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ORIGINAL RESEARCH

Cumulative Adherence to Secondary Prevention Guidelines and Mortality After Acute Myocardial Infarction

Matthew D. Solomon, MD, PhD; Thomas K. Leong, MPH; Eleanor Levin, MD; Jamal S. Rana, MD, PhD; Marc G. Jaffe, MD; Stephen Sidney, MD, MPH; Sue Hee Sung, MPH; Catherine Lee, PhD; Anthony DeMaria, MD; Alan S. Go, MD

BACKGROUND: The survival benefit associated with cumulative adherence to multiple clinical and lifestyle-related guideline recommendations for secondary prevention after acute myocardial infarction (AMI) is not well established.

METHODS AND RESULTS: We examined adults with AMI (mean age 68 years; 64% men) surviving at least 30 (N=25 778) or 90 (N=24 200) days after discharge in a large integrated healthcare system in Northern California from 2008 to 2014. The association between all-cause death and adherence to 6 or 7 secondary prevention guideline recommendations including medical treatment (prescriptions for β-blockers, renin-angiotensin-aldosterone system inhibitors, lipid medications, and antiplatelet medications), risk factor control (blood pressure <140/90 mm Hg and low-density lipoprotein cholesterol <100 mg/dL), and lifestyle approaches (not smoking) at 30 or 90 days after AMI was evaluated with Cox proportional hazard models. To allow patients time to achieve low-density lipoprotein cholesterol <100 mg/dL, this metric was examined only among those alive 90 days after AMI. Overall guideline adherence was high (35% and 34% met 5 or 6 guidelines at 30 days; and 31% and 23% met 6 or 7 at 90 days, respectively). Greater guideline adherence was independently associated with lower mortality (hazard ratio, 0.57 [95% CI, 0.49–0.66] for those meeting 7 and hazard ratio, 0.69 [95% CI, 0.61–0.78] for those meeting 6 guidelines versus 0 to 3 guidelines in 90-day models, with similar results in the 30-day models), with significantly lower mortality per each additional guideline recommendation achieved.

CONCLUSIONS: In a large community-based population, cumulative adherence to guideline-recommended medical therapy, risk factor control, and lifestyle changes after AMI was associated with improved long-term survival. Full adherence was associated with the greatest survival benefit.

Key Words: guideline adherence ■ myocardial infarction ■ mortality

Randomized trials have shown that secondary prevention after acute myocardial infarction (AMI) reduces mortality and cardiovascular events,[1–8] improves quality of life, and is generally considered cost-effective.[9,10] Subsequent evidence-based guidelines have been developed,[11] and both payer and healthcare quality organizations require that secondary prevention metrics are met to receive payment and quality designations.[12,13] Although various studies in "real-world" populations have described adherence rates and associated outcomes of specific guideline recommendations,[14–18] few studies have investigated the cumulative adherence and potential clinical impact of meeting multiple secondary prevention guideline recommendations across varying domains of care, at different time points after AMI, and in diverse community-based populations.

To address this, we examined adherence to: (1) guideline-recommended medical therapy, (2) optimal

Correspondence to: Matthew D. Solomon, MD, PhD, Division of Research, Kaiser Permanente Northern California, 2000 Broadway, Oakland, CA 94611. Email: matthew.d.solomon@kp.org

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CLINICAL PERSPECTIVE

What Is New?

- Various studies have described adherence rates to specific guideline recommendations after myocardial infarction and associated outcomes in selected patients.
- However, previous studies have not investigated the cumulative adherence and clinical impact of meeting multiple secondary prevention guideline recommendations across varying domains of care and within diverse community-based populations.

What Are the Clinical Implications?

- Our findings suggest that cumulative adherence to guideline-recommended medical therapies, cardiovascular risk factor control, and lifestyle modification at 30 and 90 days after discharge for myocardial infarction is associated with significantly lower long-term mortality.
- The observed incremental favorable associations with long-term survival for adherence to every additional guideline metric, even at high levels of adherence, supports efforts to maximize adherence to all guideline-based recommendations.

Nonstandard Abbreviations and Acronyms

AMI	acute myocardial infarction
LDL-C	low-density lipoprotein cholesterol
KPNC	Kaiser Permanente Northern California
BP	blood pressure
HR	hazard ratio
ACEI	angiotensin-converting enzyme inhibitor
ARB	angiotensin receptor blocker

risk factor control, and (3) recommended lifestyle interventions at 30 and 90 days after AMI and the associations of cumulative and individual guideline adherence with all-cause mortality.

METHODS

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Sample

We identified patients 18 years and older hospitalized with AMI between 2008 and 2014 in Kaiser Permanente Northern California (KPNC), a large integrated healthcare delivery system providing outpatient, emergency department, and inpatient care to >4.4 million people across Northern California. Its membership is highly representative of the local and state-wide population with regard to age, sex, race/ethnicity, and socioeconomic status.[19]

This study was approved by the KPNC institutional review board. Waiver of informed consent was obtained because of the nature of the study.

Study Design

Using previously validated methods, we defined hospitalization for AMI as a primary discharge diagnosis (*International Classification of Diseases, Ninth Revision* [*ICD-9*] code 410.x); or elevated troponin I (≥0.1 ng/mL) with a primary discharge diagnosis of unstable angina (411.x) or a primary discharge diagnosis of coronary artery disease (414.0) plus a secondary discharge diagnosis of unstable angina (411.x).[20] We excluded patients without known sex and those with <12 months of continuous health plan membership and pharmacy benefits before their index date, defined as the date of their first hospitalization for AMI during the study period.

Follow-up occurred through December 31, 2014, with censoring for health plan disenrollment, organ transplantation, or death.

Exposure of Interest

Our primary exposure was patient-level adherence to guideline-recommended treatment goals at 2 time points after AMI. We identified patients who survived to 30 days after index discharge with: (1) a filled prescription for an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, (2) a filled prescription for a β-blocker, (3) a filled prescription for an antiplatelet agent (P2Y12 inhibitors), (4) a filled prescription for a lipid-lowering agent (statin and nonstatin agents), (5) outpatient blood pressure (BP) <140/90 mm Hg, and (6) not smoking tobacco after discharge.[1,11,21] At each time point examined, patients needed to have a dispensed prescription and remain adherent to the medication across the studied point in time (ie, 30 and 90 days). Similarly, the BP value, lipid value, and smoking status observed closest to the studied time point was used to determine guideline adherence. We also examined adherence to these 6 guidelines plus achieving a low-density lipoprotein cholesterol (LDL-C) <100 mg/dL among those surviving to 90 days post-discharge. This longer period allowed time for patients to have LDL-C retested after initiation or intensification of cholesterol treatment after AMI.

Covariates

In addition, based on validated algorithms,[22] we used health plan administrative and clinical data, pharmacy

databases, and laboratory databases to identify the following comorbidities before index date: prior AMI; ischemic stroke or transient ischemic attack; prior coronary angiography, coronary artery bypass grafting, percutaneous coronary intervention, implantable cardioverter-defibrillator or pacemaker; hypertension; dyslipidemia; diabetes mellitus; heart failure; atrial fibrillation; ventricular tachycardia or fibrillation; mitral or aortic valvular disease; peripheral artery disease; cognitive impairment; depression; liver disease; lung disease; thyroid disease; cancer; and previous hospitalization for bleeding events.

Using pharmacy databases, we identified receipt of medications before the index AMI admission for aldosterone antagonists, anti-arrhythmic agents, NSAIDs, α-blockers, diuretics, calcium channel blockers, hydralazine, other hypertension medications, nitrates, vasodilators, digoxin, anti-coagulants, and diabetes mellitus therapies, and we calculated whether patients had an active prescription at the time of admission for AMI to identify baseline medication usage. We ascertained the most recent outpatient results for estimated glomerular filtration rate,[23] high-density lipoprotein cholesterol, glycated hemoglobin, and the most recent outpatient BP measurement. All covariate variables were also updated in a time-varying manner during follow-up, including occurrence of recurrent AMI events.

