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Full Prescription Coverage Versus Usual Prescription Coverage After Coronary Artery Bypass Graft Surgery

Analysis From the Post-Myocardial Infarction Free Rx Event and Economic Evaluation (FREEE) Randomized Trial

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Background—Eliminating out-of-pocket costs for patients after myocardial infarction (MI) improves adherence to preventive therapies and reduces clinical events. Because adherence to medical therapy is low among patients treated with coronary artery bypass graft surgery (CABG), we evaluated the impact of providing full prescription coverage to this patient subgroup.

Methods and Results—The MI Free Rx Event and Economic Evaluation (FREEE) trial randomly assigned 5855 patients with MI to full prescription coverage or usual formulary coverage for all statins, β -blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers. We assessed the impact of full prescription coverage on adherence, clinical outcomes, and healthcare costs using adjusted models among the 1052 patients who underwent CABG at the index hospitalization and 4803 who did not. CABG patients were older and had more comorbid illness ($P<0.01$). After MI, CABG patients were significantly more likely to receive β -blockers and statins but were less likely to receive angiotensin-converting enzyme inhibitor/angiotensin receptor blocker therapy ($P<0.01$). Receiving full drug coverage increased rates of adherence to all preventative medications after CABG (all $P<0.05$). Full coverage was also associated with nonsignificant reductions in the rate of major vascular events or revascularization for patients treated with CABG (hazard ratio, 0.91; 95% confidence interval, 0.66–1.25) or without CABG (hazard ratio, 0.93; 95% confidence interval, 0.82–1.06), with no interaction noted ($P_{\text{int}}=\text{NS}$). After CABG, full prescription coverage significantly reduced patient out-of-pocket spending for drugs ($P=0.001$) without increasing overall health expenditures ($P=\text{NS}$).

Conclusions—Eliminating drug copayments after MI provides consistent benefits to patients treated with or without CABG, leading to increased medication adherence, trends toward improved clinical outcomes, and reduced patient out-of-pocket expenses. (*Circulation*. 2013;128[suppl 1]:S219-S225.)

Key Words: coronary artery bypass graft surgery ■ prevention ■ prescription coverage

Coronary artery bypass graft surgery (CABG) is an effective treatment for patients with severe coronary artery disease, reducing adverse events and improving health-related quality of life.^{1,2} Compared with patients with coronary artery disease treated with nonsurgical therapies, CABG patients tend to have more extensive disease and a higher incidence of diabetes mellitus and other comorbid conditions.^{1,3} Secondary preventative medications after CABG are, therefore, critical to the long-term care of this at-risk population.⁴ Substantial clinical improvements have been demonstrated with their administration, including better graft patency and event-free survival.⁴⁻⁷

Despite their known benefits, adherence to evidence-based medications after CABG remains quite poor.^{3,8,9} With important consequences, previous studies have reported that low adherence to secondary preventative therapy post-CABG significantly increases the risks of myocardial infarction (MI) and death after surgery.^{9,10} Although recent initiatives have been directed toward increasing prescription rates at CABG discharge,¹¹ limited efforts have been focused on improving long-term adherence to prevention medications for these high-risk patients. Reducing or eliminating prescription copayments has been advocated as a method for improving adherence and reducing health spending in some patient groups.^{12,13}

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Referred to in the recently passed Patient Protection and Affordable Care Act, this approach (sometimes referred to as value-based insurance design) may have particular merit after CABG, given the low reported adherence rates in this population and the high volumes of medications typically received postoperatively.^{3,8,9}

Recently published, the Post-Myocardial Infarction Free Rx and Economic Evaluation (MI FREEE) trial assessed the impact of eliminating patient copayments for preventive medications after hospitalization for MI.¹⁴ In this secondary analysis of the MI FREEE trial, we sought to evaluate the relative effectiveness of providing full prescription coverage, compared with usual prescription coverage, for patients treated with or without CABG after recent MI.

