

Statin Adherence and Mortality in Patients Enrolled in a Secondary Prevention Program

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Numerous clinical trials support the use of HMG-CoA reductase inhibitors (statins) in reducing morbidity and mortality in patients with cardiovascular disease (CVD).¹⁻⁵ Despite the evidence supporting the use of statins and availability of widely distributed clinical practice guidelines supporting their use, a significant proportion of patients are not treated to recommended lipid goals.⁶⁻⁸ Poor medication adherence is likely one of the contributors to this treatment gap. Between 40% and 60% of patients discontinue their statin within 1 year of initiation.⁹⁻¹⁶

Cardiovascular disease prevention programs have been developed in an attempt to improve implementation of and adherence to evidence-based therapy.¹⁷⁻²⁰ These programs typically utilize multidisciplinary teams to focus on cardiac risk factor modification. Although most of these programs have been successful in improving the processes of care, prescribing patterns, and lipid results, and in reducing hospital admissions,²¹⁻²³ patients typically are enrolled for a short period of time, medication adherence is not always addressed, and the impact of medication adherence on long-term clinical outcomes has not been ascertained.

The purpose of this study was to assess statin adherence rates in patients enrolled in a cardiovascular secondary disease prevention program and to evaluate the impact of statin adherence over time on subsequent clinical events.

METHODS

Setting

This study was conducted at Kaiser Permanente Colorado (KPCO), a group-model, closed-panel, nonprofit health maintenance organization (HMO) that provides integrated healthcare services to more than 480,000 members at 18 medical offices in the Denver-Boulder metropolitan area. The study was approved by the KPCO Institutional Review Board.

Since 1998, the Clinical Pharmacy Cardiac Risk Service (CPCRS) at KPCO has been utilized increasingly by multidisciplinary teams to manage acute and long-term issues related to secondary prevention of CVD.

Patients with incident or recurrent coronary events (acute myocardial infarction [AMI], coronary artery bypass graft [CABG] surgery, percutaneous coronary intervention [PCI] with or without stent placement, or catheterizations demonstrating $\geq 50\%$

Objectives: To determine statin adherence rates in patients enrolled in a cardiovascular secondary disease prevention program and to evaluate the impact of adherence on subsequent clinical events.

Methods: Patients who had an incident cardiac event between January 1, 2000, and December 31, 2005, and began statin therapy within 90 days of that event were identified and followed until death, a recurrent nonfatal cardiac event, or December 31, 2006. Analysis was conducted in 2007 and 2008. Adherence was calculated using proportion of days covered (PDC), which was dichotomized into overall PDC $>80\%$ and PDC $\leq 80\%$. Cox proportional hazards models were used to assess the association between PDC and time to death from any cause and/or recurrent nonfatal events.

Results: There were 2201 patients in the study. The overall PDC was 75.4% over 3 years. The risk of any-cause death was lower in patients with a PDC $>80\%$ compared with those with a PDC $\leq 80\%$ (adjusted hazard ratio [HR] = 0.44; 95% confidence interval [CI] = 0.30, 0.64). There was no difference between groups in nonfatal cardiac events. Patients with a PDC $>80\%$ had decreased risk of the combined outcome of death or nonfatal recurrent cardiac event compared with those with a PDC $\leq 80\%$ (HR = 0.75; 95% CI = 0.61, 0.93).

Conclusion: Although our adherence rates were higher than those previously reported in the literature, statin nonadherence still is associated with higher mortality, demonstrating the need to continue to improve statin adherence in this population.

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Take-Away Points

Numerous studies support the use of statins in reducing morbidity and mortality; however, despite this evidence a significant proportion of patients are not treated to recommended goals.

- Statin nonadherence is likely one of the factors contributing to the significant proportion of patients not treated to recommended lipid goals.
- Focusing on the transition of care from the inpatient setting to the outpatient setting is important for providing interventions geared at improving adherence and clinical outcomes over the long term.
- Because statin nonadherence even in a program designed for close follow-up is associated with increased mortality, the need continues to improve adherence to statin therapy.

utilized for ongoing clinical management, patient tracking, and quality improvement activities.