Outcome

Our primary outcome was death from any cause identified from electronic medical records, Social Security Administration vital status, and California death certificates. These approaches have yielded >97% vital status information in prior studies.[24]

Statistical Analysis

We used SAS version 9.3 (SAS Institute Inc.) for all analyses, with a 2-sided $P<0.05$ considered significant. We estimated unadjusted Kaplan–Meier survival curves by categories of guideline adherence, as well as multivariable Cox regression models with time-updated covariates to examine the independent association between categories of 30- or 90-day guideline adherence and all-cause mortality (ie, adherence to 0–2, 3, 4, 5, or all 6 guidelines at 30 days; 0–3, 4, 5, 6, or all 7 guidelines at 90 days). To facilitate interpretation of our model results, we generated adjusted cumulative incidence curves, which represent predictions of mortality in each category of guideline adherence for the average patient in our sample based on the fully adjusted models. All models accounted for censoring at health plan disenrollment, organ transplantation, or death (the primary outcome).

To test the independent association of meeting individual guideline recommendations with mortality, we examined models with indicator variables for adherence to each individual guideline at the 2 time points after AMI. We similarly examined the linear association of guideline achievement with mortality by using number of guidelines achieved as a single continuous variable. We also conducted subgroup analyses by age group, sex, chronic kidney disease status (estimated glomerular filtration rate <60 versus ≥60 mL/min per 1.73 m^2), and diabetes mellitus status.

To further address potential unmeasured confounding, we estimated a high-dimensional propensity score for high guideline adherence (defined as adherence to 5 or 6 guidelines at 30 days and 6 or 7 guidelines at 90 days) for each patient using SAS macros[25,26] (Data S1) to include as a continuous variable into final regression models that also adjusted for baseline demographics and baseline and time-updated comorbidities, laboratory results, prescriptions, and outpatient vital signs. In addition, we performed sensitivity analyses that included the Elixhauser index to further account for confounding caused by competing risks of death.

Finally, we also assessed the robustness of our results to unmeasured confounding using the E-value methodology of VanderWeele and Ding.[27] This estimates what the relative risk would have to be for any unmeasured confounder to negate the observed association of guideline adherence and mortality (Data S1).

RESULTS

Study Cohort and Follow-Up

We identified 25 788 and 24 200 eligible adults hospitalized with AMI between 2008 and 2014 surviving to 30 and 90 days postdischarge, respectively (Figure 1). Patients were older (mean age 68 years), predominantly men (64%), and had broad racial/ethnic diversity (Table 1). For >90% of patients, the index AMI was their first documented AMI in our system. The proportion of patients already taking guideline-directed secondary prevention medications at the time of the AMI admission was highest for statins (51%) and lowest for nonaspirin antiplatelet agents (10%). Among patients with available outpatient BP measurements, one fifth were not controlled at baseline (>140/90 mm Hg) and slightly more than half (52%) had LDL-C <100 mg/dL before the index AMI. Patients eligible for 30-day analyses were followed for a median of 2.8 years after index AMI (interquartile range 1.0–4.3 years); those eligible for 90-day analyses had similar follow-up. During follow-up, 4590 (17.8%) and 3916 (16.2%) patients died

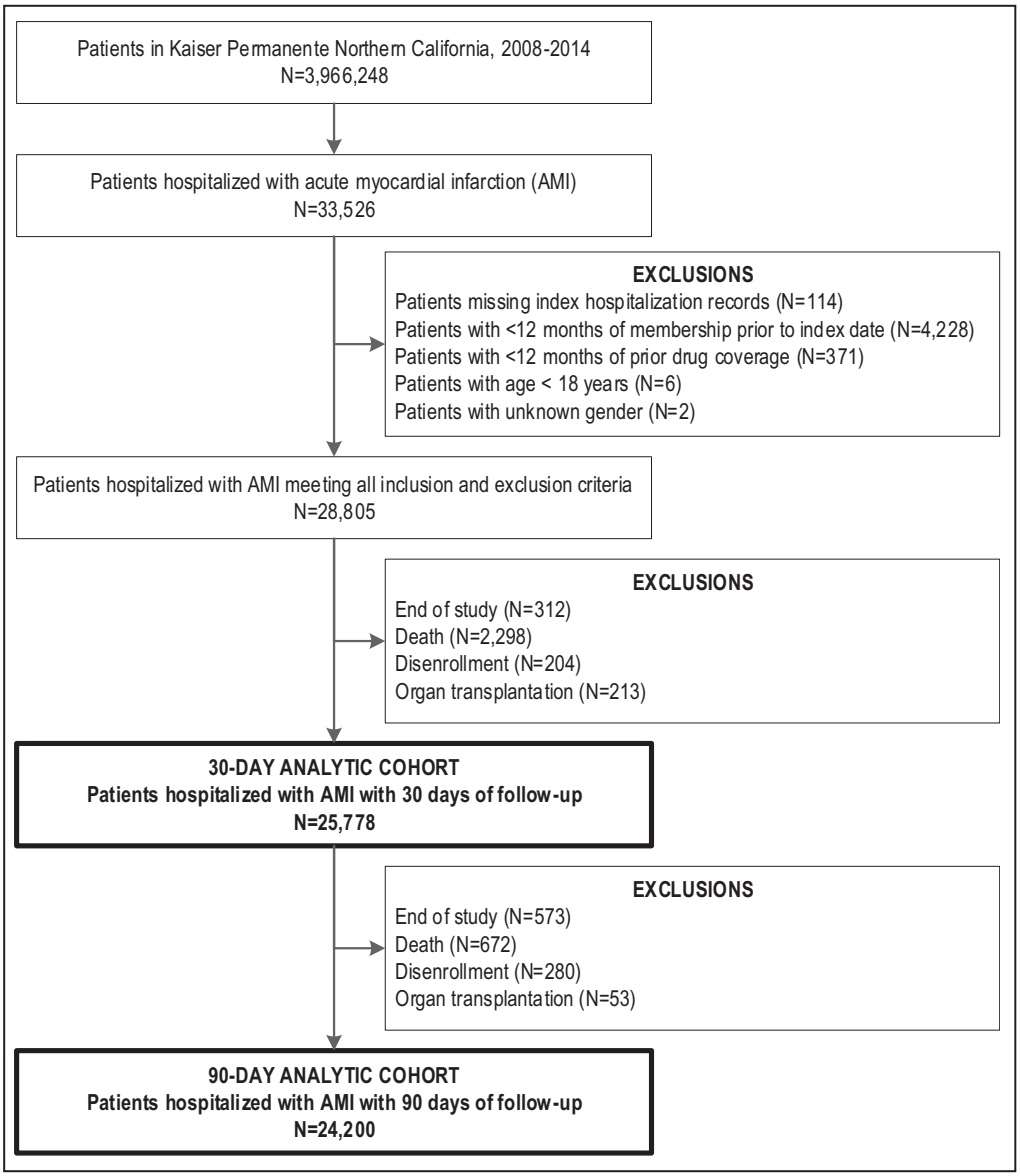

Figure 1. Study cohort of eligible adults hospitalized with acute myocardial infarction (AMI), 2008–2014.

among those eligible for 30- and 90-day analyses, respectively.