Methods

Study Design

The MI FREEE trial was an investigator-initiated, cluster-randomized, controlled policy study. Details of the study design have previously been described.^{14,15} In brief, MI FREEE prospectively evaluated the impact of eliminating cost-sharing (copayments, coinsurance, or contribution to deductibles) for secondary preventive medications in patients discharged from hospital after MI. The study randomized 5855 patients to either full prescription coverage (n=2845) or usual prescription coverage (n=3010) for any brand name or generic statin, β -blocker, angiotensin-converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB).¹⁵

Patients were assigned to full or usual coverage by cluster randomizing their plan sponsor, ensuring that all eligible employees of a given plan sponsor received the same coverage after randomization. After the initiation of the trial, all patients of a plan sponsor who were

subsequently discharged from hospital after MI were included in the study and assigned to the same group. Treatment choices were at the discretion of patients and their treating physician. The study was approved by the institutional review board at Brigham and Women's Hospital and was monitored by an independent data and safety monitoring committee.

The primary results of MI FREEE demonstrated that the elimination of copayments for secondary preventive therapies increased medication adherence and reduced patients' out-of-pocket spending for drugs, without increasing overall healthcare costs. Full prescription coverage led to a nonsignificant reduction in the study's primary outcome (major vascular event or coronary revascularization, $P=0.21$) and significantly reduced the prespecified secondary outcomes of total major vascular events or revascularization ($P=0.03$) and the incidence of major vascular event, excluding revascularization ($P=0.03$).¹⁴

Outcomes

Medication adherence was calculated based on the number of days a patient had a supply of each medication class available divided by the number of days of eligibility for that medication. Full adherence was defined as medication possession of $\geq 80\%$ throughout follow-up. The primary clinical outcome for the trial was a composite of the first readmission for a major vascular event (fatal or nonfatal MI, unstable angina, stroke, or congestive heart failure) or coronary revascularization (repeat CABG or percutaneous coronary intervention). Prespecified secondary clinical outcomes included the rate of total major vascular events or revascularization (allowing for the occurrence of >1 event per patient) and time to the first major vascular event, excluding revascularization. Among patients who did not experience an event, censoring occurred at the end of the study period on November 30, 2010, or on the date of loss of insurance eligibility, whichever came first. Healthcare spending by patients and insurers was determined using the allowed amounts appearing in the insurers' claims data for prescription medications and nondrug medical services (ie, physician visits, emergency room

Table 1. Baseline Characteristics of Participants

Characteristic	CABG (n=1052)		No CABG (n=4803)	
	Full Coverage (n=508)	Usual Coverage (n=544)	Full Coverage (n=2337)	Usual Coverage (n=2466)
Age, mean (SD)	55.3 (6.7)	55.2 (6.8)	53.2 (7.7)	53.3 (7.8)
Male sex, n (%)	417 (82.1)	450 (82.7)	1735 (74.27)	1798 (72.9)
Prehospitalization medication use, n (%)				
ACEI/ARB	232 (45.7)	236 (43.4)	1309 (56.0)	1352 (54.8)
β -Blocker	319 (62.8)	331 (60.8)	1522 (65.1)	1634 (66.3)
Clopidogrel	160 (31.5)	145 (26.7)	1381 (59.1)	1492 (60.5)
Statin	303 (59.6)	330 (60.7)	1432 (61.3)	1498 (60.7)
Warfarin	34 (6.7)	28 (5.1)	146 (6.2)	150 (6.1)
Comorbidities, n (%) ¹				
Congestive heart failure	173 (34.1)	236 (43.4)*	596 (25.5)	640 (26.0)
COPD	105 (20.7)	121 (22.2)	341 (14.6)	374 (15.2)
Diabetes mellitus	222 (43.7)	243 (44.7)	754 (32.3)	804 (32.6)
Hypertension	398 (78.3)	424 (77.9)	1629 (69.7)	1754 (71.1)
Prior MI	117 (23)	124 (22.8)	328 (14.0)	399 (16.2)†
Stroke	46 (9.1)	40 (7.4)	118 (5.0)	161 (6.5)†
Comorbidity score, mean (SD)‡	0.38 (0.53)	0.41 (0.52)	0.18 (0.35)	0.19 (0.35)

ACEI indicates angiotensin-converting-enzyme inhibitors; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft surgery; COPD, chronic obstructive pulmonary disease; and MI, myocardial infarction.

