



● LARGE SIMPLE CLINICAL TRIALS IN INSURANCE SYSTEMS

POST-MYOCARDIAL INFARCTION FREE RX EVENT AND ECONOMIC EVALUATION (MI FREEE) TRIAL

Niteesh K. Choudhry, MD, PhD

Associate Professor, Harvard Medical School

Division of Pharmacoepidemiology and Pharmacoeconomics

Department of Medicine, Brigham and Women's Hospital

Post-Myocardial Infarction Free Rx Event and Economic Evaluation (MI FREEE) Trial

MOTIVATION

- **Adherence to evidence-based medications prescribed after myocardial infarction (MI) remains poor**
 - Within 2 years of initiating therapy, only half of patients remain adherent to their prescribed statins, beta-blockers, or ACEI/ARBs
 - Profound clinical and economic consequences

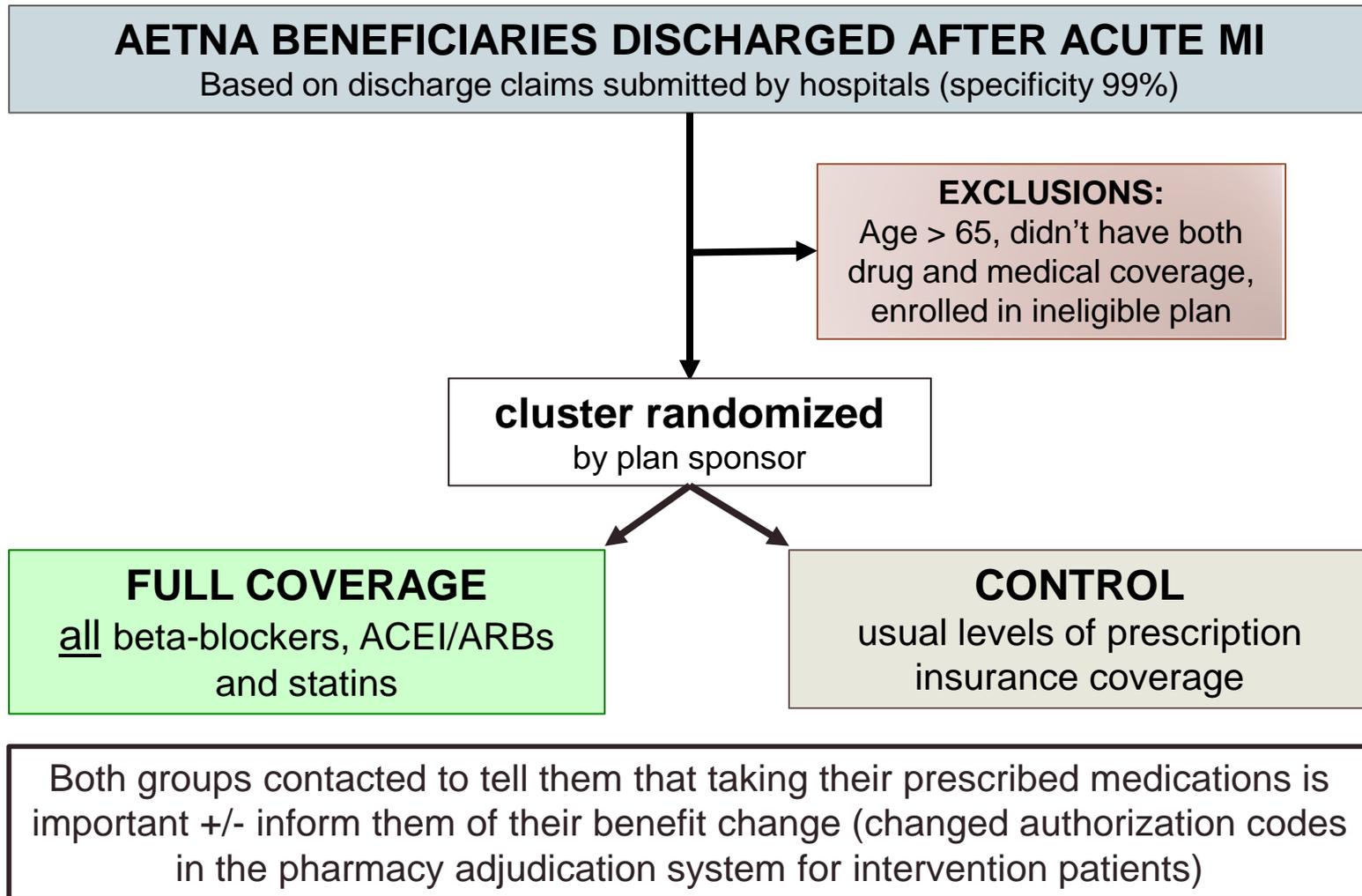
- **Drug costs appear to be a central reason for medication underuse**
 - Even among patients with insurance, utilization varies according to the comprehensiveness of coverage

- **Eliminating out-of-pocket costs for evidence-based therapies may promote adherence and improve outcomes**
 - Observational studies support the ability of this strategy to increase adherence but its impact on health outcomes and spending had not been rigorously evaluated

