes mellitus	2.1	2.2	0.33	1.5	2.3	0.51	1.3	2.7	0.63
hypertension	0.4	2.3	0.87	8.6	2.4	0.0003	6.6	2.8	0.02
malignancy	−3.1	2.7	0.26	−2.8	3.0	0.35	2.3	3.6	0.52
peripheral artery disease	−4.2	2.5	0.09	−0.7	2.8	0.81	0.4	3.4	0.91

P values for interaction between time and eGFR category for each medication class are as follows: ACEIs/ARBs = 0.05, β-blockers = 0.005, statins = 0.9.

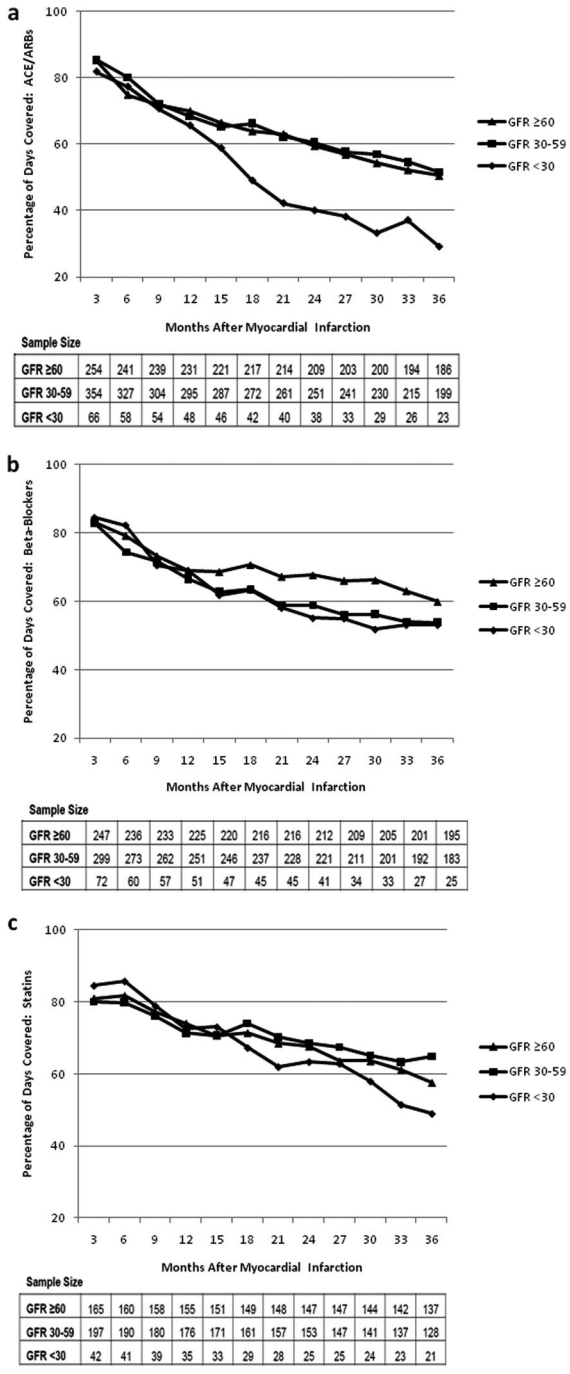

Figure 2. | Mean PDC >36 months after MI stratified by eGFR category (GFR; in ml/min per 1.73 m^2) for (a) ACEIs/ARBs), (b) β-blockers, and (c) statins.

rates of only 30% by 30 months. One reason for the slightly better statin adherence in our analysis may stem from the fact that all of our patients had experienced a MI and were being treated for secondary prevention, whereas only 7% of their cohort had a history of coronary artery disease.

In one of the few studies to focus on differences in medication adherence by kidney function (19), Muntner *et al.* showed that nearly one third of subjects regardless of CKD status forgot to take their medications. Our analysis confirms that baseline medication adherence among patients who filled a prescription for the drug of interest after discharge for MI does not differ by category of eGFR. Moreover, our analysis extends the results of Muntner's cross-sectional study by examining how long-term medication adherence differs by kidney function. We show that patients with baseline kidney dysfunction have lower long-term ACEI/ARB and β-blocker adherence compared with patients with higher baseline kidney function. The results of our analysis have important clinical implications because elderly patients with kidney dysfunction are at high risk for cardiovascular mortality (20) and may therefore benefit the most from dedicated interventions aimed at improving long-term medication adherence.

There may be several reasons why long-term adherence was lowest in patients with more severe kidney dysfunction in our analysis despite enrollment in a generous program that paid for prescription medications and required only small copayments. Studies of patients with CKD have shown high rates of functional limitations, cognitive impairment, and depression, which are associated with lower rates of medication adherence (10–12,21). Also, patients with CKD average approximately 8 prescribed medications, with some patients taking as many as 24 different medications multiple times per day (22). A recent study by Rifkin *et al.* showed that older patients with CKD that were faced with a very large pill burden were often unwilling or physically unable to be adherent to their complex medication regimens (23). In their qualitative study, patients assigned implicit priorities to their medications, skipping medications that treated asymptomatic conditions such as hyperlipidemia or hypertension in favor of medications with more obvious beneficial effects, such as pain relievers.

Our analysis did not show a significant association of older age, female sex, or black race with long-term medication adherence. We may have lacked the power to detect a significant association among these predictors with long-term medication adherence because our cohort consisted primarily of elderly white women. Another explanation may be that the age, sex, and race information that factors into the Modification of Diet in Renal Disease equation to estimate GFR may contain the contribution of these demographic factors to adherence and that kidney function may in fact mediate these previously shown associations. We did show that a history of depression predicted lower long-term β-blocker adherence, consistent with previous studies showing an association between depression and poor medication adherence (21,24).

Our analysis has several limitations. First, we used a single serum creatinine measurement taken during the hospital admission to divide patients into categories of baseline eGFR. However, many of these patients may have had some degree of acute kidney injury in the setting of their MI, thereby underestimating the true baseline kidney function. Second, our cohort was composed of elderly, low-income patients in Pennsylvania with a high proportion of whites and women. Our results may therefore not be applicable to a more racially and socioeconomically diverse population or one with a larger proportion of men. Third, by the end of the 36-month follow-up, a markedly larger proportion of patients in the lower categories of eGFR

dropped out of the cohort compared with patients with a baseline eGFR of ≥60 ml/min per 1.73 m^2, consistent with the known association between kidney dysfunction and mortality (20). However, the mortality imbalance among the eGFR categories likely biased our results toward the null because had these patients remained in the analysis, they likely would have been less medication adherent than the healthier patients. Finally, we relied on claims data as the measure of medication adherence, which do not allow us to determine the reasons for nonadherence. For example, the medication may have been purposely discontinued by the treating physician because of unwanted side effects such as hyperkalemia, sexual dysfunction, or other rational reasons. However, claims data, unlike questionnaires, are not subject to bias, and because they reflect actual filled prescriptions, they may be the closest approximation of a patient's true medication-taking activity.

In conclusion, our analysis shows that long-term medication adherence after MI in the elderly is low, especially in patients with kidney dysfunction. If long-term medication adherence is to be improved, a multifaceted approach that addresses not only financial assistance, but also a deeper understanding of physical and psychologic barriers to proper medication-taking behavior, is paramount. Future strategies should pay special attention to the elderly with kidney dysfunction because this population may be especially vulnerable to poor long-term medication adherence and its adverse consequences.

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Disclosures

None.

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