

# Rationale and design of the Post-MI FREEE trial: A randomized evaluation of first-dollar drug coverage for post-myocardial infarction secondary preventive therapies

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**Background** Medication nonadherence is a major public health problem, especially for patients with coronary artery disease. The cost of prescription drugs is a central reason for nonadherence, even for patients with drug insurance. Removing patient out-of-pocket drug costs may increase adherence, improve clinical outcomes, and even reduce overall health costs for high-risk patients. The existing data are inadequate to assess whether this strategy is effective.

**Trial Design** The Post-Myocardial Infarction Free Rx and Economic Evaluation (Post-MI FREEE) trial aims to evaluate the effect of providing full prescription drug coverage (ie, no copays, coinsurance, or deductibles) for statins,  $\beta$ -blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers to patients after being recently discharged from the hospital. Potentially eligible patients will be those individuals who receive their health and pharmacy benefits through Aetna, Inc. Patients enrolled in a Health Savings Account plan, who are  $\geq 65$  years of age, whose plan sponsor (ie, the employer, union, government, or association that sponsors the particular benefits package) has opted out of participating in the study, and who do not receive both medical services and pharmacy coverage through Aetna will be excluded. The plan sponsor of each eligible patient will be block randomized to either full drug coverage or current levels of pharmacy benefit, and all subsequently eligible patients of that same plan sponsor will be assigned to the same benefits group. The primary outcome of the trial is a composite clinical outcome of readmission for acute MI, unstable angina, stroke, congestive heart failure, revascularization, or in-hospital cardiovascular death. Secondary outcomes include medication adherence and health care costs. All patients will be followed up for a minimum of 1 year.

**Conclusion** The Post-MI FREEE trial will be the first randomized study to evaluate the impact of reducing cost-sharing for essential cardiac medications in high-risk patients on clinical and economic outcomes. (*Am Heart J* 2008;156:31-6.)

Coronary heart disease (CHD) remains the leading cause of death in the United States and other developed countries<sup>1</sup>; >1 million Americans have acute myocardial infarctions (MI) every year.<sup>2</sup> In 2008, CHD is estimated to account for >\$156 billion in direct and indirect health care costs.<sup>2</sup> Large-scale randomized trials have identified

medications that are highly effective at reducing the risk of CHD-related events.<sup>3-8</sup> Accordingly, practice guidelines recommend that all patients with acute MI receive treatment with a  $\beta$ -blocker, a statin, an angiotensin-converting enzyme (ACE) inhibitor, or an angiotensin II receptor blocker (ARB), and aspirin,<sup>9,10</sup> unless a contraindication exists.

Although rates of prescribing these medications at hospital discharge after acute MI have improved substantially,<sup>11</sup> subsequent long-term adherence to therapy continues to be poor.<sup>12</sup> Only 46% of patients with CHD report consistent  $\beta$ -blocker use within 1 year of an acute MI,<sup>13</sup> and only 50% of patients are adherent with their prescribed statin.<sup>14</sup> Less than 20% of acute MI patients use all 4 of the recommended agents.<sup>13,15</sup> Not surprisingly, nonadherent patients are at substantially higher risk of death.<sup>16,17</sup> Patients with MI who discontinue all of their medications are >3 times as likely to die than patients who remain adherent.<sup>16</sup> Therefore, the burden

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of CHD may be reduced further by improving medication adherence.

### Contribution of cost to the underuse of prescription medications

Of the many factors that contribute to poor adherence, the cost borne by patients is central.<sup>18-21</sup> In the past year, one third of Americans said that they or a family member has had difficulty paying for medications,<sup>22</sup> and a similar proportion have not filled a prescription or have reduced a prescribed dosage because of high out-of-pocket costs.<sup>23</sup> Even among individuals with insurance, medication utilization varies by the comprehensiveness of coverage.<sup>24,25</sup> For example, hypertensive Medicare beneficiaries covered by plans with higher cost-sharing and no catastrophic coverage were less likely to use medication than patients with more generous coverage.<sup>26</sup> The amount of cost-sharing faced by younger managed care enrollees also influences their use of essential medications; a doubling of copayments is estimated to reduce statin utilization by 34%.<sup>20</sup>