* $P<0.05$ compared with full coverage in CABG group.

† $P<0.05$ compared with full coverage in non-CABG group.

‡Calculated using the Ontario Acute Myocardial Infarction Mortality Prediction Rule that predicts 30-d and 1-y mortality.^{14,16} Each patient's score is calculated on the basis of published weights according to sex and the characteristics observed on the index hospitalization: shock, diabetes mellitus with complications, congestive heart failure, cancer, cerebrovascular disease, pulmonary edema, acute renal failure, chronic renal failure, and cardiac dysrhythmias.

admissions, hospitalizations, and outpatient procedures), as well as the combination of these 2 factors. Overall insurer expenses were insurer costs incurred for pharmacy expenses, nondrug medical expenses, and surgical-related expenses.

Statistical Analysis

Patient characteristics were compared using ANOVA or Wilcoxon rank-sum tests for continuous variables and χ^2 tests for categorical variables. Generalized estimating equations were used to adjust for the cluster- and block-randomized design. A logit link function with binary distributed errors was used for full adherence. Health spending was evaluated with the use of a log-link function with variances proportional to the mean. Clinical event rates are reported as the rate per 100 person-years, with comparisons between study arms performed with Cox proportional hazard models to estimate hazard ratios (HR) and 95% confidence intervals (CI). Formal interaction terms in the models were used to test for differential outcomes by study assignment between treatment groups (CABG versus no CABG). In the models, covariate adjustment was performed for age, sex, and differences in rates of coexisting illnesses between the study groups (decided a priori),¹⁶ and all outcomes presented herein are multivariate adjusted. All analyses were performed using SAS 9.2 and were based on the intention-to-treat principle. $P < 0.05$ were considered significant, with no adjustment for multiple testing. The Cox proportional hazard model assumption was assessed and confirmed to be valid.

All authors had full access to the study data and take full responsibility for the integrity of the data and the accuracy of the data analysis. All authors have read and agree to the article as written.

Results

Patient Cohort

Of the 5855 patients randomized in the trial, 1052 (18.0%) underwent CABG during their index hospitalization. Although the baseline characteristics of the patients were well balanced

between the 2 treatment arms in the trial, they differed between patients who did or did not undergo CABG (Table 1). Most notably, CABG patients were significantly older and had a greater incidence of comorbid illness compared with patients who did not undergo CABG.

CABG Versus No-CABG Comparisons

Before their index hospitalization, CABG patients were significantly less likely to have been treated with β -blocker therapy, ACEI/ARB medication, or clopidogrel ($P < 0.05$) compared with patients who did not undergo CABG. However, at the time of discharge from hospital, CABG-treated patients were significantly more likely to fill prescriptions for a β -blocker and statin but less likely to fill a prescription for clopidogrel or ACEI/ARB therapy ($P < 0.05$). After randomization, patients who underwent CABG had higher rates of full adherence to β -blockers (odds ratio [OR], 1.21; 95% CI, 1.02–1.44; $P = 0.03$) but lower rates of full adherence to ACEI/ARB therapy (OR, 0.82; 95% CI, 0.69–0.97; $P = 0.02$) compared with those who did not undergo CABG. During the time period of the trial, CABG patients had lower clinical event rates, including lower rates of the primary study outcome (HR, 0.72; 95% CI, 0.61–0.86; $P = 0.0002$) and lower rates of revascularization (HR, 0.50; 95% CI, 0.39–0.66; $P < 0.0001$).