Cumulative and Individual Adherence to Guidelines

We observed relatively few patients in the lowest categories of guideline adherence (5% adhered to 0–2 guidelines and 10% to 0 to 3 guidelines in 30- and 90-day analyses) (Table 2). A modest number of patients achieved a moderate number of guidelines (7% and 19% adhered to 3 or 4 guidelines in 30-day analyses, respectively; 12% and 23% adhered to 4 or 5 guidelines in 90-day analyses, respectively), and a larger proportion of patients adhered to all or nearly all guideline recommendations at 30 or 90 days (35% and 34% adhered to 5 or 6 guidelines in 30-day analyses; 31% and 23% adhered to 6 or 7 guidelines in 90-day analyses). Most patients adhered to each individual guideline metrics (Table 2).

Guideline Adherence and Mortality

In multivariable models, patients achieving all 6 guideline metrics at 30 days and all 7 guideline metrics at 90 days had significantly lower unadjusted and adjusted mortality relative to those achieving fewer guidelines (adjusted hazard ratio [HR], 0.61 [95% CI, 0.52–0.72] for those meeting 6 versus 0–2 guidelines in 30-day models; HR, 0.57 [95% CI, 0.49–0.66] for

Table 1. Baseline Characteristics for Patients Hospitalized With AMI, by Number of Secondary Prevention Guidelines Met at 30 and 90 Days After Discharge, 2008–2014

	No. of Guidelines Met at 30 Days After Discharge						No. of Guidelines Met at 90 Days After Discharge					
	Overall (N=25 778)	0–2 (N=1230)	3 (N=1835)	4 (N=4977)	5 (N=9062)	6 (N=8674)	Overall (N=24 200)	0–3 (N=2407)	4 (N=3011)	5 (N=5677)	6 (N=7514)	7 (N=5591)
Demographics												
Index age, mean (SD), y	68.5 (13.3)	70.4 (15.3)	70.8 (14.2)	69.8 (13.4)	68.3 (13.4)	67.3 (12.6)	68.2 (13.2)	69.2 (15.1)	68.8 (13.9)	68.9 (13.5)	67.8 (12.8)	67.1 (12.1)
Sex, No. (%)												
Women	9261 (35.9)	613 (49.8)	855 (46.6)	2024 (40.7)	3185 (35.1)	2584 (29.8)	8606 (35.6)	1195 (49.6)	1273 (42.3)	2121 (37.4)	2523 (33.6)	1494 (26.7)
Men	16 517 (64.1)	617 (50.2)	980 (53.4)	2953 (59.3)	5877 (64.9)	6090 (70.2)	15 594 (64.4)	1212 (50.4)	1738 (57.7)	3556 (62.6)	4991 (66.4)	4097 (73.3)
Race, No. (%)												
White	16 244 (63.0)	738 (60.0)	1134 (61.8)	3090 (62.1)	5733 (63.3)	5549 (64.0)	15 260 (63.1)	1420 (59.0)	1904 (63.2)	3599 (63.4)	4770 (63.5)	3567 (63.8)
Black	1899 (7.4)	157 (12.8)	198 (10.8)	461 (9.3)	644 (7.1)	439 (5.1)	1761 (7.3)	320 (13.3)	288 (9.6)	445 (7.8)	459 (6.1)	249 (4.5)
Asian	3087 (12.0)	117 (9.5)	169 (9.2)	584 (11.7)	1083 (12.0)	1134 (13.1)	2916 (12.0)	248 (10.3)	315 (10.5)	676 (11.9)	912 (12.1)	765 (13.7)
Other	2133 (8.3)	116 (9.4)	159 (8.7)	399 (8.0)	756 (8.3)	703 (8.1)	1996 (8.2)	213 (8.8)	245 (8.1)	450 (7.9)	641 (8.5)	447 (8.0)
Unknown	2415 (9.4)	102 (8.3)	175 (9.5)	443 (8.9)	846 (9.3)	849 (9.8)	2267 (9.4)	206 (8.6)	259 (8.6)	507 (8.9)	732 (9.7)	563 (10.1)
Hispanic ethnicity	3356 (13.0)	153 (12.4)	254 (13.8)	651 (13.1)	1186 (13.1)	1112 (12.8)	3144 (13.0)	293 (12.2)	394 (13.1)	724 (12.8)	986 (13.1)	747 (13.4)
Cardiovascular comorbidities, No. (%)												
AMI	1920 (7.4)	131 (10.7)	179 (9.8)	419 (8.4)	663 (7.3)	528 (6.1)	1728 (7.1)	235 (9.8)	242 (8.0)	419 (7.4)	478 (6.4)	354 (6.3)
Unstable angina	233 (0.9)	15 (1.2)	20 (1.1)	55 (1.1)	74 (0.8)	69 (0.8)	212 (0.9)	23 (1.0)	30 (1.0)	47 (0.8)	63 (0.8)	49 (0.9)
Coronary artery disease	2518 (9.8)	156 (12.7)	218 (11.9)	524 (10.5)	869 (9.6)	751 (8.7)	2301 (9.5)	274 (11.4)	301 (10.0)	561 (9.9)	665 (8.9)	500 (8.9)
Hospitalization for ischemic stroke or TIA	1021 (4.0)	69 (5.6)	123 (6.7)	227 (4.6)	351 (3.9)	251 (2.9)	901 (3.7)	120 (5.0)	148 (4.9)	225 (4.0)	248 (3.3)	160 (2.9)
Atrial flutter or fibrillation	3202 (12.4)	194 (15.8)	336 (18.3)	806 (16.2)	1114 (12.3)	752 (8.7)	2902 (12.0)	356 (14.8)	457 (15.2)	819 (14.4)	820 (10.9)	450 (8.0)
Heart failure	4044 (15.7)	290 (23.6)	434 (23.7)	1036 (20.8)	1388 (15.3)	896 (10.3)	3588 (14.8)	481 (20.0)	550 (18.3)	991 (17.5)	1055 (14.0)	511 (9.1)
Smoking status												
Nonsmoker	11 191 (43.4)	472 (38.4)	701 (38.2)	1909 (38.4)	3525 (38.9)	4584 (52.8)	10 527 (43.5)	993 (41.3)	1149 (38.2)	2191 (38.6)	3198 (42.6)	2996 (53.6)
Smoker	3630 (14.1)	275 (22.4)	404 (22.0)	1143 (23.0)	1808 (20.0)	0 (0.0)	3448 (14.2)	563 (23.4)	735 (24.4)	1182 (20.8)	968 (12.9)	0 (0.0)
Former smoker	10 268 (39.8)	390 (31.7)	648 (35.3)	1729 (34.7)	3411 (37.6)	4090 (47.2)	9561 (39.5)	695 (28.9)	1008 (33.5)	2105 (37.1)	3158 (42.0)	2595 (46.4)
Passive smoker	135 (0.5)	11 (0.9)	23 (1.3)	41 (0.8)	60 (0.7)	0 (0.0)	129 (0.5)	24 (1.0)	24 (0.8)	41 (0.7)	40 (0.5)	0 (0.0)
Unknown	554 (2.1)	82 (6.7)	59 (3.2)	155 (3.1)	258 (2.8)	0 (0.0)	535 (2.2)	132 (5.5)	95 (3.2)	158 (2.8)	150 (2.0)	0 (0.0)

(*Continued*)