Eliminating patient cost-sharing may improve both adherence and clinical outcomes. Moreover, because the cost of preventable CHD events far exceeds medication costs, providing more comprehensive drug benefits may simultaneously save lives and money.<sup>27</sup> In 2 recent cost-effectiveness analyses, we predicted that the small changes in adherence that will result from providing full prescription drug coverage (ie, without patient cost-sharing) for statins, aspirin, ACE inhibitors, and  $\beta$ -blockers to patients after acute MI will reduce mortality and rates of nonfatal reinfarction, stroke, and congestive heart failure readmission and will save substantial amounts of money as compared with usual levels of prescription drug coverage.<sup>28,29</sup>

### Limitations of the existing data and need for a randomized policy trial

No studies have adequately evaluated the impact of improving drug coverage on medication use and health outcomes for any disease. Cross-sectional studies evaluating the effects of coverage on medication adherence are inherently subject to bias. Individuals enrolled in plans with generous pharmacy benefits differ in important ways from individuals with less generous benefits, and the ability of statistical models to adjust adequately for these differences is limited. Longitudinal studies evaluating the changes in outcomes from restrictions in health benefits are not subject to selection bias, but expanding pharmacy benefits may not merely be the reciprocal of restricting coverage.<sup>30</sup> The studies that have evaluated selective copay reductions have been uncontrolled or inadequately powered to measure clinically important outcomes.<sup>31,32</sup> Even the RAND Health Insurance Experi-

ment, which is the only truly randomized intervention of different levels of patient cost-sharing for prescription drugs to date, did not measure adherence and had a relatively small sample size.<sup>33</sup>

One way to adequately evaluate the impact of expanding coverage for essential medications of proven efficacy is to conduct a prospective trial in which patients are randomized to receive full (first-dollar) or usual drug coverage. Patients who have recently been discharged from hospital after acute MI are an ideal population in which to study this question. These individuals have high cardiovascular event rates, and secondary prevention medications for acute MI are clearly efficacious, are substantially underused in part because of cost, and are inexpensive relative to the cost of the events that they are intended to prevent.

### Overall study design

The Post-Myocardial Infarction Free Rx and Economic Evaluation (Post-MI FREEE) trial will assess the clinical and economic impact of first-dollar coverage for post-MI medications. The trial will enroll patients discharged from hospital after acute MI. Randomization will occur at the level of the plan sponsor (ie, the employer, union, government, or association that sponsors the particular benefits package) so that all eligible employees of a given plan sponsor will receive the same coverage plan after randomization. This design strategy prevents the contamination of patients within a given plan sponsor and avoids the equity problems that may arise should 1 employee of a given plan sponsor be randomized to receive full drug coverage whereas another gets the usual level of pharmacy benefit.

### Subjects

Eligible subjects will be patients discharged alive from hospital after MI who received health services and prescription drug benefits through Aetna, Inc. Aetna is one of the largest health insurers in the United States providing medical coverage to 15.7 million beneficiaries and pharmacy benefits to 10.5 million beneficiaries, through numerous small, midsized, and large multisite national plan sponsors.

Patients will be identified on the basis of hospital claims submitted to Aetna with a discharge diagnosis of *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* 410.xx (except 410.x2) as the principal or secondary diagnosis and a length of stay  $\geq 3$  and  $\leq 180$  days. This algorithm has a positive predictive value, sensitivity, and specificity of 96.9%, 96%, and 99%, respectively, for the diagnosis of acute MI.<sup>34</sup> Exclusion criteria include the following: (1) enrollment in a Health Savings Account plan, as patients in these plans already receive first-dollar coverage for the study

medications; (2) age  $\geq 65$  years at the time of hospital discharge, as Medicare is the primary health insurer for such patients; (3) plan sponsor has opted out of participating in the study; and (4) patients who receive only medical services or pharmacy coverage but not both through Aetna.

