Untangling the relationship between medication adherence and post–myocardial infarction outcomes: Medication adherence and clinical outcomes

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Background Patients who adhere to medications experience better outcomes than their nonadherent counterparts. However, these observations may be confounded by patient behaviors. The level of adherence necessary for patients to derive benefit and whether adherence to all agents is important for diseases that require multiple drugs remain unclear. This study quantifies the relationship between medication adherence and post–myocardial infarction (MI) adverse coronary events.

Methods This is a secondary analysis of the randomized MI FREEE trial. Patients who received full prescription coverage were classified as adherent (proportion of days covered ≥80%) or not based upon achieved adherence in the 6 months after randomization. First major vascular event or revascularization rates were compared using multivariable Cox models adjusting for comorbidity and health-seeking behavior.

Results Compared with patients randomized to usual care, full coverage patients adherent to statin, β-blocker, or angiotensin-converting enzyme inhibitor/angiotensin receptor blocker were significantly less likely to experience the study's primary outcome (hazard ratio [HR] range 0.64-0.81). In contrast, nonadherent patients derived no benefit (HR range 0.98-1.04, $P \leq .01$ for the difference in HRs between adherent and nonadherent patients). Partially adherent patients had no reduction in clinical outcomes for any of the drugs evaluated, although their achieved adherence was higher than that among controls.

Conclusion Achieving high levels of adherence to each and all guideline-recommended post-MI secondary prevention medication is associated with improved event-free survival. Lower levels of adherence appear less protective. (Am Heart J 2014;167:51-58.e5.)

Efforts to improve medication adherence have received increasing attention as strategies for quality improvement,[1] motivated by the observation that adherent patients experience better clinical outcomes and consume fewer health care resources than nonadherent ones.[2,3] Unfortunately, the actual value of adherence remains undefined because existing estimates generally come from nonrandomized studies where outcome differences between adherent and nonadherent individuals could be attributable to confounding by patients' health status or practices, such as preventive services use.[4-6]

It also remains unclear whether adherence to all agents is important for diseases that require patients to take multiple drugs. Patients discharged from hospital after myocardial infarction (MI) are routinely prescribed ≥4 new medications intended for life-long use.[7] Given that such complexity can undermine long-term adherence,[8] patients and physicians often struggle with medication prioritization; trials validating their use were conducted iteratively, and the benefit of drugs whose roles were defined first is unclear when used in the context of newer therapies.

Data from the recently published MI FREEE trial,[9] a randomized evaluation aimed to enhance adherence by eliminating copayments for post-MI secondary prevention medications, provide the opportunity to evaluate the implications of achieved levels of adherence on health outcomes.

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Methods

The study population was derived from MI FREEE—a randomized policy study evaluating the impact of copayments for β-blocker, statin, angiotensin-converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB) prescribed to patients discharged from hospital after MI. Full details of the trial have previously been published.[9] To evaluate the impact of adherence on clinical outcomes, we restricted the cohort to patients who had filled a prescription for at least one of the study medications after randomization (which occurred a median of 49 days after hospital discharge [95% of patients were randomized within 100 days]) and who did not die or lose insurance eligibility in the 6 months after randomization (n = 4,117 [70%] of the 5,855 patients in the full MI FREEE study cohort).

Adherence assessment

Medication adherence achieved by each patient in the first 6 months after randomization was evaluated by calculating the days of medication available or the "proportion of days covered" (PDC) for each drug class prescribed.[10-12] We created a supply diary for each patient-day by aggregating fills of each medication class based on dispensing dates and days of medication supplied during this period. Drugs dispensed within a therapeutic class were considered interchangeable. When a dispensing occurred before the previous dispensing should have run out, utilization of the new medication was assumed to begin the day after the end of the old dispensing.

Patients randomized to full coverage were classified as being adherent or not to each of the study medications based upon whether they achieved a PDC of ≥80% in the 6 months after randomization.[13] To evaluate the impact of adherence to >1 drug class simultaneously, patients were considered to be adherent if they achieved a PDC of ≥80% for each of the component classes.[14] Analyses were repeated classifying intervention patients into 3 groups: adherent (PDC ≥80%), partially adherent (PDC 60%-79%), or nonadherent (PDC <60%); the threshold between adherent and partially adherent was based upon the average achieved adherence among control patients (Table I).

Clinical outcomes

Analyses focused on the trial's prespecified primary outcome, first readmission for a major vascular event (fatal or nonfatal acute MI, unstable angina, stroke, congestive heart failure), or coronary revascularization (coronary bypass, stenting, or angioplasty). We included all events that occurred after randomization rather than limiting the analysis to events after any specific time point, as any outcome misclassification would bias the analysis toward the null. To test the validity of this choice, we re-ran our models considering only outcomes that occurred at least 6 months after randomization, although doing so would reduce statistical power. We also evaluated the impact of adherence on time to first major vascular event (ie, the primary composite outcome excluding revascularization), one of the trial's prespecified secondary outcomes.

Statistical analyses

Outcome rates among full coverage patients adherent and nonadherent to each medication, 2-group combination, and all 3 study medications were compared with those in the usual coverage group using Cox proportional hazards models. Rather than directly compare intervention patients who did and did not achieve high levels of adherence, we compared each of these subgroups to the entire eligible usual care group, as this allowed for a more direct assessment of the impact of adherence achieved from the intervention.

To account for differences in adherent and nonadherent patients, we adjusted for age and comorbidity using the Ontario Acute Myocardial Infarction Mortality Prediction Rule.[15] Each patient's score was calculated using published weights for gender and characteristics observed on index hospitalization. Weights for age were not included as all patients in the trial were ≤65 years, but our models adjusted for age. Because individuals who achieved high levels of adherence may have been healthier in unobserved ways than nonadherent patients, we also adjusted for covariates that represent health-seeking behavior,[16] including income, receipt of influenza vaccination, pneumococcal vaccination, mammography (for women), prostate-specific antigen testing (for men), and colorectal cancer screening. We adjusted for clustering using a robust sandwich estimator for the covariance matrix.[17] We used likelihood ratio tests to test the null hypothesis that the impact of full coverage for adherent and nonadherent subjects did not differ relative to usual care.

To evaluate alternative adherence definitions, we repeated our analysis defining adherence as adherent (PDC ≥80%), partially adherent (PDC 40%-79%), or nonadherent (PDC <40%) based upon thresholds from the published literature.[5] We assessed the incremental impact of adherence to each additional class of post-MI secondary prevention by restricting our cohort to patients who filled all 3 study medications (n = 2,365) and categorizing them by the number of medications they adhered to. Outcome rates among patients in the full coverage arm who achieved adherence to none, 1, 2, and all 3 study medications were compared with controls, and a test of trend was performed.