Table 1. Continued

	No. of Guidelines Met at 30 Days After Discharge						No. of Guidelines Met at 90 Days After Discharge					
	Overall (N=25 778)	0–2 (N=1230)	3 (N=1835)	4 (N=4977)	5 (N=9062)	6 (N=8674)	Overall (N=24 200)	0–3 (N=2407)	4 (N=3011)	5 (N=5677)	6 (N=7514)	7 (N=5591)
Cardiovascular procedures, No. (%)												
Coronary artery bypass graft surgery	186 (0.7)	10 (0.8)	12 (0.7)	41 (0.8)	68 (0.8)	55 (0.6)	179 (0.7)	22 (0.9)	19 (0.6)	43 (0.8)	57 (0.8)	38 (0.7)
Percutaneous coronary intervention	1030 (4.0)	48 (3.9)	72 (3.9)	188 (3.8)	357 (3.9)	365 (4.2)	967 (4.0)	79 (3.3)	111 (3.7)	236 (4.2)	290 (3.9)	251 (4.5)
Other comorbidities, No. (%)												
Hypertension	18 771 (72.8)	861 (70.0)	1392 (75.9)	3815 (76.7)	6660 (73.5)	6043 (69.7)	17 512 (72.4)	1695 (70.4)	2178 (72.3)	4232 (74.5)	5477 (72.9)	3930 (70.3)
Dyslipidemia	19 527 (75.8)	777 (63.2)	1373 (74.8)	3914 (78.6)	6880 (75.9)	6583 (75.9)	18 280 (75.5)	1602 (66.6)	2239 (74.4)	4354 (76.7)	5835 (77.7)	4250 (76.0)
Hospitalization for bleeding events	848 (3.3)	80 (6.5)	103 (5.6)	213 (4.3)	296 (3.3)	156 (1.8)	746 (3.1)	125 (5.2)	127 (4.2)	210 (3.7)	185 (2.5)	99 (1.8)
Chronic lung disease	6032 (23.4)	361 (29.3)	546 (29.8)	1294 (26.0)	2066 (22.8)	1765 (20.3)	5587 (23.1)	640 (26.6)	757 (25.1)	1416 (24.9)	1657 (22.1)	1117 (20.0)
Diabetes mellitus	8868 (34.4)	442 (35.9)	697 (38.0)	1874 (37.7)	3161 (34.9)	2694 (31.1)	8170 (33.8)	835 (34.7)	994 (33.0)	1965 (34.6)	2595 (34.5)	1781 (31.9)
Medications at time of AMI, No. (%)												
ACEI	8413 (32.6)	234 (19.0)	487 (26.5)	1537 (30.9)	3125 (34.5)	3030 (34.9)	7886 (32.6)	572 (23.8)	880 (29.2)	1848 (32.6)	2565 (34.1)	2021 (36.1)
ARB	3473 (13.5)	83 (6.7)	187 (10.2)	634 (12.7)	1243 (13.7)	1326 (15.3)	3209 (13.3)	193 (8.0)	329 (10.9)	705 (12.4)	1125 (15.0)	857 (15.3)
β-Blocker	11 146 (43.2)	340 (27.6)	761 (41.5)	2331 (46.8)	4097 (45.2)	3617 (41.7)	10 360 (42.8)	806 (33.5)	1221 (40.6)	2550 (44.9)	3379 (45.0)	2404 (43.0)
Any antihypertensive agent	18 352 (71.2)	650 (52.8)	1320 (71.9)	3733 (75.0)	6560 (72.4)	6089 (70.2)	17 134 (70.8)	1433 (59.5)	2083 (69.2)	4169 (73.4)	5441 (72.4)	4008 (71.7)
Statin	13 268 (51.5)	378 (30.7)	859 (46.8)	2725 (54.8)	4848 (53.5)	4458 (51.4)	12 379 (51.2)	791 (32.9)	1425 (47.3)	3026 (53.3)	4128 (54.9)	3009 (53.8)
Other lipid-lowering agent	1397 (5.4)	21 (1.7)	75 (4.1)	243 (4.9)	530 (5.8)	528 (6.1)	1329 (5.5)	71 (2.9)	153 (5.1)	317 (5.6)	447 (5.9)	341 (6.1)
Nonaspirin antiplatelet agent	2637 (10.2)	92 (7.5)	143 (7.8)	453 (9.1)	965 (10.6)	984 (11.3)	2406 (9.9)	184 (7.6)	250 (8.3)	534 (9.4)	837 (11.1)	601 (10.7)
Anticoagulant	1679 (6.5)	69 (5.6)	174 (9.5)	439 (8.8)	587 (6.5)	410 (4.7)	1533 (6.3)	155 (6.4)	254 (8.4)	428 (7.5)	468 (6.2)	228 (4.1)
Vital signs, No. (%)												
Body mass index, mg/kg^2												
<18.5	354 (1.4)	38 (3.1)	56 (3.1)	89 (1.8)	110 (1.2)	61 (0.7)	312 (1.3)	75 (3.1)	52 (1.7)	86 (1.5)	70 (0.9)	29 (0.5)
18.5–24.9	5670 (22.0)	330 (26.8)	482 (26.3)	1200 (24.1)	1974 (21.8)	1684 (19.4)	5207 (21.5)	629 (26.1)	714 (23.7)	1319 (23.2)	1530 (20.4)	1015 (18.2)
25–29.9	8225 (31.9)	296 (24.1)	519 (28.3)	1550 (31.1)	2929 (32.3)	2931 (33.8)	7720 (31.9)	626 (26.0)	884 (29.4)	1774 (31.2)	2521 (33.6)	1915 (34.3)

(*Continued*)