Patients will be recruited over a 1.5-year period and followed up for a minimum of 1 year.

## Intervention

Patients will be randomized to first-dollar drug coverage or usual pharmacy benefits based on the group to which their plan sponsor is randomized (see below for details). Patients whose sponsor is randomized to first-dollar coverage will have their pharmacy benefits changed so that they have no out-of-pocket costs for any brand-name or generic  $\beta$ -blocker, angiotensin-converting enzyme inhibitor (ACEI), angiotensin II receptor blocker (ARB), and statin for every subsequent prescription after randomization. All copays and coinsurance will be waived at the point of care (ie, pharmacy) as will any contribution that the cost of these drugs makes to a patient's deductible. We anticipate that 80% of randomized patients will be contacted within 2 months of hospital discharge; thus, first-dollar coverage will begin before patients fill their second prescription for most individuals randomized to this group and will continue for the duration of the study. Patients randomized to usual coverage will have no change in their existing benefits.

## Randomization and patient recruitment

All plan sponsors will be contacted by mail before the study starts and given the opportunity to opt-out of study participation. Because plan sponsors may differ from each other in important ways, simple cluster randomization may result in plan sponsors with larger numbers of patients or those with particular prognostic factors being unequally distributed between the 2 randomized groups. Therefore, we will categorize plan sponsors into 1 of 6 blocks based on characteristics that were found to predict cluster size or health status in preliminary analyses: (1) whether the plan sponsor is nationally based (defined as being a Fortune 500 company with  $>3,000$  employees or a governmental plan sponsor) and (2) the generosity of the existing levels of prescription-drug insurance coverage that each of the plan sponsor offers (3 levels). Insurance generosity was calculated by averaging the copayments for all statins, ACEI/ARBs, and  $\beta$ -blockers filled by patients of eligible plan sponsors between January 1 and June 30, 2007.

When a newly eligible post-MI patient is identified, an investigator blinded to the identity of the plan sponsor will determine whether that patient's plan sponsor has

**Table I.** Outcomes under study and their measurements

Outcome	Description
Primary	First occurrence of fatal or nonfatal acute MI, unstable angina, stroke, congestive heart failure, or revascularization (coronary bypass, stent insertion, or angioplasty)
Secondary	First occurrence of fatal or nonfatal acute MI, unstable angina, stroke, or congestive heart failure
	First occurrence of fatal or nonfatal acute MI, unstable angina, stroke, congestive heart failure or out-of-hospital cardiac death
	Rate of fatal or nonfatal acute MI, unstable angina, stroke, or congestive heart failure, or revascularization (coronary bypass, stent insertion, or angioplasty)
	Medication adherence (ie, the mean medication possession ratio and the proportion of patients fully adherent to each and all 3 of the study medications)*
	Health care utilization (ie, use of physician visits, emergency department admissions, hospitalizations or other resources)*
	Total pharmacy and health care costs during follow-up*

\*See text for more details.

previously been randomized, and if not, the plan sponsor's block assignment. Plan sponsors will be randomly assigned in a 1:1 ratio to intervention or control using a random number generator. All subsequent patients of that plan sponsor will be assigned to the same group.

Patients in both groups will be contacted by mail and telephone by Aetna and will be told, very briefly, of the importance of taking their medications as prescribed. In addition, patients in the intervention group will be informed of their benefit change. Medication choices and treatment decisions will be left entirely to the discretion of patients' treating physicians. Although patients in the intervention group will be given the option to opt-out of receiving their medications without cost-sharing, no specific patient-level informed consent will be sought because all patients, at a minimum, will receive their usual level of prescription drug coverage. This study was approved by the institutional review board of Brigham and Women's Hospital and is registered with clinicaltrials.gov (NCT00566774).