All patients with an IE between January 1, 2000, and December 31, 2005, were identified via the HealthTrac database. The KPCO pharmacy-record databases were used to identify statin generic name, dosage strength, quantity dispensed, days supply, and patient purchase dates

stenosis in 1 or more coronary vessels) are enrolled into a registered nurse–run cardiac rehabilitation program for 3 to 6 months, after which time care is transferred to the CPCRS to ensure adherence to the treatment strategies over the long term. Patients are evaluated for lipid-lowering, antihypertensive, antiplatelet, and angiotensin-converting enzyme (ACE) inhibitor therapy, β -blocker use post-AMI. The program, although voluntary, is instituted by default with approximately 0.3% refusing the service. That is, CPCRS is implemented for all KPCO patients and only limited by patient refusal and provider preference. Currently, more than 12,000 patients with CVD are enrolled in the CPCRS. The CPCRS has demonstrated improvements on a number of surrogate (blood pressure control, low-density lipoprotein cholesterol [LDL-C] levels, patient satisfaction) and clinical (mortality) outcomes of the patients enrolled.^{20,24,25}

Study Design

This was a retrospective, longitudinal cohort study. Patients were eligible for inclusion if they had an incident coronary event (IE) defined as an AMI, CABG surgery, or PCI between January 1, 2000, and December 31, 2005; were enrolled in the CPCRS; and initiated statin therapy within 90 days of the IE. Additionally, patients had to have had continuous KPCO membership throughout the study evaluation period. Patients, who were older than age 80 years at the time of their IE, died within 30 days of the IE, or who were receiving statin therapy within 1 year prior to the IE were excluded. The observation period was from the statin initiation date until the study end date, which was the date of termination of KPCO membership, death, or a recurrent cardiac event, or December 31, 2006, whichever came first.

Study Procedures

The CPCRS utilizes a Web-based tracking database (HealthTrac), which houses information on all validated patients enrolled in the program and is regularly updated with pertinent administrative, laboratory, pharmacy, diagnosis/procedure, vital sign, and demographic data. The database is

within the observation period. Statins included pravastatin, lovastatin, atorvastatin, simvastatin, simvastatin/ezetimibe, rosuvastatin, and fluvastatin.

Approximately 98% of KPCO members have a prescription drug benefit with nominal copayments, which is an incentive for members to fill their prescriptions within the KPCO system. Information on all medication purchases and sale dates were extracted for the 6 months prior to the IE in order to calculate each patient's chronic disease score (CDS),²⁶ an indicator of baseline health status, and to identify the purchase of a β -blocker, ACE inhibitor, and/or prescription antiplatelet medication. The KPCO medical-record databases were queried to identify an ambulatory diagnosis of diabetes mellitus, congestive heart failure, hypertension, chronic renal insufficiency (serum creatinine >2.0 mg/dL), cancer, or depression within 1 year prior to the IE. The KPCO laboratory-record databases were queried to identify LDL-C and blood pressure values most proximal but within the 1 year prior to each patient's IE and the number of LDL-C laboratory tests performed during the observation period. Information on death or recurrent nonfatal cardiac events occurring during the observation period was obtained from queries of the HealthTrac database. Information on membership termination was obtained from the KPCO membership records.

Outcome Measures

The primary outcome was the overall statin adherence rate for the population during the entire observation period. Secondary outcome measures were the association of overall statin adherence, adherence within 6 months of the IE, and adherence 6 months prior to study end with deaths from any cause, recurrent nonfatal cardiac events, and the combined end point of death and recurrent nonfatal cardiac events. Predictors of nonadherence also were identified. Recurrent cardiac events were defined as nonfatal AMI, CABG, or PCI that occurred at least 90 days after the IE, based on the assumption that events within 90 days were related to the IE. Cause of death was verified through death certificates. For the combined end point, the date of either death or the first

recurrent nonfatal cardiac event was used in the analysis. In the event that patients had a cardiac event that resulted in death the same day, the code was entered as “death” in the analysis.