Table 1. Continued

	No. of Guidelines Met at 30 Days After Discharge						No. of Guidelines Met at 90 Days After Discharge					
	Overall (N=25 778)	0–2 (N=1230)	3 (N=1835)	4 (N=4977)	5 (N=9062)	6 (N=8674)	Overall (N=24 200)	0–3 (N=2407)	4 (N=3011)	5 (N=5677)	6 (N=7514)	7 (N=5591)
30–39.9	7319 (28.4)	261 (21.2)	484 (26.4)	1326 (26.6)	2520 (27.8)	2728 (31.5)	6951 (28.7)	562 (23.3)	809 (26.9)	1576 (27.8)	2183 (29.1)	1821 (32.6)
≥40	822 (3.2)	42 (3.4)	53 (2.9)	155 (3.1)	295 (3.3)	277 (3.2)	791 (3.3)	74 (3.1)	89 (3.0)	197 (3.5)	245 (3.3)	186 (3.3)
Unknown	3388 (13.1)	263 (21.4)	241 (13.1)	657 (13.2)	1234 (13.6)	993 (11.4)	3219 (13.3)	441 (18.3)	463 (15.4)	725 (12.8)	965 (12.8)	625 (11.2)
Systolic BP, mm Hg												
<120	7318 (28.4)	318 (25.9)	534 (29.1)	1374 (27.6)	2532 (27.9)	2560 (29.5)	6782 (28.0)	612 (25.4)	806 (26.8)	1605 (28.3)	2076 (27.6)	1683 (30.1)
120–139	11 061 (42.9)	395 (32.1)	678 (36.9)	2024 (40.7)	3955 (43.6)	4009 (46.2)	10 414 (43.0)	865 (35.9)	1167 (38.8)	2396 (42.2)	3377 (44.9)	2609 (46.7)
140–159	3573 (13.9)	201 (16.3)	301 (16.4)	740 (14.9)	1216 (13.4)	1115 (12.9)	3370 (13.9)	385 (16.0)	470 (15.6)	818 (14.4)	1010 (13.4)	687 (12.3)
160–180	989 (3.8)	82 (6.7)	106 (5.8)	240 (4.8)	339 (3.7)	222 (2.6)	934 (3.9)	147 (6.1)	156 (5.2)	235 (4.1)	250 (3.3)	146 (2.6)
≥180	296 (1.1)	28 (2.3)	32 (1.7)	98 (2.0)	97 (1.1)	41 (0.5)	273 (1.1)	55 (2.3)	59 (2.0)	74 (1.3)	59 (0.8)	26 (0.5)
Unknown	2541 (9.9)	206 (16.7)	184 (10.0)	501 (10.1)	923 (10.2)	727 (8.4)	2427 (10.0)	343 (14.3)	353 (11.7)	549 (9.7)	742 (9.9)	440 (7.9)
Diastolic BP, mm Hg												
≤80	18 372 (71.3)	795 (64.6)	1319 (71.9)	3585 (72.0)	6424 (70.9)	6249 (72.0)	17 136 (70.8)	1592 (66.1)	2078 (69.0)	4084 (71.9)	5315 (70.7)	4067 (72.7)
81–89	3495 (13.6)	161 (13.1)	222 (12.1)	603 (12.1)	1238 (13.7)	1271 (14.7)	3331 (13.8)	302 (12.5)	408 (13.6)	737 (13.0)	1072 (14.3)	812 (14.5)
90–99	1029 (4.0)	45 (3.7)	74 (4.0)	207 (4.2)	367 (4.0)	336 (3.9)	981 (4.1)	121 (5.0)	116 (3.9)	217 (3.8)	309 (4.1)	218 (3.9)
100–109	252 (1.0)	15 (1.2)	22 (1.2)	58 (1.2)	86 (0.9)	71 (0.8)	241 (1.0)	35 (1.5)	38 (1.3)	63 (1.1)	62 (0.8)	43 (0.8)
≥110	89 (0.3)	8 (0.7)	14 (0.8)	23 (0.5)	24 (0.3)	20 (0.2)	84 (0.3)	14 (0.6)	18 (0.6)	27 (0.5)	14 (0.2)	11 (0.2)
Unknown	2541 (9.9)	206 (16.7)	184 (10.0)	501 (10.1)	923 (10.2)	727 (8.4)	2427 (10.0)	343 (14.3)	353 (11.7)	549 (9.7)	742 (9.9)	440 (7.9)
Laboratory values, No. (%)												
Estimated glomerular filtration rate, mL/min per 1.73 m^2												
≥150	1 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
90–150	3924 (15.2)	155 (12.6)	250 (13.6)	677 (13.6)	1403 (15.5)	1439 (16.6)	3766 (15.6)	335 (13.9)	469 (15.6)	795 (14.0)	1230 (16.4)	937 (16.8)
60–89	10 097 (39.2)	338 (27.5)	579 (31.6)	1697 (34.1)	3440 (38.0)	4043 (46.6)	9621 (39.8)	710 (29.5)	1001 (33.2)	2124 (37.4)	3095 (41.2)	2691 (48.1)
45–59	3963 (15.4)	171 (13.9)	284 (15.5)	793 (15.9)	1417 (15.6)	1298 (15.0)	3684 (15.2)	337 (14.0)	417 (13.8)	920 (16.2)	1151 (15.3)	859 (15.4)
30–44	2349 (9.1)	129 (10.5)	229 (12.5)	606 (12.2)	840 (9.3)	545 (6.3)	2109 (8.7)	241 (10.0)	325 (10.8)	568 (10.0)	657 (8.7)	318 (5.7)
15–29	984 (3.8)	80 (6.5)	127 (6.9)	300 (6.0)	342 (3.8)	135 (1.6)	838 (3.5)	152 (6.3)	167 (5.5)	240 (4.2)	217 (2.9)	62 (1.1)
<15	163 (0.6)	18 (1.5)	32 (1.7)	54 (1.1)	41 (0.5)	18 (0.2)	146 (0.6)	34 (1.4)	32 (1.1)	47 (0.8)	27 (0.4)	6 (0.1)
Dialysis	601 (2.3)	59 (4.8)	79 (4.3)	170 (3.4)	198 (2.2)	95 (1.1)	523 (2.2)	103 (4.3)	101 (3.4)	133 (2.3)	131 (1.7)	55 (1.0)
Transplant	9 (0.0)	2 (0.2)	0 (0.0)	3 (0.1)	3 (0.0)	1 (0.0)	8 (0.0)	2 (0.1)	2 (0.1)	2 (0.0)	1 (0.0)	1 (0.0)
Unknown	3687 (14.3)	277 (22.5)	255 (13.9)	677 (13.6)	1378 (15.2)	1100 (12.7)	3504 (14.5)	493 (20.5)	497 (16.5)	848 (14.9)	1005 (13.4)	661 (11.8)

(*Continued*)

Table 1. Continued

	Overall (N=25 778)	No. of Guidelines Met at 30 Days After Discharge						No. of Guidelines Met at 90 Days After Discharge						
		0–2 (N=1230)	3 (N=1835)	4 (N=4977)	5 (N=9062)	6 (N=8674)	Overall (N=24 200)	0–3 (N=2407)	4 (N=3011)	5 (N=5677)	6 (N=7514)	7 (N=5591)	
LDL-C, mg/dL													
≥200	383 (1.5)	18 (1.5)	35 (1.9)	60 (1.2)	134 (1.5)	136 (1.6)	366 (1.5)	50 (2.1)	67 (2.2)	96 (1.7)	109 (1.5)	44 (0.8)	
160–199	1572 (6.1)	63 (5.1)	104 (5.7)	317 (6.4)	532 (5.9)	556 (6.4)	1497 (6.2)	186 (7.7)	217 (7.2)	360 (6.3)	455 (6.1)	279 (5.0)	
130–159	3094 (12.0)	106 (8.6)	200 (10.9)	572 (11.5)	1044 (11.5)	1172 (13.5)	2948 (12.2)	330 (13.7)	426 (14.1)	658 (11.6)	877 (11.7)	657 (11.8)	
100–129	5003 (19.4)	212 (17.2)	332 (18.1)	913 (18.3)	1686 (18.6)	1860 (21.4)	4731 (19.5)	548 (22.8)	666 (22.1)	1100 (19.4)	1381 (18.4)	1036 (18.5)	
70–99	7153 (27.7)	302 (24.6)	505 (27.5)	1383 (27.8)	2571 (28.4)	2392 (27.6)	6707 (27.7)	391 (16.2)	624 (20.7)	1569 (27.6)	2247 (29.9)	1876 (33.6)	
<70	3982 (15.4)	160 (13.0)	293 (16.0)	861 (17.3)	1438 (15.9)	1230 (14.2)	3659 (15.1)	229 (9.5)	367 (12.2)	847 (14.9)	1278 (17.0)	938 (16.8)	
Unknown	4591 (17.8)	369 (30.0)	366 (19.9)	871 (17.5)	1657 (18.3)	1328 (15.3)	4292 (17.7)	673 (28.0)	644 (21.4)	1047 (18.4)	1167 (15.5)	761 (13.6)	

ACEI, angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; BP, blood pressure; LDL-C, low-density lipoprotein cholesterol; and TIA, transient ischemic attack.

those meeting 7 versus 0–3 guidelines in 90-day models) (Figure 2 and Table 2). There was also a significant favorable association with mortality with adherence to each additional guideline (HR, 0.89 [95% CI, 0.86–0.92] for the 30-day model; HR, 0.92 [95% CI, 0.90–0.94] for the 90-day model) (Table 2). Findings were similar across important patient subgroups (Figure 3). All models included adjustment for continuous high-dimensional propensity score, which discriminated moderately well between higher versus lower guideline adherence (c=0.68 in both 30- and 90-day analyses).

In addition to cumulative adherence to multiple guideline recommendations, we also evaluated the association of adherence to individual guideline recommendations and mortality. Patient adherence to individual guideline-indicated medications within the studied time windows after AMI (antiplatelet agent, lipid-lowering medication) was independently associated with lower mortality in both 30- and 90-day models (Table 2). Achieving BP <140/90 mm Hg, not smoking, and receipt of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker were not independently associated with mortality after accounting for patient characteristics and adherence to other guidelines. Receipt of a β-blocker was associated with reduced mortality in 30-day but not 90-day models, while achievement of an LDL-C <100 mg/dL at 90 days post-AMI was independently associated with lower mortality.