## Outcomes

The primary outcome for this study will be the first admission after the initial hospital discharge for fatal or nonfatal acute MI, unstable angina, stroke, congestive heart failure, or coronary revascularization (coronary bypass, stenting, or angioplasty) (see Table D). All patients will be followed-up for a minimum of 1 year; patients recruited at the beginning of the study may contribute up to 2.5 years follow-up time. We chose a minimum of 1-year follow-up based on results of cost-effectiveness models that suggest that a meaningful difference in outcomes should be observable within this time frame.<sup>28,29</sup>

Outcomes will be assessed by applying validated diagnostic algorithms with specificities of at least 95%

**Table II.** Criteria for identifying patients with clinical outcomes

Outcome	Criteria *	Specificity of criteria (%)
Acute MI	ICD-9 410.x (except 410.x2) as the principal or secondary diagnosis and a length of stay of >3 and <180 days	99 <sup>34</sup>
Unstable angina	ICD-9 411 as the principal diagnosis	96 <sup>35</sup>
Stroke	ICD-9 433.x1, 434 (excluding 434.x0), 435.xx, 436.xx, 437.1x or 437.9x in any diagnosis position	99 <sup>36</sup>
Congestive heart failure	ICD-9 428.x as the principal diagnosis	97 <sup>35</sup>

\*Based on hospital discharge codes during follow-up time.

(see Table II) to Aetna's health care utilization databases. This source contains data for all filled prescriptions, procedures, physician encounters, hospitalizations, and inpatient deaths for the patients in this cohort.

The secondary clinical outcomes will include the following: (1) the primary outcome, but patients will not be censored at the time of their first event (ie, patients may experience multiple events); (2) the primary outcome excluding revascularization; and (3) the primary outcome including rates of outpatient cardiac death as assessed with the Center for Disease Control's National Death Index.

Other secondary outcomes will include measures of medication adherence, health care utilization, and health care costs. Medication adherence will be assessed by calculating the mean medication possession ratio (ie, the proportion of days for which patients have medication) and the mean proportion of patients fully adherent (defined as a medication possession ratio  $\geq 80\%$ ) to each and all of the 3 study medications ( $\beta$ -blockers, statins, ACEI/ARB) throughout follow-up. Days in acute care during follow-up will be subtracted from the denominator of the medication possession ratio, and patients who die or lose insurance eligibility during follow-up will be censored at that point. Utilization will be assessed with annual rates of physician visits, emergency department admissions, hospitalizations, and other health care services (eg, revascularization). The cost of cardiovascular and overall health care will be estimated by summing total expenditures for medications, physician and professional fees, hospitalizations, other health care services, and long-term care facility admissions throughout follow-up.

## Analytic plan

We will report means and frequencies of prerandomization variables separately for intervention and control subjects. The primary outcome will be compared based on intention-to-treat principles using proportional hazards regression. The model will adjust for clustering

**Table III.** Statistical power based on expected event rates in control patients and relative risk reductions from full drug coverage

Proportion of control patients experiencing primary outcome	Relative risk reduction from full drug coverage				
	0.15	0.2	0.25	0.3	0.35
0.2	0.70	0.92	0.99	1.0	1.0
0.25	0.79	0.96	1.0	1.0	1.0
0.3	0.85	0.98	1.0	1.0	1.0
0.35	0.89	0.99	1.0	1.0	1.0
0.4	0.92	1.0	1.0	1.0	1.0

using a robust sandwich estimate for the covariance matrix<sup>37</sup> and the blocking factors used for sample stratification, as well as differences in baseline characteristics between study groups. Patients will be censored after they experience an event, if they lose insurance eligibility (eg, if they change employers), at age 65 years, or administratively at the study end.

Medication adherence and health care costs for both treatment groups will be compared. Generalized estimating equations will be used to adjust for the cluster and block randomized design.

## Sample size considerations

Our study should be sufficiently powered to detect relatively small changes in the primary outcome. Using data from our published economic models<sup>28,29</sup> and pilot data from Aetna, we estimate that 35% of our control population will experience the primary study end point. We estimate that eliminating cost-sharing will increase adherence by 13%.<sup>25,38</sup> Using efficacy data from randomized trials, we estimate that this improvement in adherence will reduce the relative risk of the primary end point by 20%.