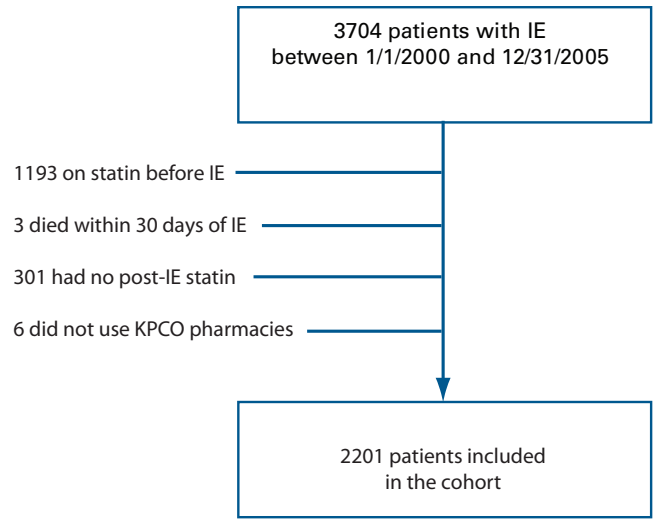
Statistical Analysis

Adherence was reported as the proportion of days covered (PDC),^{10,13,15,27,28} calculated using the days supply from each purchased statin prescription within the observation period. The *overall PDC* for the observation period was calculated between the first statin sold date and study end date. The *initial PDC* was calculated between the first statin sold date and first 6 months of statin therapy. The *final PDC* was calculated for the 6 months prior to the study end date for each patient. Using predefined PDC cutoffs from prior studies of statin adherence,^{10,13-15} patients were assigned to 1 of 3 groups: PDC >80%, PDC 20% to ≤80%, and PDC <20%. Patients were also dichotomized into overall PDC >80% or PDC ≤80%.

Patient characteristics were reported as means, medians, and standard deviations for interval-level and ratio-level variables (eg, age, CDS) and proportions for nominal-level and ordinal-level data (eg, sex, cardiovascular event history). Interval-level variables were assessed for normality of their distributions, and appropriate tests (eg, *t* test, rank-sum test) were used to assess differences in mean values between groups. Pearson’s χ^2 test of association was utilized to assess differences in proportions between groups on categorical variables.

Kaplan-Meier survival curves were constructed to describe the combined end point of death/recurrent nonfatal cardiac events over time for the PDC >80% and PDC ≤80% groups. Cox proportional hazards regression models were constructed to assess the association between categorical PDC groups and the time to death from any cause, recurrent nonfatal cardiac events, and the combined end point of death/recurrent nonfatal cardiac events with and without adjustment for potentially confounding variables (ie, age, sex, CDS, IE type, year of IE, purchases of an antiplatelet agent and β -blocker, and diagnoses of chronic heart failure and diabetes mellitus) and were reported as hazard ratios (HRs) with 95% confidence intervals (CIs). Multivariate logistic regression modeling of age, sex, CDS, number of LDL-C laboratory tests per year, non-statin medication use, diagnoses of diabetes, heart failure, and hypertension, IE year, and IE type was performed to identify predictors of an overall PDC ≤80% and reported using odds ratios (ORs) with 95% CI. An alpha level of <.05 was considered statistically significant. All analyses were performed in 2007 and 2008 using the SAS statistical package version 9.1 (SAS Institute Inc, Cary, NC).

■ **Figure 1. Patient Disposition**



IE indicates incident cardiac event; KPCO, Kaiser Permanente Colorado.