In sensitivity analyses using E-values, we found that the observed HR of 0.57 for the impact of full guideline adherence at 90 days (or 0.92 for per-guideline impact) on mortality could be explained by an unmeasured confounder that was associated with both full guideline adherence (or adhering to 1 additional guideline) and mortality by a risk ratio of 2.31 (or 1.31) each, above and beyond the measured confounders. These effect sizes are beyond those seen for any individual variable in our study, making the likelihood of unmeasured confounding fully explaining our results less likely. Finally, in sensitivity analyses including the Elixhauser index into the model, there was no appreciable change in results.[28]

DISCUSSION

In a large, demographically diverse, community-based population eligible for secondary prevention after AMI, we found that cumulative adherence to: (1) guideline-recommended medical therapy, (2) optimal cardiovascular risk factor control, and (3) lifestyle interventions at 30 and 90 days after the event was associated with significantly lower long-term mortality. We also observed that while achieving any individual secondary prevention guideline recommendation

Table 2. Impact of Cumulative and Individual Adherence to Guideline-Recommended Medical Therapy, Control of Cardiovascular Risk Factors, and Lifestyle Practices on All-Cause Mortality After AMI

	Guideline Adherence at 30 days (N=25 778)			Guideline Adherence at 90 days (N=24 200)			
	No. (%)	HR	95% CI		No. (%)	HR	95% CI
Categorical				Categorical			
0 to 2 Guidelines	1230 (5)	Reference		0 to 3 Guidelines	2407 (10)	Reference	
3 Guidelines	1835 (7)	0.94	0.80 to 1.11	4 Guidelines	3011 (12)	0.84*	0.74 to 0.96
4 Guidelines	4977 (19)	0.87	0.74 to 1.01	5 Guidelines	5677 (23)	0.75*	0.66 to 0.85
5 Guidelines	9062 (35)	0.82*	0.70 to 0.95	6 Guidelines	7514 (31)	0.69*	0.61 to 0.78
6 Guidelines	8674 (34)	0.61*	0.52 to 0.72	7 Guidelines	5591 (23)	0.57*	0.49 to 0.66
Continuous				Continuous			
Per guideline		0.89*	0.86 to 0.92	Per guideline		0.92*	0.90 to 0.94
By Guideline				By Guideline			
BP <140/90 mm Hg	22 041 (86)	1.03	0.95 to 1.12	BP <140/90 mm Hg	20 644 (85)	1.08	0.98 to 1.19
Not smoking after event	21 459 (83)	0.97	0.85 to 1.10	Not smoking after event	20 088 (83)	0.93	0.81 to 1.07
Prescribed ARB/ACEI	19 076 (74)	0.94	0.87 to 1.02	Prescribed ARB/ACEI	17 026 (70)	0.93	0.86 to 1.01
Prescribed β-blocker	22 325 (87)	0.90*	0.82 to 1.00	Prescribed β-blocker	19 672 (81)	0.93	0.84 to 1.02
Prescribed antiplatelet	17 319 (67)	0.77*	0.71 to 0.82	Prescribed antiplatelet	15 444 (64)	0.81*	0.75 to 0.88
Prescribed lipid medication	22 647 (88)	0.90*	0.81 to 1.00	Prescribed lipid medication	20 714 (86)	0.76*	0.69 to 0.84
				LDL-C <100 mg/dL	17 073 (71)	0.91*	0.84 to 0.98

ACEI indicates angiotensin-converting enzyme inhibitor; AMI acute myocardial infarction; ARB, angiotensin receptor blocker; BP, blood pressure; HR, hazard ratio; and LDL-C, low-density lipoprotein cholesterol.

*$P<0.05$.

after AMI is associated with modest benefits, the favorable association of adherence to multiple guideline recommendations with longer survival is both statistically and clinically significant. For example, adherence to 1 additional guideline was associated with lower adjusted rates of death by 8% to 11%, but there was a 39% to 43% lower mortality rate in patients meeting all guideline-recommended treatments. These beneficial associations were observed even within a cohort demonstrating high levels of adherence to each individual guideline recommendation. Further, full adherence to all guideline-recommended treatments was associated with an additional 12% to 21% improvement in long-term survival compared with those achieving 1 less than full adherence (ie, comparing results for 6 versus 5 and 7 versus 6 in 30- and 90-day models, respectively). Our findings provide support for providers and healthcare delivery systems to systematically and aggressively promote comprehensive secondary prevention efforts across multiple avenues of care. Patients and providers can use this information to understand the incremental and cumulative benefits of achieving the maximum number of guideline-recommended strategies possible.

As an observational study, there is the potential for residual confounding that may influence our results. However, we present both unadjusted and fully adjusted models that controlled for observed baseline and time-updated comorbidities, laboratory results, prescriptions and vital signs, recurrent AMI events, and a high-dimensional propensity score. Our comprehensive electronic medical record system allows for complete follow-up for these patient-related factors, providing the opportunity to adjust for potential confounders across many clinical care domains at baseline and during follow-up. After adjustment, our results make clear that the monotonic relationship between achieving each additional guideline recommendation and mortality, although attenuated, remains both clinically and statistically significant across the entire range of adherence.

Previous studies have examined whether guideline metrics at AMI admission, such as door-to-balloon time and other acute interventions, affect long-term outcomes,[29] but little evidence exists about post-discharge adherence to multiple diverse elements of guideline-directed therapy. Prior work has focused on the impact of limited specific medications or classes but has not examined risk factor control or lifestyle interventions,[14–18,30] have relied on self-reported outcomes rather than clinical data from electronic medical records,[31] or have examined international settings, which may not be generalizable to the United States.[31] To our knowledge, none have examined the association of combining multiple elements of guideline recommendations across varied clinical domains with