Pilot data indicate that approximately 5,000 Aetna beneficiaries per year will be eligible for randomization, and therefore, we will recruit 7,500 patients during the 1.5 years of planned recruitment. We assume that 15% of subjects will be noninformatively lost to follow-up annually (eg, because of change in employment or benefit program). With this sample, we should have sufficient power to detect plausible changes in event rates that are expected from full drug coverage (see Table III).

## Data-monitoring committee

An independent data-monitoring committee (DMC) will meet twice a year to review unblinded data including the number of patients randomized, baseline characteristics, and patterns of medication filling. The DMC will also monitor the overall event rate and whether the assumptions underlying the study's size and expected duration are being met. At appropriate time points, the DMC will

also consider unblinded data with respect to study efficacy and make recommendations on whether to continue the study using the Haybittle-Peto stopping rule.<sup>39,40</sup> This group-sequential method maintains an overall  $\alpha$  of .05 by applying a very stringent level of significance for interim analyses (ie,  $P < .001$ ). The DMC will include a cardiologist, an internist, and a statistician.

## Funding and responsibilities

The trial was designed as an investigator-initiated protocol from the Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School. The study is sponsored by Aetna, Inc. Aetna staff have been involved in refining the study design and assessing its feasibility and will be responsible for the day-to-day operations of the trial, as described above. All data analysis and outcome assessment will be performed independent of the trial sponsor.

## Limitations

There are several limitations to this trial that must be acknowledged. First, this trial will only evaluate the impact of cost-sharing on adherence to post-MI medications based on the hypothesis that even small improvements in adherence that are likely to result will be sufficient to improve clinical outcomes and reduce overall health care costs. As such, we will not assess other reasons for nonadherence, such as medication complexity and patient comprehension. Interventions to address these reasons for nonadherence have been evaluated.<sup>41</sup>

Second, patients will be enrolled using hospital discharge claims. Although this will enhance the generalizability of our findings to other insurers who seek to institute similar copayment reduction plans, there will be a lag between hospital discharge and randomization, during which some patients may not fill newly prescribed medications or may become nonadherent to the medications they have filled. This may diminish the effect of eliminating cost-sharing on medication use and clinical outcomes should one exist. Because we anticipate that 80% of patients will be contacted within 2 months of hospital discharge and therefore that first-dollar coverage will begin before patients fill their second prescription for most individuals randomized to this group, the magnitude of this bias should be small.

Third, patients randomized to the intervention group will not receive full coverage for clopidogrel, and thus, our results will only be generalizable to the medications being studied. Clopidogrel is costly, and rates of adherence to clopidogrel are fairly high<sup>42</sup>; thus, the trade-off between reduced cost-sharing for this drug and averted clinical events is likely less favorable than for the other post-MI medications. Accordingly, if clopidogrel was included among the covered medications and if

ultimately this study shows no benefit from full coverage, it will be unclear whether the concept of eliminating cost-sharing for effective medications is itself flawed or more simply whether the cost of clopidogrel has extinguished the cost-savings derived from the other drugs being studied. In addition, clopidogrel is not intended for indefinite use after MI unlike other secondary prevention medications. As such, for the insurance coverage being evaluated to be truly evidence based, we would have to provide intervention group patients with full coverage for 1 year only and then return their coverage to usual levels. Doing so would influence clinical decision making and would confound our assessment of the relationship between selective copay reduction and improvements in medication adherence.

## Summary

The Post-MI FREEE trial will be the first randomized study to rigorously evaluate the impact of reducing patient cost-sharing for essential cardiac medications in high-risk patients on clinical and economic outcomes. The study is powered to detect differences in clinically important outcomes in addition to medication adherence and health care costs. A positive finding from this trial will dramatically influence the nature of prescription drug coverage for essential cardiac medications. The results will also inform the nature and structure of coverage for many other chronic medications for which the cost of full drug coverage may be more than offset by the clinical and economic savings resulting from better adherence to these therapies.

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