RESULTS

Between January 1, 2000, and December 31, 2005, 3704 patients were identified with an incident IE (Figure 1). Of these, 1503 (40.6%) were excluded; 1193 (79.4%) had a statin dispensed prior to their IE, 301 (20.0%) did not receive a statin within 90 days after the IE, 6 did not use KPCO pharmacies, and 3 died within 30 days of the IE. Thus, 2201 patients were included in the analysis. The majority of patients were followed until December 31, 2006 (1428 [65.0%]), while 408 (18.5%) cancelled their KPCO membership, 122 (5.5%) died, and 243 (11.0%) had a nonfatal recurrent cardiac event.

The mean age of the total cohort was 62 years and 70% were male (Table 1). The overall PDC for the entire cohort was 75.4% over an average follow-up of 3 years. The majority (59.2%) of patients had an overall PDC >80%, 35.7% had a PDC between 20% and 80%, and 5.2% had a PDC <20%. Differences across the PDC groups included age, index cardiac event type and year, CDS, diagnoses of congestive heart failure and diabetes, number of LDL-C laboratory tests per year, and systolic blood pressure (all *P* <.05).

Overall, 122 (5.5%) patients died from any cause during the observation period (Table 2). There were 71 (7.9%) and 51 (3.9%) deaths in the overall PDC ≤80% and PDC >80% groups, respectively (*P* <.001). After adjustment for baseline covariates, an adjusted HR of 0.44 (95% CI = 0.30, 0.64) for death was identified for the PDC >80% group.

There were 99 (11%) and 144 (11.1%) nonfatal cardiac events in the overall PDC ≤80% and PDC >80% groups, respectively (*P* >.05) (adjusted HR = 0.99; 95% CI = 0.76,

■ **Table 1.** Patient Characteristics

Characteristic	Overall (N = 2201)	PDC <20% (n = 114)	PDC 20%-80% (n = 785)	PDC >80% (n = 1302)	P ^a
Mean age (SD), y	62.2 (10.6)	61.7 (11.2)	61.3 (11.2)	62.8 (10.2)	.02
Female, %	29.4	28.1	31.5	28.2	.27
Mean chronic disease score (SD)	2.4 (2.7)	2.4 (2.7)	2.4 (2.8)	2.4 (2.7)	.92
Cardiac event type, %					
AMI only	11.1	15.8	12.7	9.8	.03
PCI ± AMI	67.3	66.7	64.2	69.2	.06
CABG ± AMI	21.6	17.5	23.1	21.0	.31
Cardiac event year, %					
2000-2001	27.9	34.2	30.1	26.0	.04
2002-2003	36.9	36.8	36.4	37.2	.94
2004-2005	35.2	29.0	33.5	36.8	.11
Comorbidity, %					
Renal insufficiency	1.2	1.2	3.5	1.0	.06
Depression	1.9	0.9	1.5	2.2	.43
Hypertension	33.4	35.1	32.6	33.8	.80
Congestive heart failure	1.8	2.6	2.8	1.2	.02
Diabetes	13.3	21.9	16.6	10.6	<.001
Cancer	8.5	9.7	9.9	7.5	.13
Medication purchase, %					
β-Blocker	90.9	89.5	89.6	91.9	.18
Antiplatelet	25.0	18.4	22.7	27.0	.02
ACE inhibitor	60.9	60.5	62.2	60.2	.67
ARB	8.1	7.0	7.9	8.4	.84
Any ARB, ACE inhibitor, or β-blocker	95.6	97.4	94.9	95.9	.35
Mean number of LDL-C lab tests per year (SD)	2.4 (1.2)	1.8 (1.4)	2.4 (1.2)	2.5 (1.1)	<.001
Mean LDL-C (SD), mg/dL	130.5 (30.9)	121.9 (34.3)	128.8 (33.0)	131.8 (29.6)	.21
Mean systolic blood pressure (SD), mm Hg	134.9 (20.8)	138.5 (21.5)	136.2 (21.2)	133.9 (20.4)	.04
Mean diastolic blood pressure (SD), mm Hg	81.0 (12.1)	81.4 (11.9)	81.7 (12.6)	80.6 (11.8)	.28
Mean observation time (SD), y	3.0 (1.8)	3.0 (1.8)	2.9 (1.8)	3.1 (1.7)	.19

ACE indicates angiotensin-converting enzyme; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft surgery; LDL-C, low-density lipoprotein cholesterol; PCI, percutaneous coronary intervention; PDC, proportion of days covered.