To determine whether our a priori 80% threshold, widely used in the literature, is the optimal cut point for defining adherence, we also divided patients in the full coverage arm into quintiles of achieved PDC to each and all combinations of the study drugs.

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Results

The proportion of patients in the full and usual coverage groups who were fully and nonadherent to the study medications is presented in online Appendix A (top panel). Table I shows the baseline characteristics of all patients randomized to the full and usual coverage arms, stratified by study medication and achieved adherence. Age, gender, comorbidity scores, and copayment were similar across groups. Nonadherent patients in the full coverage cohort were slightly less likely to have

Table I. Baseline characteristics of patients in the usual and full prescription coverage groups according to study medication and whether full coverage patients achieved full adherence

	Statin			β-Blocker			ACEI/ARB		
Characteristics	**Full coverage: adherent (n = 919)**	**Full coverage: non-adherent (n = 884)**	**Usual coverage (n = 1881)**	**Full coverage: adherent (n = 726)**	**Full coverage: non-adherent (n = 1027)**	**Usual coverage (n = 1843)**	**Full coverage: adherent (n = 664)**	**Full coverage: non-adherent (n = 778)**	**Usual coverage (n = 1476)**
Age, mean (SD)	54.0 (7.2)	53.2 (7.6)	53.7 (7.3)	54.13 (7.0)	53.2 (7.6)	53.9 (7.3)	54.1 (7.2)	53.3 (7.5)	54.0 (7.2)
Male gender, n (%)	709 (77.1)	677 (76.6)	1445 (76.8)	554 (76.3)	786 (76.5)	1398 (75.9)	522 (78.6)	582 (74.8)	1126 (76.3)
Prehospitalization medication use, n (%)									
ACEI/ARB	531 (57.8)	485 (54.9)	1045 (55.6)	434 (59.8)	564 (54.9)	1049 (56.9)	480 (72.3)	492 (63.2)	995 (67.4)
β-Blocker	646 (70.3)	567 (64.1)	1294 (68.8)	548 (75.5)	708 (68.9)	1330 (72.2)	460 (69.3)	524 (67.4)	1020 (69.1)
Clopidogrel	550 (59.8)	495 (56.0)	1113 (59.2)	436 (60.1)	573 (55.8)	1063 (57.7)	386 (58.1)	435 (55.9)	849 (57.5)
Statins	673 (73.2)	558 (63.1)	1281 (68.1)	489(67.4)	637 (62.0)	1158 (62.8)	439 (66.1)	482 (62.0)	929 (62.9)
Warfarin	61 (6.6)	39 (4.4)	99 (5.3)	45(6.2)	64 (6.2)	105 (5.7)	41 (6.2)	48 (6.2)	89 (6.0)
Comorbidities, n (%)									
CHF	226 (24.6)	224 (25.3)	506 (26.9)	186(25.6)	271(26.4)	512 (27.8)	166 (25.0)	228 (29.3)	455 (30.8)
COPD	118 (12.8)	131 (14.8)	287 (15.3)	103 (14.2)	142 (13.8)	288 (15.6)	93 (14.0)	116 (14.9)	224 (15.2)
Diabetes	266 (28.9)	325 (36.7)	620 (33.0)	211 (29.1)	368 (35.8)	622 (33.7)	193 (29.1)	306 (39.3)	537 (36.4)
Hypertension	613 (66.7)	643 (72.7)	1344 (71.5)	498 (68.6)	748 (72.8)	1360 (73.8)	471 (70.9)	588 (75.6)	110 (74.9)
MI	128 (13.9)	139 (15.7)	298 (15.8)	101 (13.9)	161 (15.7)	308 (16.7)	76 (11.4)	132 (17.0)	249 (16.9)
Stroke	37 (4.0)	45 (5.1)	111 (5.9)	34 (4.7)	61 (5.9)	113 (6.1)	30 (4.5)	46 (5.9)	107 (7.2)
Procedures on MI hospitalization, n (%)									
Angiography	889 (96.7)	842 (95.2)	1798 (95.6)	698 (96.1)	976 (95.1)	1745 (94.7)	635 (95.6)	735 (94.5)	1396 (94.6)
CABG	186 (20.2)	158 (17.9)	332 (17.7)	160 (22.0)	179 (17.4)	321 (17.4)	106 (16.0)	139 (17.9)	235 (15.9)
PCI	667 (72.6)	607 (68.7)	1339 (71.2)	509 (70.1)	698 (68.0)	1284 (69.7)	488 (73.5)	530 (68.1)	1059 (71.7)
Comorbidity score*, mean (SD)	0.20 (0.34)	0.21 (0.36)	0.21 (0.37)	0.21 (0.36)	0.20 (0.37)	0.22 (0.38)	0.19 (0.33)	0.22 (0.36)	0.22 (0.38)
Copayments between discharge and randomization, mean (SD)									
ACEI/ARB	$13.36 ($11.26)	$13.24 ($11.33)	$12.90 ($10.19)	$14.27 ($12.32)	$12.72 ($10.56)	$13.02 ($10.01)	$13.95 ($11.55)	$12.97 ($11.34)	$13.18 ($10.25)
β-Blocker	$12.90 ($10.63)	$12.10 ($10.48)	$13.84 ($13.10)	$13.71 ($12.00)	$12.00 ($10.12)	$13.95 ($13.05)	$13.19 ($10.60)	$11.68 ($10.53)	$13.99 ($13.62)
Statin	$26.17 ($20.82)	$26.36 ($22.14)	$24.63 ($20.65)	$26.05 ($20.98)	$26.29 ($22.17)	$24.66 ($20.89)	$26.64 ($21.41)	$25.86 ($22.53)	$25.02 ($20.66)
Achieved adherence during the 6 m after randomization	92.3	48.5	54.0	92.9	56.4	49.4	92.9	44.0	39.6