Medication Adherence: Full Coverage Versus Usual Coverage

Providing full coverage increased adherence both for patients undergoing CABG and those not undergoing CABG (Table I in the online-only Data Supplement). Among patients treated with

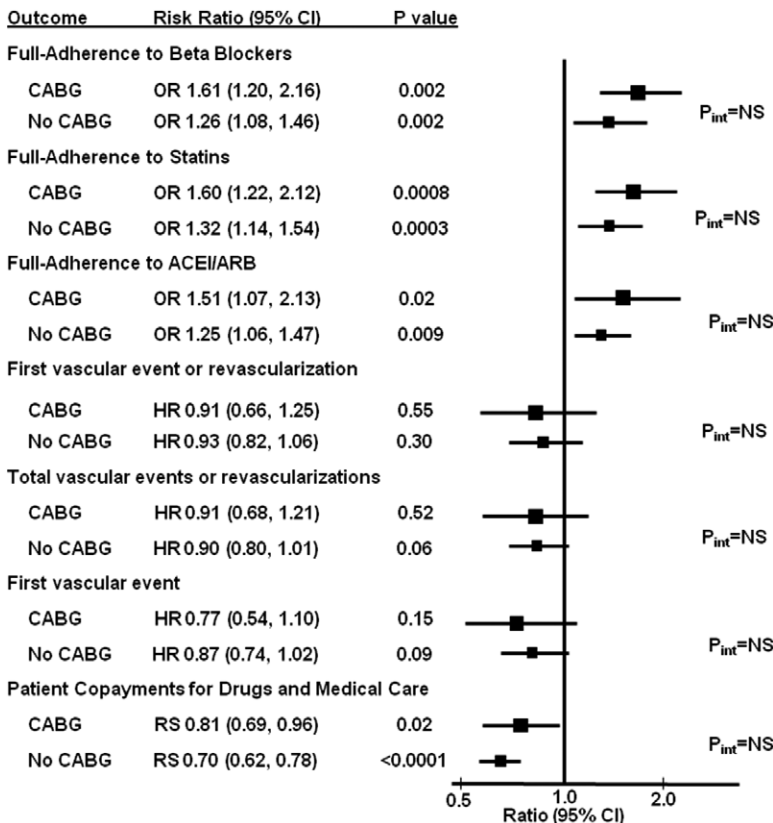


Figure 1. Study outcomes for patients who did and did not undergo coronary artery bypass graft surgery (CABG) in the trial. For the adherence outcomes, an odds ratio >1.0 represents an increase in medication adherence. HR indicates hazard ratio; NS, nonsignificant; OR, odds ratio; and RS, relative spending.

CABG, full prescription coverage increased the proportion of patients fully adherent to β -blockers (OR, 1.61; 95% CI, 1.20–2.16; $P=0.002$), ACEI/ARB therapy (OR, 1.51; 95% CI, 1.07–2.13; $P=0.02$), statins (OR, 1.60; 95% CI, 1.22–2.12; $P=0.0008$), and all 3 medications (OR, 1.67; 95% CI, 1.04–2.67; $P=0.03$). Full prescription coverage also led to increases in adherence among those not undergoing CABG; however, the relative effect of the intervention seemed greater for each of the drug classes among those treated with CABG (Table I in the online-only Data Supplement). There were no significant interactions (Figure 1) among randomized study assignment, treatment strategy (CABG versus no CABG), and adherence to medications ($P_{\text{int}}=NS$).

Clinical Outcomes: Full Coverage Versus Usual Coverage

Providing full coverage for secondary preventive therapy had similar effects on clinical outcomes for both CABG and non-CABG patients (Figure 2). Among subjects undergoing CABG, full coverage led to a nonsignificant 9.1% reduction in the HR for the

primary study outcome (HR, 0.91; 95% CI, 0.66, 1.25; $P=0.55$). Similar findings were noted among patients who did not undergo CABG (Table 2). There was no significant interaction (Figure 1) among treatment strategy (CABG versus no CABG), study assignment, and the rate of the primary study outcome ($P_{\text{int}}=NS$).

Similar nonsignificant risk reductions associated with full prescription coverage were noted among CABG and non-CABG patients for the prespecified secondary clinical outcomes, including total major vascular events or revascularization, and first major vascular event, excluding revascularization (Table 2). There were no significant interactions (Figure 1) among treatment strategy (CABG versus no CABG), study assignment, and the prespecified secondary clinical outcomes ($P_{\text{int}}=NS$).