^aAcross groups.

1.30). With regard to the combined end point of any-cause death or nonfatal cardiac event, the overall PDC >80% group had a decreased risk of death or recurrent cardiac event compared with the overall PDC ≤80% group (adjusted HR = 0.75; 95% CI = 0.61, 0.93) (Figure 2).

Patients with an initial PDC >80% within the first 6 months of their IE were less likely to die (4.3%) than those with a PDC ≤80% (7.7%) (HR = 0.60; 95% CI = 0.41, 0.88). There were no differences between groups in nonfatal cardiac events or the combined end point of any-cause death or nonfatal cardiac event (both P >.05). There were no differences between groups in any clinical outcome when the final PDC was evaluated.

Independent predictors of nonadherence were female sex (OR = 1.23; 95% CI = 1.01, 1.50), congestive heart failure (OR = 2.63; 95% CI = 1.34, 5.17), and diabetes mellitus (OR = 1.79; 95% CI = 1.35, 2.36) (Table 3). Conversely, an increasing number of LDL-C laboratory tests performed per year (OR = 0.87; 95% CI = 0.81, 0.94) and age (OR = 0.99; 95% CI = 0.98, 0.99) were independent predictors of decreased nonadherence (Table 3).

DISCUSSION

We sought to evaluate statin adherence among patients with CVD enrolled in a cardiovascular secondary prevention pro-

Table 2. Clinical Outcomes by Adherence Group

Outcome	Adherence Group			P	Hazard Ratio	
	Overall (N = 2201)	PDC ≤80% (n = 899)	PDC >80% (n = 1302)		Unadjusted ^a (95% CI)	Adjusted ^b (95% CI)
Death or cardiac event	16.6 (365)	18.9 (170)	15.0 (195)	.015	0.77 (0.63, 0.95)	0.75 (0.61, 0.93)
Death only	5.5 (122)	7.9 (71)	3.9 (51)	<.001	0.48 (0.34, 0.69)	0.44 (0.30, 0.64)
Nonfatal cardiac event	11.0 (243)	11.0 (99)	11.1 (144)	.972	0.99 (0.77, 1.28)	0.99 (0.76, 1.30)

CI indicates confidence interval; PDC, proportion of days covered.

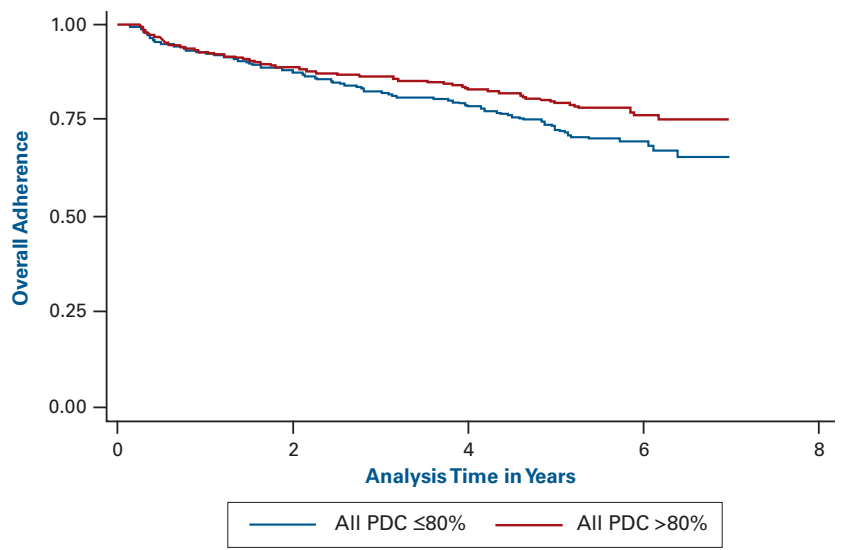
^aReferent category: PDC ≤80%.