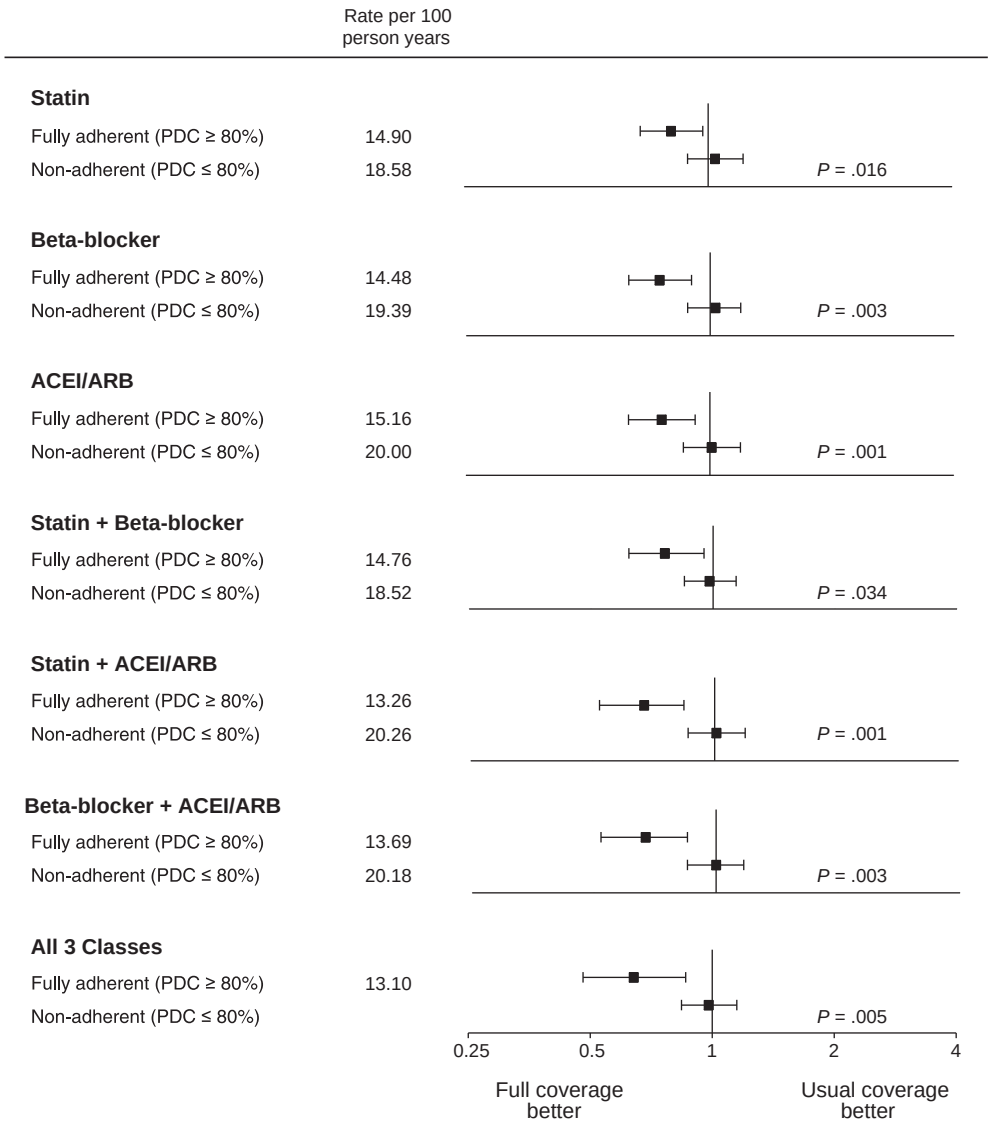
Abbreviations: *CHF*, Congestive heart failure; *COPD*, chronic obstructive pulmonary disease; *CABG*, coronary artery bypass graft; *PCI*, percutaneous coronary intervention.
*Calculated using the Ontario Acute Myocardial Infarction Mortality Prediction Rule, which predicts 30-day and 1-year mortality.[15] Full adherence defined by a PDC ≥80%.

used cardiovascular medications before their MI, less likely to have undergone revascularization during their index MI admission, and more likely to have had comorbid conditions than adherent patients. Full coverage patients who were and were not adherent to their prescribed statin had an average adherence (measured by PDC) of 92% and 48%, respectively, as compared with 54% among controls (Table I). Similar differences were observed for ACEI/ARBs and β-blockers.

Impact of achieving full adherence on clinical outcomes

As previously reported, eliminating copayments did not significantly reduce the trial's primary outcome, first major vascular event, or revascularization (hazard ratio [HR] 0.93, 95% CI 0.82-1.04, $P = .21$), in the trial population.[9] However, when stratified by achieved adherence, patients with ≥80% adherence to each of the study medications were significant less likely than controls to experience a major vascular event or undergo revascularization (Figure 1). By contrast, nonadherent patients in the full coverage cohort had events rates comparable with those among controls ($P < .01$ for all interaction terms between adherent and nonadherent patients). For example, full coverage patients who were adherent had a 24% lower hazard of event-free survival than controls (HR 0.76, 95% CI 0.63-0.92, $P < .01$) whereas nonadherent full coverage patients had no such advantage (HR 1.01, 95% CI 0.86-1.19, $P = .90$). Similar significant reductions were seen in the other 2 targeted drug classes. The same was true for patients who were adherent to all 2 group combinations and to all 3 of the study medications when considered together. The results were virtually identical in models that adjusted for markers of health-seeking behavior (Table II).

Figure 1



Adjusted HR (95% CI) of first major vascular event or revascularization by adherence level achieved among patients in the full coverage study arm compared with patients randomized to the usual coverage. Each point represents the HR in the adherence stratum of the full coverage group compared to usual coverage. Also shown are event rates per 100 person-years. Data adjusted for age, gender, and comorbidity score as well as the cluster and block randomized study design. The *P* values represent the results of a likelihood ratio test for the null hypothesis that the impact of full coverage for adherent and nonadherent subjects did not differ relative to usual care.

Impact of lower levels of adherence on clinical outcomes

After categorizing adherence into 3 groups, the proportion of patients in the full and usual coverage groups who were fully, partially, and nonadherent to the study medications is presented in online Appendix A (bottom panel). Partially adherent patients in the full coverage cohort (PDC 60%-79%) had no significant reduction in clinical outcomes for any of the drugs evaluated compared with controls (Figure 2), despite achieving greater medication adherence (online Appendix B). For example, full coverage patients who were partially adherent to β-blockers had an average adherence of 71% compared with 49% among the entire control group but had an equivalent risk of major vascular events or revascularization than controls (HR 1.01, 95% CI 0.79-1.29, P = .96, interaction P-value between adherent and nonadherent patients <.01). Reclassifying partially adherent patients as those who achieved a PDC between 40% and 79% yielded very similar results (Table III).