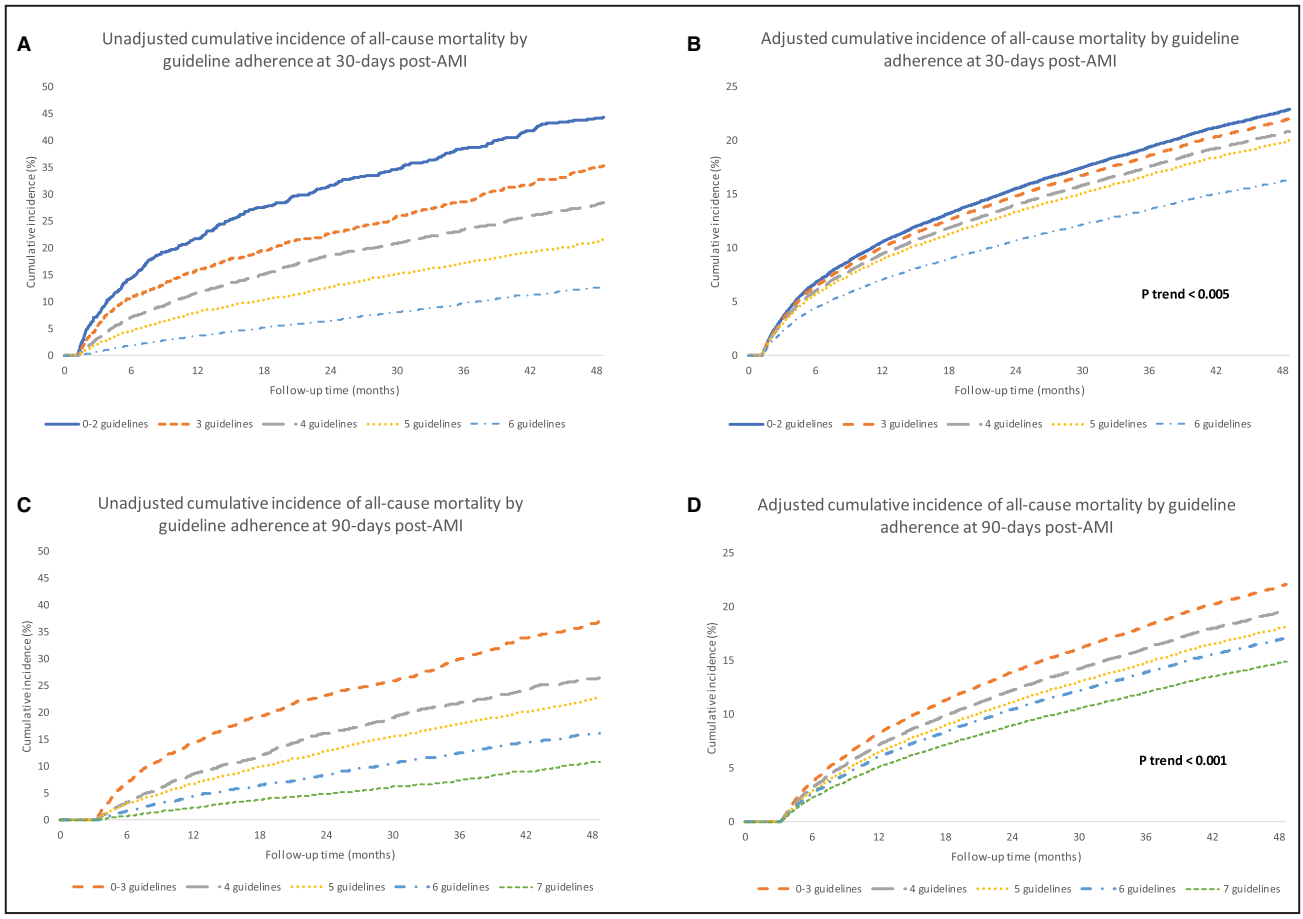

Figure 2. A, Thirty-day unadjusted, (B) 30-day adjusted, (C) 90-day unadjusted, and (D) 90-day adjusted cumulative incidence of all-cause mortality, stratified by adherence to secondary prevention guidelines after acute myocardial infarction (AMI).

long-term mortality. Furthermore, since our source population included >4.4 million people (≈1.5% of the US population) receiving care within a large integrated healthcare delivery system, our findings are more likely to be representative of real-world outcomes compared with those in clinical trial volunteer samples, select patient registries, or tertiary care/referral practice settings.

As prior studies typically measured the impact of fewer guidelines, it remained unknown whether adherence to additional recommendations had a meaningful impact on outcomes, or whether at some point there were diminishing returns, and whether full adherence to multiple diverse guideline recommendations continued to demonstrate a protective effect at higher absolute levels of guideline achievement. Importantly, our data suggest that full adherence to guideline-recommended therapy may be required to realize the greatest overall impact on mortality. However, even if full guideline adherence was not accomplished at 30 and 90 days post-AMI, each incrementally achieved guideline recommendation was associated with lower adjusted mortality, overall and within key clinical subgroups.

We chose to examine guideline adherence within 30- and 90-day periods post-discharge, whereas many prior studies examined guideline adherence at discharge after AMI or at later intervals (eg, 6 months and 1 year). Little evidence suggests that allowing patients a longer postdischarge "buffer" period to meet guideline-directed therapy correlates with improved outcomes. In current practice, most patients have a follow-up visit after AMI within 1 month, so our methodology would allow treating physicians to fill any gaps missed between the time of discharge after AMI and the initial follow-up visit. There is evidence that early follow-up after AMI is associated with higher rates of recommended medication use,[32] and since this study was performed in an integrated healthcare delivery system with a long-standing post-AMI cardiac rehabilitation program, it is possible that our rates of long-term persistence are higher than in other settings. We did find sustained adherence between 30 and 90 days; for individual guideline metrics, >89% to 90% of those adherent at 30 days remained adherent at 90 days.

Our findings demonstrated a high degree of adherence to secondary prevention guidelines after

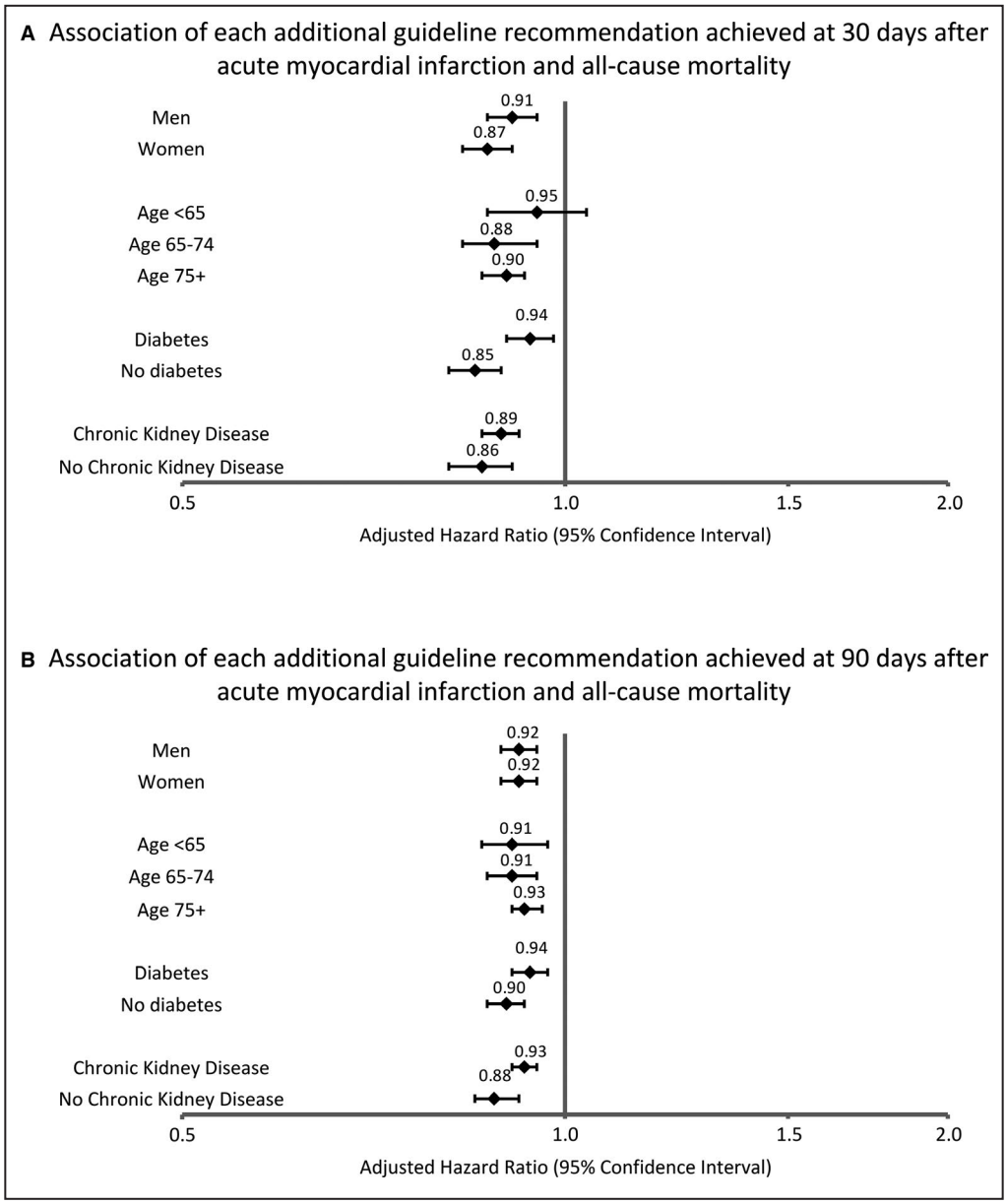

Figure 3. Multivariable association of achieving 1 additional secondary prevention guideline after acute myocardial infarction (AMI) with all-cause mortality, stratified by patient subgroup. **A,** Association of each additional guideline recommendation achieved at 30 days after AMI and all-cause mortality. **B,** Association of each additional guideline recommendation achieved at 90 days after AMI and all-cause mortality.