Health Spending: Full Coverage Versus Usual Coverage

For patients who underwent CABG, full coverage led to a 27% relative reduction in patient out-of-pocket payments for prescriptions (relative spending, 0.73; 95% CI, 0.61–0.89;

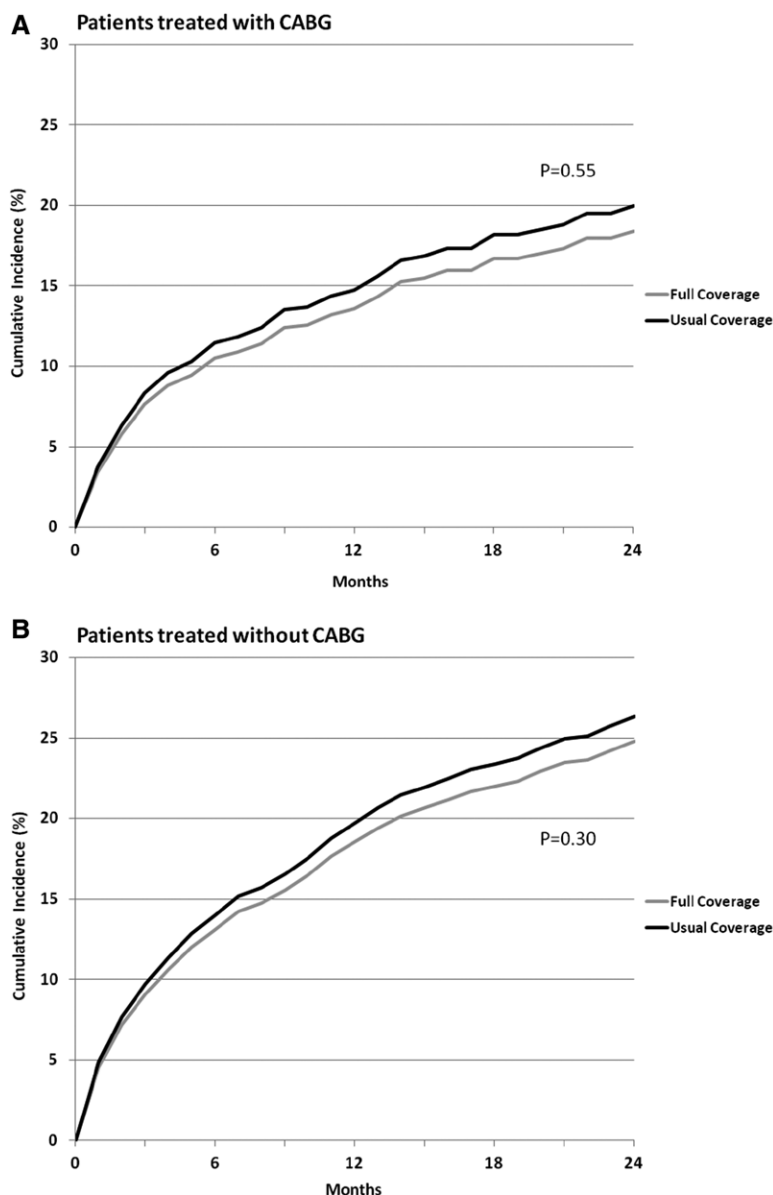


Figure 2. Cumulative incidence of the primary outcome for patients treated with coronary artery bypass graft surgery (CABG; **A**) and without CABG (**B**). Primary outcome defined as fatal or nonfatal vascular event or coronary revascularization. P values determined from the adjusted Cox proportional hazard models.