Table II. Adjusted HR (95% CI) of first major vascular event or revascularization by adherence level achieved among patients in the full prescription coverage study arm compared with patients randomized to the usual coverage

	Statin	β-Blocker	ACEI/ARB	Statin + β-Blocker	Statin + ACEI/ARB	β-Blocker + ACEI/ARB	All 3 classes
Unadjusted							
Fully adherent	0.82 (0.68-0.97)	0.75 (0.63-0.91)	0.75 (0.62-0.91)	0.77 (0.62-0.96)	0.66 (0.52-0.84)	0.67 (0.52-0.85)	0.64 (0.48-0.86)
Nonadherent	1.03 (0.88-1.21)	1.01 (0.87-1.19)	0.99 (0.84-1.17)	0.98 (0.84-1.13)	0.99 (0.84-1.17)	0.98 (0.83-1.15)	0.97 (0.82-1.14)
Interaction *P* value	.023	.005	.015	.045	.001	.004	.007
Age, gender, and comorbidity score							
Fully adherent	0.81 (0.68-0.97)	0.75 (0.63-0.90)	0.76 (0.63-0.92)	0.76 (0.62-0.95)	0.67 (0.52-0.84)	0.67 (0.52-0.85)	0.64 (0.48-0.86)
Nonadherent	1.04 (0.89-1.22)	1.03 (0.88-1.19)	1.01 (0.86-1.19)	0.98 (0.85-1.14)	1.01 (0.86-1.19)	1.00 (0.85-1.17)	0.98 (0.84-1.15)
Interaction *P* value	0.016	0.003	0.01	0.034	0.001	0.003	0.005
Adjusted for age, gender, comorbidity, and healthy user characteristics*							
Fully adherent	0.82 (0.69-0.97)	0.75 (0.62-0.90)	0.76 (0.62-0.92)	0.77 (0.62-0.95)	0.67 (0.53-0.85)	0.67 (0.52-0.85)	0.65 (0.49-0.87)
Nonadherent	1.04 (0.88-1.22)	1.02 (0.87-1.19)	1.00 (0.84-1.18)	0.98 (0.84-1.14)	1.00 (0.85-1.18)	0.99 (0.84-1.16)	0.97 (0.82-1.15)
Interaction *P* value	.023	.004	.015	.041	.002	.004	.008

All analyses are adjusted for the cluster and block randomized study design in addition to the listed covariates. The *P* values represent the results of a likelihood ratio test for the null hypothesis that the impact of full coverage for adherent and nonadherent subjects did not differ relative to usual care. Full and nonadherence were defined based on PDC of ≥80% and <80%, respectively.
* See text for details.

Sensitivity analyses

To evaluate whether the impact of adherence was similar on other outcomes, we repeated our analyses using rates of major vascular events, a prespecified secondary outcome, and found very similar results (online Appendix C). Patients in the full coverage group who were fully adherent to the study medications had a 25% to 30% lower hazard of this outcome compared with controls, whereas partially and nonadherent patients derived no benefit from therapy.

We assessed the incremental impact of adherence to each additional class of post-MI secondary prevention by categorizing patients in the full coverage arm who filled prescriptions for all 3 study medications based upon the number of these classes to which they were fully adherent. The benefit of therapy increased linearly with the number of medications to which patients were adherent (online Appendix D, $P < .001$ for linear trend). However, only full coverage patients who were adherent to all 3 classes had outcome rates significantly different than controls (HR 0.65, 95% CI 0.48-0.86).

The results of our analysis identifying the optimal cut point to distinguish adherent from nonadherent patients are presented in online Appendix E. Although adherence in each quintile differed from drug to drug, across drug classes, adherence was associated with significant reductions in clinical outcomes beginning in those quintiles corresponding to a mean PDC of 70% and 80%.

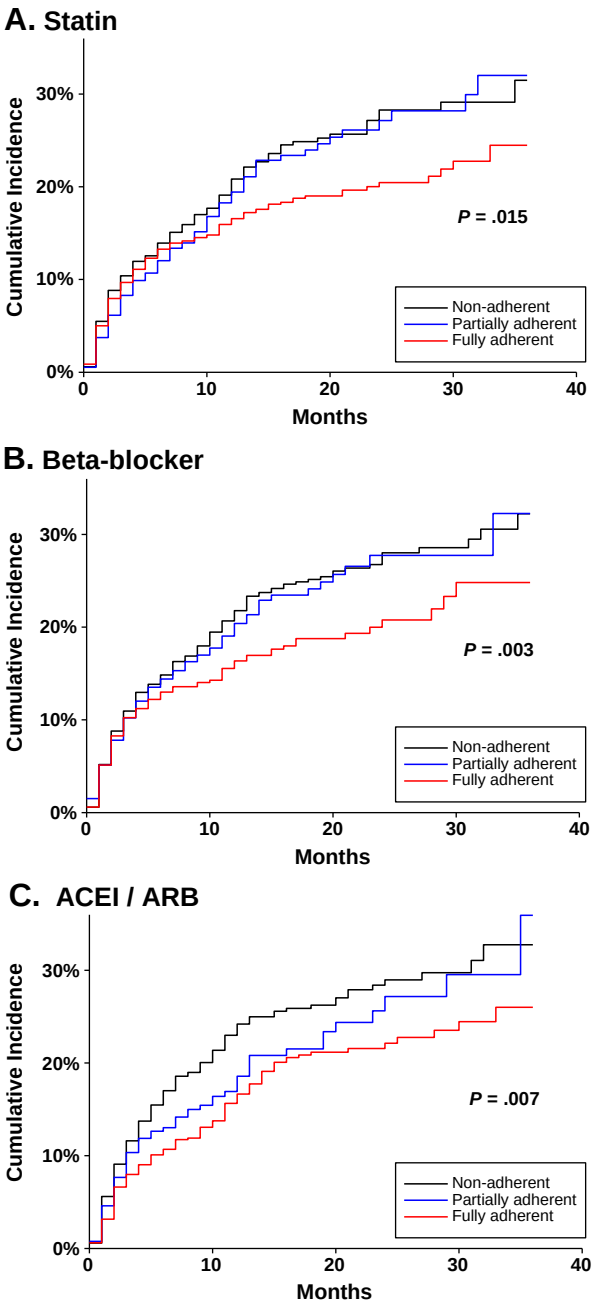
Finally, although our primary analyses evaluated all outcomes occurring after randomization, we repeated these analyses excluding events during the 6 months after randomization. We found a similar pattern, except that ACEI/ARB adherence was no longer associated with a reduction in major vascular event or revascularization (online Appendix F).