AMI including medication use, cardiovascular risk factor control, and lifestyle intervention—a combination of measures beyond that observed in other registries[33–35] and at rates consistent with pooled analyses of large clinical trials.[36] In addition to aggressive primary prevention efforts,[37] these may help to explain the significant reductions in AMI rates and heart disease mortality within KPNC, which have surpassed national rates over the past decade.[20,38] Although our findings are observational and not considered causal, it is helpful for both providers and patients to know that adherence to each additional guideline by 90 days is associated with an 8% lower adjusted rate of long-term mortality, with an overall 43% lower mortality rate if all guideline metrics are achieved.

Improving adherence to secondary prevention measures will require systematic, multipronged, coordinated programs that use technology-based tools for population-level outreach and patient management, leverage the full spectrum of physician and nonphysician providers, reduce barriers for patients, and apply

validated clinical algorithms to improve adherence to recommended therapies.[37,39]

Limitations

Our study has several limitations. We focused primarily on recommendations from the 2014 American College of Cardiology/American Heart Association (ACC/AHA) Guideline for the Management of Patients With Non–ST-Elevation Acute Myocardial Infarction[40] and an updated hypertension management guideline,[6] which have been stable since earlier versions of similar guidelines.[41,42] Despite controversy about whether to target a specific LDL-C level for secondary prevention, our internal guidelines during the study period did not change and were consistent with pre-2013 ACC/AHA atherosclerotic cardiovascular disease risk and cholesterol guidelines that recommended specific LDL targets.[43] In addition, although our electronic medical record system allowed for ascertainment of the 7 examined guideline metrics, our antiplatelet metric included receipt of PY2Y12 inhibitors but not aspirin, for which data were not comprehensively available from pharmacy records, as it is commonly purchased over the counter. We also did not exclude patients ineligible for specific guideline-recommended therapies, such as those with a relative or absolute contraindication to β-blockers or angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Review of internal data suggests that nearly 20% of patients post-AMI in our system are ineligible for β-blockers per Healthcare Effectiveness Data and Information Set (HEDIS) guidelines, so our study population included patients ineligible for this therapy. Given that our goal was to examine the association of guideline adherence and mortality in all-comers after AMI, and assessing the eligibility for all guideline metrics was not operationally feasible given the large number of relative and absolute contraindications, we elected to retain these patients in our analyses. Further, patients not receiving guideline-directed therapy, even if contraindicated, would not receive the potential benefit from the therapy. We also did not have the capacity to identify patients who may have discontinued therapy because of side effects. In addition, we did not examine whether medications were titrated to doses used in pivotal randomized trials, which could modify their effect on long-term outcomes,[44] did not examine the impact of changes in guideline adherence or persistence after 90 days post-AMI, and could not ascertain other preventive measures such as dietary or exercise patterns. We also could not capture individual patient-level participation in home-based cardiac rehabilitation, which could influence the likelihood of adherence to guideline-directed therapies, in a systematic manner during our study period from available data within our system. We examined all-cause mortality, as cardiovascular-specific mortality is difficult to discern because of inaccurate death certificate data and lack of confirmed cause of death for most out-of-hospital deaths.[45,46] However, given that all patients in our cohort had an AMI, most deaths were likely attributable to cardiovascular disease. Certain guideline metrics, such as smoking status, may be subject to misclassification, but systematic efforts within KPNC to closely track this information help minimize this risk, as we have successfully encouraged >100 000 smokers to quit smoking in the past 5 to 10 years. KPNC members are routinely screened for smoking at outpatient appointments by medical assistants and their primary care physicians, and smoking is considered an additional "vital sign."[47] While subject to misclassification, there is no a priori reason to believe that misclassification varies across categories of guideline adherence. In addition, as this is an observational analysis using information collected as part of usual clinical care, we did not have complete data for selected baseline variables included in our models, which is a limitation. However, we included a category for missingness for these variables in our regression models and it was not significantly or strongly associated with the outcome of interest for variables with missing data. Finally, there remains the potential for bias as a result of unmeasured confounders, and patients who were more adherent to guideline-directed therapies may have been overall healthier. However, we employed advanced techniques including a machine-learning method to construct a high-dimensional propensity score to account for unmeasured confounding, and conducted sensitivity analyses that included a frailty index, to control for a large range of patient-related factors that could influence the relationship between the exposure and outcome. Our findings should be considered hypothesis generating, and our main goal was to demonstrate the magnitude of the association of poor guideline adherence with all-cause mortality—regardless of the cause of poor adherence—to highlight the worse outcomes in poorly adherent patients. This could encourage more aggressive secondary prevention outreach efforts and could potentially provide patients with additional incentive to follow-up (ie, if physicians can articulate the potential survival benefit to cumulative secondary prevention guideline adherence), which could affect other health behaviors linked to longer survival.

CONCLUSIONS

Within a large real-world population eligible for secondary prevention after AMI, we found that cumulative adherence to guideline-recommended medical therapies, cardiovascular risk factor control, and lifestyle modification at 30 and 90 days after discharge

was associated with significant long-term reductions in mortality. The associated benefit continued to accrue all the way to full adherence of the examined guideline metrics, without significant diminishing returns. Future research should examine the population-, system-, and individual-level barriers to achieving full adherence to guideline-recommended therapy to optimize secondary prevention after AMI.

ARTICLE INFORMATION

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Affiliations

From the Division of Research, Kaiser Permanente Northern California, Oakland, CA (M.D.S., T.K.L., J.S.R., S.S., S.H.S., C.L., A.S.G.); Division of Cardiology, Kaiser Permanente Oakland Medical Center, Oakland, CA (M.D.S., J.S.R.); Division of Cardiology, Kaiser Permanente Santa Clara Medical Center, Santa Clara, CA (E.L.); Division of Endocrinology, Kaiser Permanente South San Francisco Medical Center, San Francisco, CA (M.G.J.); Division of Cardiology, University of California at San Diego, CA (A.D.); Departments of Epidemiology, Biostatistics and Medicine, University of California, San Francisco, CA (A.S.G.); Departments of Medicine, Health Research and Policy, Stanford University, Palo Alto, CA (A.S.G.).

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Disclosures

None.

Supplementary Materials

Data S1

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SUPPLEMENTAL MATERIAL

Data S1.

High-dimensional propensity score

The high-dimensional propensity score was derived from a multivariable logistic regression initially evaluating up to 600 variables in categories of demographics, diagnoses, procedures and prescriptions, selected by an algorithm that ranked candidate variables by their potential to minimize confounding based on the bivariate associations of each variable with the treatment and with the outcome.[1]

E-Values

We assessed the robustness of our results to unmeasured confounding using the E-Value methodology of VanderWeele and Ding.[2] Calculated E-values for the hazard ratios found in the 90-day guideline analyses are shown below.

E-Values for Hazard Ratios in 90-Day Analysis

Variable	HR	95% CI	E-value	E-value for 95% C.I. closest to Null
0-3 guidelines	ref			
4 guidelines	0.84	(0.74-0.96)	1.51	1.20
5 guidelines	0.75	(0.66-0.85)	1.74	1.48
6 guidelines	0.69	(0.61-0.78)	1.91	1.66
7 guidelines	0.57	(0.49-0.66)	2.31	2.00
Per guideline	0.92	(0.90-0.94)	1.31	1.26

Supplemental References:

1. Rassen JA, Schneeweiss S. Using high-dimensional propensity scores to automate confounding control in a distributed medical product safety surveillance system. *Pharmacoepidemiol Drug Saf*. 2012;21 Suppl 1:41-49.

2. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the e-value. *Ann Intern Med*. 2017;167:268-274.