^bReferent category: PDC ≤80%, adjusted for age, sex, chronic disease score, index event type and year, antiplatelet and β-blocker use, congestive heart failure, and diabetes mellitus.

gram. To our knowledge, studies have not examined the relationship between statin adherence and clinical outcomes among patients enrolled in secondary prevention disease management programs. Of the 2201 patients evaluated over an average of 3 years of follow-up, the overall statin adherence rate was 75.4%. Although there was no association between PDC and nonfatal cardiac events, patients with a PDC >80%, both over the entire observation period and within the first 6 months after their index event, had a reduced risk of death from any cause.

Prior studies evaluating statin adherence among the general population have demonstrated that PDC decreases over time with discontinuation rates between 40% and 60% at 1 year after statin initiation.¹⁰ Benner and colleagues evaluated statin adherence rates in 34,501 patients and demonstrated that PDC decreased over time with a mean PDC of 79% in the first 3 months, 56% in the second quarter of the first year, and only 42% at 120 months.¹⁰ Another study evaluated long-term adherence rates (ie, over 7 years) to evidence-based secondary prevention therapies (lipid-lowering agents, β-blockers, antiplatelet agent, ACE inhibitors) in patients with CVD.¹¹ This study found that overall use of lipid-lowering therapy actually increased over time but “consistent” use was only 44% over the 7-year period.¹¹ These findings indicate that statin adherence becomes suboptimal relatively quickly after initiation and continues to decrease with time. Systems to monitor adherence over the long term are needed and would likely improve patient outcomes. The adherence rate demonstrated in this study was much higher than that reported in the literature, most likely the result of close follow-up and monitoring of the patients followed within the CPCRS secondary prevention program.

Figure 2. Kaplan-Meier Death/Second Event Survival Curves by Overall Adherence Groups



PDC indicates proportion of days covered.

Statin adherence is correlated to improved clinical outcomes. One study of 31,455 patients with prior AMI followed over 2.4 years evaluated adherence to evidence-based secondary prevention therapy and found that compared with patients with a PDC ≥80%, the risk of death was 12% higher among those with a PDC of 40% to 79%, and 25% higher among those with a PDC of <40%.²⁹ These data are consistent with our findings of increased risk of death in patients with a PDC ≤80%. Additionally, another study found that adherence rates ≥80% were associated with decreased occurrences of AMI compared with adherence rates <80%.³⁰ Although these studies provide some insight into the relationship between adherence and clinical outcomes among the general population, they do not provide information regarding the impact a secondary disease prevention program can have on medication adherence and clinical outcomes. In our program, we not only found that adherence was higher but the risk of death was decreased from any cause.

Although numerous initiatives have been implemented and evaluated to target initiation of statins at hospital discharge, little has been done to focus on improving long-term adherence after discharge. Patients without follow-up with their cardiologist, primary care physician, or a collaborative care service within 1 month after AMI are less likely to survive or be on evidence-based therapies 6 months after their cardiac event.³¹ Furthermore, patients who discontinue their medication within 1 month after a cardiac event have higher 1-year mortality rates than patients who do not discontinue.³¹ Indeed, in our study, we found that adherence within the first 6 months after an IE was associated with all-cause mortality. However, statin adherence immediately prior to death/recurrent cardiac event/study end was not associated with clinical outcomes (death, cardiac event). All of these findings suggest that medication adherence needs to be assessed relatively early after a cardiac event and maintained over time. In addition, secondary prevention programs should be designed to include long-term follow-up to monitor adherence to proven secondary prevention medications.