Discussion

The broad use of secondary prevention medications in patients after MI has made substantial contributions to reductions in cardiovascular mortality.[18] However, the benefits of these therapies[19] are limited by patient adherence to treatment.[20,21] Although the role of consistent long-term medication use is appreciated by clinicians and policymakers, its actual impact on clinical outcomes and the level of drug use required to derive benefit have required further clarification. We evaluated the impact of adherence by post-MI patients enrolled in a randomized adherence improvement trial and found that patients randomized to full prescription drug coverage who achieved full adherence to their prescribed secondary prevention medications had significantly better event-free survival. However, patients with more moderate levels of adherence had no protective benefit.

Existing studies comparing adherence to outcomes consistently demonstrate that better adherence is associated with better outcomes.[22] The magnitude of that relationship in our findings was qualitatively similar to previous research. However, those studies are largely retrospective and cross-sectional, and virtually none adjust for a patient's propensity to participate in other healthy behaviors that can strongly influence key outcomes.[4] The phenomenon, sometimes referred to as the "healthy user effect," may explain why adherent patients are less likely to have adverse health outcomes both related and unrelated (eg, motor vehicle accidents) to the

Figure 2



Cumulative incidence of major vascular event or revascularization among full coverage patients stratified by level of adherence to each of the 3 study medications in the 6 months after randomization. Full, partial, and nonadherence were defined based on PDC of ≥80%, 60% to 79%, and <60%, respectively.

drug's therapeutic.[6] By embedding our study in a prospective randomized controlled adherence improvement trial where enrollment was triggered by hospital discharge for acute MI, we reduced confounding by design and directly assessed the temporality of adherence and outcomes.

We demonstrate that adherence to statins, β-blockers, and ACEI/ARBs and all combinations of these drugs was associated with better outcomes. As with other chronic diseases, patients discharged from the hospital after MI are often prescribed numerous medications for lifelong use. Because this therapeutic complexity can undermine adherence,[20] determining which drug class(es) to emphasize is often a challenge. Our results suggest that all guideline-recommend therapies[7] are, in fact, necessary, with better adherence to each drug being associated with reduced risk.

The level of consumption that defines adherence has been conventionally set at ≥80%. The empirical basis of this definition is limited and originates from studies conducted decades ago, which found that blood pressure falls significantly only when patients take >80% of their prescribed medication.[23] Our analysis provides validation for this threshold, as we observed that intervention patients who achieved moderate levels of adherence, defined as a PDC of 60% to 79%, have very similar event rates to those among controls, although their adherence level was higher.

Several limitations should be noted. We restricted our analysis to patients who filled at least 1 prescription after hospital discharge as we sought to evaluate the impact of adherence, rather than treatment initiation, on outcomes, and because patients who do not fill medications post-MI may differ systematically from those who do. This decision may influence the generalizability of our results, although it should also enhance their validity. It is reassuring that our analysis included 70% of the overall trial population. We evaluated outcomes from the time of randomization, giving rise to questions of temporality; poor outcomes may have led to poor adherence during the first 6 months after randomization. Our choice was guided by a desire to include all postrandomization events, our expectation that outcome misclassification would bias toward the null, and the enhanced statistical power of more included events. With the exception of ACEI/ARBs, restricting the analysis to outcomes occurring only after the first 6 months yielded similar results. We used administrative claims data to perform our analyses. While we relied on covariates for which there are highly accurate claims-based algorithms, unmeasured confounding remains a potential concern. Similarly, our design could not entirely eliminate bias related to health-seeking behaviors. It is reassuring that when controlling for the use of preventive health services, shown to be more commonly used by adherent individuals,[4] our conclusions remained unchanged. The only way to entirely avoid these biases would be to randomize patients to different levels of adherence; unfortunately,

Table III. Adjusted HR (95% CI) of first major vascular event or revascularization by adherence level achieved among patients randomized to the full prescription coverage study arm, categorized in 3 groups, compared with patients randomized to usual coverage

	Statin	β-Blocker	ACEI/ ARB	Statin + β-blocker	Statin + ACEI/ARB	β-Blocker + ACEI/ARB	All 3 classes
Classifying partial adherence based on a PDC of 60%-79%							
Fully adherent	0.81 (0.68-0.97)	0.75 (0.63-0.90)	0.76 (0.63-0.92)	0.78 (0.63-0.97)	0.66 (0.52-0.84)	0.69 (0.54-0.87)	0.65 (0.49-0.87)
Partially adherent	1.01 (0.80-1.28)	1.01 (0.79-1.29)	0.92 (0.70-1.2)	1.10 (0.75-1.60)	0.79 (0.52-1.2)	0.89 (0.58-1.36)	0.72 (0.38-1.35)
Nonadherent	1.06 (0.88-1.29)	1.03 (0.88-1.22)	1.06 (0.88-1.27)	1.13 (0.90-1.42)	1.08 (0.83-1.39)	1.20 (0.98-1.47)	1.13 (0.87-1.48)
Interaction *P* value	.015	.003	.007	.017	.001	.001	.002
Classifying partial adherence based on a PDC of 40%-79%							
Fully adherent	0.81 (0.68-0.97)	0.75 (0.63-0.90)	0.76 (0.63-0.92)	0.79 (0.64-0.97)	0.66 (0.52-0.84)	0.68 (0.54-0.87)	0.65 (0.49-0.87)
Partially adherent	1.00 (0.83-1.21)	1.06 (0.87-1.28)	0.94 (0.75-1.16)	1.20 (0.94-1.53)	0.89 (0.68-1.17)	1.09 (0.83-1.44)	1.01 (0.71-1.43)
Nonadherent	1.12 (0.88-1.42)	0.98 (0.8-1.21)	1.11 (0.89-1.38)	1.11 (0.83-1.48)	1.15 (0.82-1.60)	1.17 (0.87-1.57)	1.17 (0.83-1.66)
Interaction *P* value	.01	.003	.005	.01	.001	.001	.004

Data adjusted for age and comorbidity score, which includes gender, as well as the cluster and block randomized study design. The *P* values represent the results of a likelihood ratio test for the null hypothesis that the impact of full coverage did not differ by adherence achieved relative to usual care. Full, partial, and nonadherence were defined based on PDC of ≥80%, 60% to 79%, and <60%, respectively.

this approach is unfeasible. Although pharmacy refill claims are widely believed to be a valid method for assessing compliance,[12] this measure does not indicate with certainty which medications are consumed. Any resulting misclassification should bias our findings to the null. This may be particularly relevant for our finding that partial adherence confers no protective effect against adverse cardiovascular events, although it seems doubtful that the magnitude of such bias, should it exist, would be sufficient to explain a complete absence of effect in all of the analyses that we performed. Nevertheless, our analysis was underpowered to exclude small effects of partial adherence on clinical outcomes.