Table 2. Clinical Outcome Rates

	Full Prescription Coverage		Usual Prescription Coverage		Hazard Ratio* (95% Confidence Interval)	P Value
	n	Rate/100 person-years	n	Rate/100 Person-years		
CABG patients (n=1052)						
Fatal or nonfatal vascular event or revascularization						
First event	69	12.7	77	14.5	0.91 (0.66–1.25)	0.55
Total events	89	16.1	99	18.2	0.91 (0.68–1.21)	0.52
First fatal or nonfatal vascular event	49	8.7	64	11.7	0.77 (0.54–1.10)	0.15
Myocardial infarction or unstable angina	24	4.1	26	4.4	0.93 (0.53–1.06)	0.78
Stroke	8	1.3	16	2.7	0.47 (0.21–1.06)	0.07
Congestive heart failure	30	5.1	40	7.0	0.78 (0.49–1.23)	0.28
Revascularization	35	6.0	25	4.3	1.43 (0.88–2.34)	0.15
Non-CABG patients (n=4803)						
Fatal or nonfatal vascular event or revascularization						
First event	424	18.7	485	19.7	0.93 (0.82–1.06)	0.30
Total events	537	22.9	642	24.9	0.90 (0.80–1.01)	0.06
First fatal or nonfatal vascular event	280	11.6	341	13.0	0.87 (0.74–1.02)	0.09
Myocardial infarction or unstable angina	163	6.5	210	7.6	0.84 (0.69–1.02)	0.08
Stroke	52	2.0	76	2.6	0.74 (0.52–1.06)	0.10
Congestive heart failure	120	4.7	142	5.0	0.90 (0.69–1.17)	0.41
Revascularization	258	10.7	273	10.2	1.03 (0.88–1.20)	0.73

CABG indicates coronary artery bypass graft surgery.

*Hazard ratios have been adjusted for the cluster- and block-randomized design.

$P=0.001$) and 19% reduction in overall healthcare expenses incurred by patients (relative spending, 0.81, 95% CI, 0.69–0.96; $P=0.02$) compared with usual formulary coverage. In contrast, there was a significant increase in pharmacy spending by insurers (relative spending, 1.34; 95% CI, 1.05–1.71, $P=0.02$). However, there was no increase in insurer spending for nondrug medical services (relative spending, 0.70; 95% CI, 0.29–1.69; $P=0.42$) or insurer expenses overall (relative spending, 0.86; 95% CI, 0.39–1.90; $P=0.70$). Similar findings were noted among patients who did not undergo CABG (Table II in the online-only Data Supplement). There were no significant interactions (Figure 1) among treatment strategy (CABG versus no CABG), study assignment, and drug expenses or overall costs.

Discussion

The administration of secondary preventive medications, including statins, β -blockers, and ACEI/ARB therapy, is the mainstay of treatment for patients recovering from CABG.⁴ After surgery, these agents lower rates of mortality and adverse cardiovascular events.^{4–7} Notwithstanding these benefits, adherence to preventative medical therapy after CABG remains low.^{3,8,9} Poor adherence to evidence-based medications leads to a rise in healthcare costs¹⁷ and significantly increases the risk of MI and death after CABG.^{9,10} Improving

long-term adherence to secondary prevention therapies is, therefore, of critical importance for this high-risk population.

In this post hoc analysis of the MI FREEE trial, we sought to evaluate the impact of eliminating out-of-pocket expenses on adherence to secondary preventative therapies after CABG. Compared with usual coverage, full coverage significantly increased rates of adherence to all secondary preventative medications (all $P<0.05$) and was associated with a non-significant reduction in the rate of major vascular events or coronary revascularization. Furthermore, full prescription coverage after surgery significantly reduced patient out-of-pocket spending for drugs ($P=0.001$) without increasing overall health expenditures ($P=NS$).