Given our strict inclusion and exclusion criteria, and because we limited our analysis to only incident events, our final cohort for analysis represented a small portion of the number of patients enrolled in the CPCRS. Despite the intensive follow-up and monitoring conducted by the CPCRS, 25% of the patients followed still were classified as nonadherent. We did not determine the reasons patients were classified with a PDC <80%. It is likely that many of these patients experienced adverse effects that prevented them from taking the statin as prescribed. It is unlikely that any intervention would result in a 100% adherence rate. Although an outcome of death due to cardiac events would have been more relevant given our look at statin usage, we chose to use all-cause mortality because of our strict inclusion criteria and because we know based on numerous previous studies that statins reduce all-cause mortality in addition to cardiac events.

Although we observed lower rates of death, both over the entire observation period and within 6 months after the IE among the cohort with PDC >80%, we did not observe differences in recurrent cardiovascular events at any time point.

Although our average follow-up time was 3 years, this may not have been an adequate amount of time to observe differences in recurrent cardiovascular events within our population. The inability to observe a difference also may have been a result of the small sample size or because event rates for recurrent cardiovascular events were relatively low, given that patients are aggressively managed with regard to cardiovascular risk factors and evidence-based medication use as part of the CPCRS. We evaluated adherence at 3 arbitrary, predefined cut points (overall, 6 months following IE, and 6 months prior to study end) to determine the time frame at which adherence most impacted results. Although we found overall adherence and adherence within 6 months of the IE were associated with reductions in mortality, it is unclear whether different cut points would have shown the same findings.

In conclusion, we found that over the course of 3 years, adherence was 75% for this CVD population and death or recurrent events was decreased by 25% in the population with

■ **Table 3.** Predictors of PDC ≤80%

Potential Predictor	Adjusted Odds Ratio (95% Confidence Interval)
Age	0.99 (0.98, 0.99)
Chronic disease score	0.97 (0.93, 1.01)
Number of LDL-C lab tests per year	0.87 (0.81, 0.94)
Female ^a	1.23 (1.01, 1.50)
Antiplatelet ^b	0.81 (0.58, 1.13)
Angiotensin receptor blocker ^b	1.01 (0.60, 1.72)
ACE inhibitor ^b	1.11 (0.91, 1.36)
β-Blocker ^b	0.74 (0.49, 1.12)
Use of at least 1 antihypertensive medication ^b	0.98 (0.54, 1.79)
Use of any antihypertensive medication ^b	0.87 (0.44, 1.69)
Congestive heart failure	2.63 (1.34, 5.17)
Diabetes mellitus	1.79 (1.35, 2.36)
Hypertension	0.95 (0.77, 1.18)
Index event year ^c	
2002-2003	0.82 (0.66, 1.02)
2004-2005	0.91 (0.66, 1.24)
Index event type ^d	
PCI ± AMI	0.77 (0.58, 1.03)
CABG ± AMI	0.83 (0.60, 1.15)

ACE indicates angiotensin-converting enzyme; AMI, acute myocardial infarction; CABG, coronary artery bypass graft, LDL-C, low-density lipoprotein cholesterol; PCI, percutaneous coronary intervention.

^aReference group: male.

^bReference group: no purchase of corresponding medication.

^cReference group: index event year 2000-2001.

^dReference group: AMI only.

a PDC >80%. This study is important in that it provides information on adherence rates within a secondary disease prevention program designed to provide long-term follow-up of these patients to ensure adherence to treatment strategies. Although our adherence rates were higher than those reported in previous studies, nonadherence still was associated with adverse outcomes. Adherence rates continue to need improvement in this population. This study will help guide future investigations in implementing better long-term follow-up of this patient population and continuing to improve the transition from the inpatient setting to the outpatient setting.

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