The results of our analysis highlight the importance of full adherence to post-MI secondary prevention, emphasize that all of the guideline-recommended drug classes are associated with substantial benefit, demonstrate that patients must adhere to all of these classes to derive maximal benefit, and provide empirical support for defining full adherence as a PDC of ≥80%. These findings underscore the need for interventions to improve adherence. The MI FREEE trial on which our analysis was based involved reducing financial barriers to evidence-based mediation use, which may be a promising contributor to this complex problem.[8] In addition, interventions that simplify treatment regimens, remind, and motivate patients about the importance of taking their therapies as prescribed may hold substantial promise and should be explored further.[24]

Acknowledgements

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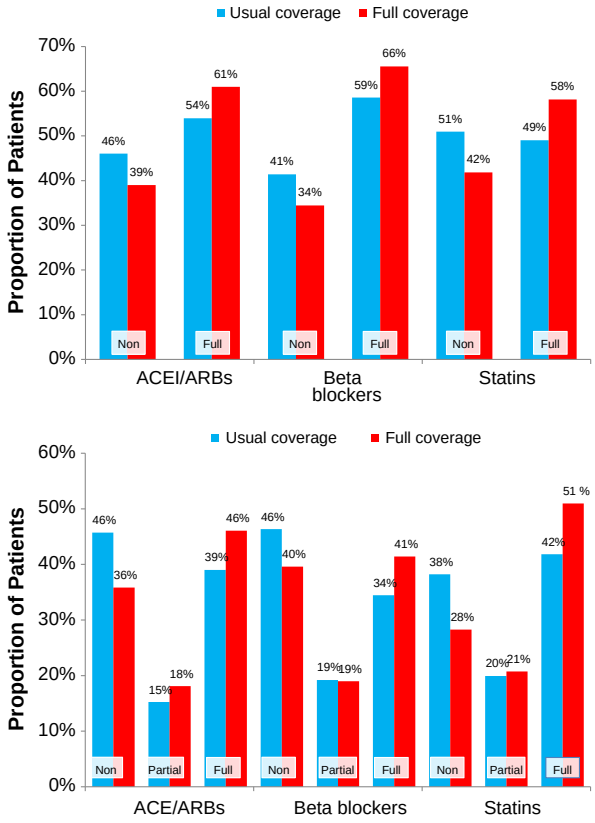
Appendix A

Supplementary Figure 1



Proportion of patients in the full and usual coverage groups according to level of adherence achieved stratified by study medication. The top panel classifies patients as fully or nonadherent based on a proportion of days covered (PDC) of 80%. The bottom panel classifies patients as full, partially, and nonadherent based on PDC of ≥80%, 60% to 79%, and <60%, respectively.

Appendix B

Supplementary Table I. Baseline characteristics of patients in the usual and full coverage arm according to according to study medication and level of adherence achieved. *Partial adherence* was defined as a PDC between 60% and 79%

	Statin				β-Blockers				ACE/ARB			
Characteristics	**Full prescription coverage: adherent (n = 919)**	**Full prescription coverage: partially adherent (n = 374)**	**Full prescription coverage: nonadherent (n = 510)**	**Usual prescription coverage (n = 1881)**	**Full prescription coverage: adherent (n = 726)**	**Full prescription coverage: partially adherent (n = 333)**	**Full prescription coverage: nonadherent (n = 694)**	**Usual prescription coverage (n = 1843)**	**Full prescription coverage: adherent (n = 664)**	**Full prescription coverage: partially adherent (n = 261)**	**Full prescription coverage: nonadherent (n = 517)**	**Usual prescription coverage (n = 1476)**
Age, mean (SD)	54.0 (7.2)	53.6 (7.3)	52.99 (7.9)	53.7 (7.3)	54.1 (7.0)	53.7 (7.4)	52.9 (7.7)	53.9 (7.3)	54.1 (7.2)	53.4 (7.2)	53.3 (7.7)	54.0 (7.2)
Male gender, n (%)	709 (77.1)	287 (76.7)	390 (76.5)	1445 (76.8)	554 (76.3)	262 (78.7)	524 (75.5)	1398 (75.9)	522 (78.6)	203 (77.8)	379 (73.3)	1126 (76.3)
Prehospitalization medication use, n (%)												
ACE/ARB	531 (57.8)	222 (59.4)	263 (51.6)	1045 (55.6)	434 (59.8)	192 (57.7)	372 (53.6)	1049 (56.9)	480 (72.3)	183 (70.1)	309 (59.8)	995 (67.4)
β-Blocker	646 (70.3)	247 (66)	320 (62.7)	1294 (68.8)	548 (75.5)	244 (73.3)	464 (66.9)	1330 (72.2)	460 (69.3)	186 (71.3)	338 (65.4)	1020 (69.1)
Clopidogrel	550 (59.8)	228 (61)	267 (52.4)	1113 (59.2)	436 (60.1)	195 (58.6)	378 (54.5)	1063 (57.7)	386 (58.1)	166 (63.6)	269 (52)	849 (57.5)
Statins	673 (73.2)	42 (11.2)	289 (56.7)	1281 (68.1)	489 (67.4)	224 (67.3)	413 (59.5)	1158 (62.8)	439 (66.1)	174 (66.7)	308 (59.6)	929 (62.9)
Warfarin	61 (6.6)	269 (71.9)	23 (4.5)	99 (5.3)	45 (6.2)	22 (6.6)	42 (6.1)	105 (5.7)	41 (6.2)	13 (5)	35 (6.8)	89 (6.0)
Comorbidities, n (%)												
CHF	226 (24.6)	83 (22.2)	141 (27.6)	506 (26.9)	186 (25.6)	81 (24.3)	190 (27.4)	512 (27.8)	166 (25)	64 (24.5)	164 (31.7)	455 (30.8)
COPD	118 (12.8)	56 (15)	75 (14.7)	287 (15.3)	103 (14.2)	49 (14.7)	93 (13.4)	288 (15.6)	93 (14)	37 (14.2)	79 (15.3)	224 (15.2)
Diabetes	266 (28.9)	133 (35.6)	191 (37.5)	620 (33.0)	211 (29.1)	116 (34.8)	252 (36.3)	622 (33.7)	193 (29.1)	103 (39.5)	203 (39.3)	537 (36.4)
Hypertension	613 (66.7)	281 (75.1)	362 (71)	1344 (71.5)	498 (68.6)	248 (74.5)	500 (72)	1360 (73.8)	471 (70.9)	196 (75.1)	392 (75.8)	110 (74.9)
MI	128 (13.9)	61 (16.3)	78 (15.3)	298 (15.8)	101 (13.9)	51 (15.3)	110 (15.9)	308 (16.7)	76 (11.4)	44 (16.9)	88 (17.0)	249 (16.9)
Stroke	37 (4)	17 (4.5)	28 (5.5)	111 (5.9)	34 (4.7)	18 (5.4)	43 (6.2)	113 (6.1)	30 (4.5)	12 (4.6)	34 (6.6)	107 (7.2)
Procedures on MI hospitalization, n (%)												
Angiography	889 (96.7)	358 (95.7)	484 (94.9)	1798 (95.6)	698 (96.1)	320 (96.1)	656 (94.5)	1745 (94.7)	635 (95.6)	250 (95.8)	485 (93.8)	1396 (94.6)
CABG	186 (20.2)	70 (18.7)	88 (17.3)	332 (17.7)	160 (22)	55 (16.5)	124 (17.9)	321 (17.4)	106 (16)	41 (15.7)	98 (19.0)	235 (15.9)
PCI	667 (72.6)	260 (69.5)	347 (68)	1339 (71.2)	509 (70.1)	236 (70.9)	462 (66.6)	1284 (69.7)	488 (73.5)	192 (73.6)	338 (65.4)	1059 (71.7)
Comorbidity score, mean (SD)*	0.2 (0.34)	0.21 (0.40)	0.20 (0.34)	0.21 (0.37)	0.21 (0.36)	0.18 (0.36)	0.22 (0.38)	0.22 (0.38)	0.19 (0.33)	0.16 (0.29)	0.22 (0.4)	0.22 (0.38)
Baseline copayments, mean (SD)												
ACEI/ARB	$13.36 ($11.26)	$13.62 ($12.52)	$12.95 ($10.33)	$12.90 ($10.19)	$14.27 ($12.32)	$12.69 ($10.04)	$12.74 ($10.81)	$13.02 ($10.01)	$13.95 ($11.55)	$13.3 ($10.29)	$12.78 ($11.91)	$13.18 ($10.25)
β-Blocker	$12.90 ($10.63)	$12.67 ($10.99)	$11.70 ($10.10)	$13.84 ($13.10)	$13.71 ($12.00)	$12.34 ($9.89)	$11.83 ($10.24)	$13.95 ($13.05)	$13.19 ($10.60)	$11.63 ($9.40)	$11.7 ($11.06)	$13.99 ($13.62)
Statin	$26.17 ($20.82)	$27.53 ($22.97)	$25.44 ($21.45)	$24.63 ($20.65)	$26.05 ($20.98)	$27.11 ($24.06)	$25.9 ($21.23)	$24.66 ($20.89)	$26.64 ($21.41)	$25.74 ($23.71)	$25.91 ($21.93)	$25.02 ($20.66)
Achieved adherence during the 6 m after randomization	92.3	70.3	32.5	54.0	92.9	70.3	32.7	49.4	92.9	70.6	30.6	39.6