Previously advocated for other populations,^{12,13} this study is the first to date to demonstrate the benefits of eliminating prescription copayments after CABG. With results comparable with the overall trial findings,¹⁴ the current data suggest that full prescription coverage improves medication adherence rates after MI, irrespective of whether patients are treated with CABG or nonsurgical therapies. Of interest, we noted less use and lower adherence rates to ACEI/ARB therapy for CABG patients enrolled in MI FREEE. We believe this finding may relate to the mixed results published in the literature regarding ACEI/ARB medications after CABG and the frequent side effects associated with their use.^{7,18}

Overall, less than half of the patients in the current study were fully adherent to prescribed therapies, regardless of treatment strategy and study assignment. Given the invasive nature of surgical revascularization, we had previously assumed that CABG patients would exhibit the highest level of health-conscious behavior after hospital discharge, leading to favorable medication adherence during the course of follow-up.³ However, in previous work evaluating adherence to statin therapy in patients with active coronary artery disease, we noted the opposite. Patients with coronary artery disease who were treated with CABG had lower adherence rates compared with those treated with medical therapy, possibly as a result of less symptom recurrence or a lower perceived need for medical therapy after coronary revascularization.³ In the current study, no significant interaction was noted between medication adherence rates and treatment with CABG, suggesting that patients with MI recovering from surgery are no more adherent with secondary prevention than those treated with nonsurgical therapies.

Adherence to medical therapy is clearly a complex process, affected by a variety of factors, including perceptions and understanding of disease burden.¹⁹ Several methods for improving long-term medication adherence have been promoted in the literature, including early physician follow-up, as well as enrollment in cardiac rehabilitation and patient education programs.^{19–22} Of note, patients with MI who undergo outpatient physician follow-up within 1 month after hospital discharge have significantly higher rates of medication use 6 months later.²³ Modest improvements in adherence were noted with the elimination of medication copayments in the MI FREEE trial¹⁴ and in the current surgical subgroup analysis. Nevertheless, despite the positive findings in the trial, overall adherence remained low. Therefore, interventions that focus on other contributing factors will be necessary to further improve patient compliance to prescribed therapies, including patient knowledge and attitude toward medications, improving medication access, and reducing prescribed regimen complexity.^{24,25}

Our results should be interpreted in the context of several limitations. For the purpose of this study, we relied on administrative claims to identify patients and evaluate outcomes. Although the use of these data has previously been validated for the purpose of outcomes research, no adjudication process was incorporated into the trial. Furthermore, the administrative data we used did not contain detailed clinical information, such as cholesterol levels or symptom recurrence. Because patients enrolled in the study were relatively young and all had medical insurance, our results may not necessarily be generalizable to all patients with MI or those who receive health benefits through other means. The primary outcome was not significantly reduced in the current study, which is likely a reflection of the smaller size of the CABG subgroup compared with the overall study cohort, as well as the lower clinical event rate after CABG revascularization. Post hoc power calculations revealed that our analysis had 22% power to detect a significant difference in the primary outcome, although our CABG subgroup was adequately powered to exclude the larger effects (20% reduction in primary outcome) that we had anticipated in our a priori assumptions. Finally, pill

counts to confirm medication ingestion were not performed in MI FREEE, but we have no reason to believe that patients who filled their prescriptions subsequently discarded them. Adherence to secondary preventative therapy was estimated using pharmacy claims data that have demonstrated a high degree of concordance with other measures of adherence, including pill counts, self-report, medication monitoring devices, and drug level.¹⁹

In conclusion, in this surgical post hoc analysis of the MI FREEE randomized trial, the elimination of prescription copayments after CABG significantly increased adherence to secondary preventative therapy and reduced patient out-of-pocket costs, without changing overall health spending. Full prescription coverage was associated with trends toward improved clinical outcomes both for patients treated with and without CABG, suggesting that this strategy may help improve the quality of care for all patients recovering from MI.

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Disclosures

Dr Choudhry received consulting fees from Mercer Health and Benefits and grant support from CVS Caremark; Dr Glynn received consulting and lecture fees from Merck and grant support from AstraZeneca and Novartis; Dr Reisman is an employee of Aetna and has an equity interest in Aetna; Dr Brennan is an employee of CVS Caremark, has an equity interest in CVS Caremark, and receives board membership fees from CVS Caremark; and Dr Shrank received consulting fees from United Healthcare and grant support from CVS Caremark and Express Scripts. The other authors report no conflicts.

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