Abbreviations: *CHF*, Congestive heart failure; *COPD*, chronic obstructive pulmonary disease; *CABG*, coronary artery bypass graft; *PCI*, percutaneous coronary intervention.
*Calculated using the Ontario Acute Myocardial Infarction Mortality Prediction Rule, which predicts 30-day and 1-year mortality. Because all patients in the trial were ≤65 years, weights for age were not included in our calculations.

Appendix C

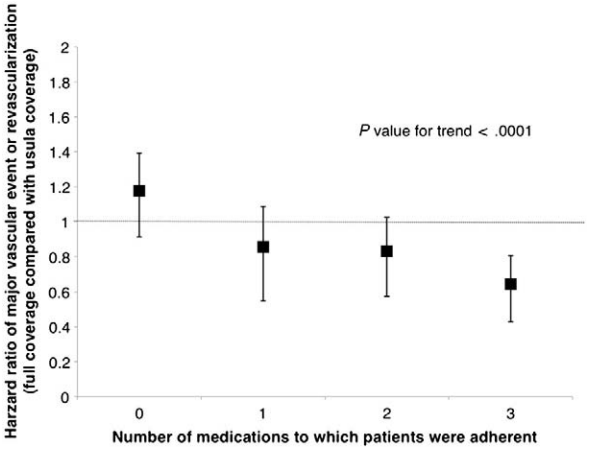
Supplementary Table II. Adjusted hazard ratio (95% CI) of the trial's secondary outcome, first major vascular event, by adherence level achieved in the first 6 months after randomization

	Statin	β-Blocker	ACEI/ARB	Statin + β-blocker	Statin + ACEI/ARB	BETA-blocker + ACEI/ARB	All 3 classes
2-group comparison							
Fully adherent	0.73 (0.59-0.91)	0.70 (0.56-0.87)	0.75 (0.59-0.94)	0.70 (0.54-0.92)	0.62 (0.46-0.83)	0.67 (0.50-0.91)	0.59 (0.41-0.86)
Nonadherent	0.97 (0.80-1.19)	0.98 (0.82-1.18)	1.04 (0.85-1.26)	0.91 (0.76-1.10)	1.03 (0.85-1.25)	1.00 (0.83-1.21)	0.99 (0.81-1.20)
Interaction *P* value	.027	.008	.015	.075	<.001	<.001	<.001
3-group comparison							
Fully adherent	0.73 (0.59-0.91)	0.70 (0.56-0.87)	0.75 (0.59-0.94)	0.74 (0.57-0.97)	0.62 (0.46-0.84)	0.70 (0.52-0.95)	0.61 (0.42-0.88)
Partially adherent	0.90 (0.66-1.21)	1.01 (0.76-1.34)	0.95 (0.69-1.31)	1.08 (0.69-1.7)	0.93 (0.56-1.54)	1.16 (0.73-1.83)	0.99 (0.50-1.95)
Nonadherent	1.03 (0.81-1.30)	0.97 (0.79-1.18)	1.08 (0.86-1.34)	1.17 (0.88-1.55)	1.17 (0.87-1.56)	1.28 (1.00-1.65)	1.26 (0.91-1.75)
Interaction *P* value	0017	.008	.003	.056	<.001	.001	.002

Data are adjusted for age, gender, and comorbidity score as well as the cluster and block randomized study design. The *P* values represent the results of a likelihood ratio test for the null hypothesis that the impact of full coverage for adherent and nonadherent subjects did not differ relative to usual care. Full and nonadherence were defined based on PDC of ≥80% and <80%, respectively for 2-group comparisons; full, partial and nonadherence were defined based on PDC of ≥80%, 60% to 79%, and <60%, respectively for 3-group comparisons.

Appendix D

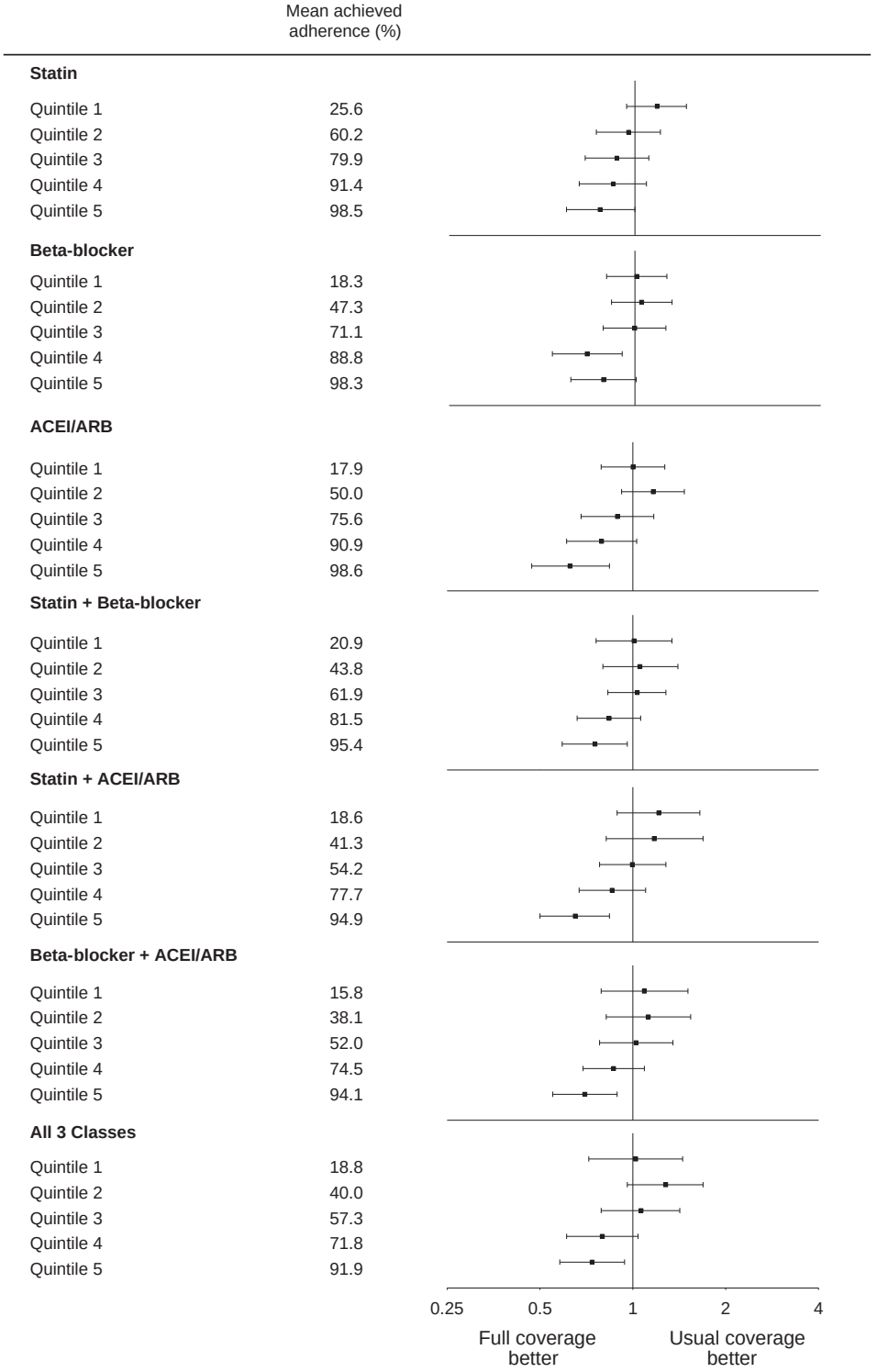
Supplementary Figure 2



Adjusted hazard ratio (95% CI) of first major vascular event or revascularization for patients who filled all 3 study medications by the number of medications to which they were adherent during the 6 months after randomization. Each point represents the hazard ratio in the specific adherence stratum of the full coverage group compared to usual coverage. Data are adjusted for age, gender, and comorbidity score as well as the cluster and block randomized study design. The *P* values represent the results of a test for trend.

Appendix E

Supplementary Figure 3



Adjusted hazard ratio (95% CI) of first major vascular event or revascularization by quintile of adherence level achieved. Each point represents the hazard ratio in the specific adherence quintile of the full coverage group compared to usual coverage. Also shown is the mean level of adherence achieved in that stratum. Data are adjusted for age, gender, and comorbidity score as well as the cluster and block randomized study design.

Appendix F

Supplementary Table III. Adjusted hazard ratio (95% CI) of first major vascular event or revascularization by adherence level achieved excluding outcome events that occurred in the first 6 months after randomization

	Statin	β-Blocker	ACEI/ARB	Statin + β-blocker	Statin + ACEI/ARB	β-Blocker + ACEI/ARB	All 3 classes
Fully adherent	0.62 (0.45-0.85)	0.78 (0.58-1.05)	1.01 (0.76-1.33)	0.62 (0.42-0.92)	0.63 (0.43-0.94)	0.85 (0.58-1.23)	0.64 (0.39-1.05)
Non-adherent	1.29 (1.01-1.65)	1.11 (0.86-1.41)	1.03 (0.79-1.34)	1.09 (0.86-1.38)	1.20 (0.94-1.55)	1.08 (0.84-1.39)	1.11 (0.86-1.44)
Interaction *P* value	<0.001	0.044	0.886	0.007	0.002	0.247	0.027

Data are adjusted for age, gender, and comorbidity score as well as the cluster and block randomized study design. The *P* values represent the results of a likelihood ratio test for the null hypothesis that the impact of full coverage for adherent and nonadherent subjects did not differ relative to usual care. Full and nonadherence were defined based on PDC of ≥80% and <80%, respectively.