SOURCE: Choudhry et al. Circulation 2008;117;1261-1268



MI Free Rx Event and Economic Evaluation (MI FREEE) Trial





MI Free Rx Event and Economic Evaluation (MI FREEE) Trial

RANDOMIZATION AND OUTCOME ASSESSMENT

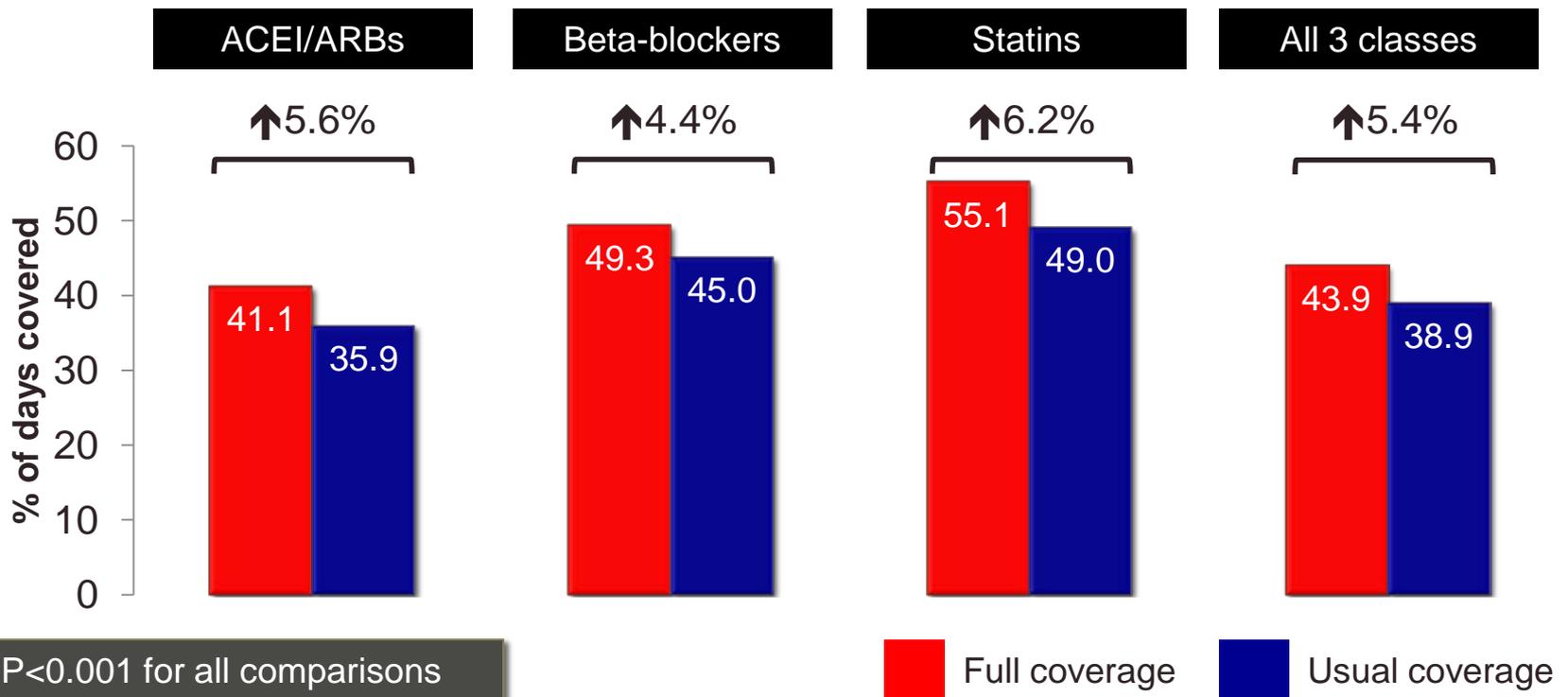
- **Randomized “plan sponsors” rather than individual patients**
 - All beneficiaries of one employer received the same benefits
 - Randomized plan sponsors in “blocks”
- **Outcomes were assessed using validated claims-based algorithms and based on intention to treat principles**
 - Focused on clinical outcomes but captured their occurrence using health services research techniques

Primary	First major vascular event* or revascularization
Secondary	First major vascular event
	Total major vascular events and revascularization
	Medication adherence (proportion of days covered)
	Pharmacy and medical spending

*re-admission for MI, unstable angina, CHF or stroke

Lowering copayments improved medication adherence

MI FREEE



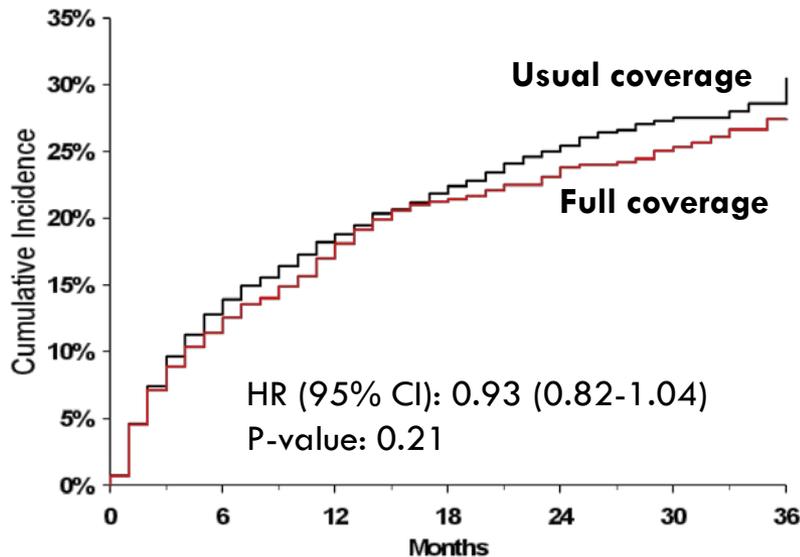
SOURCE: Choudhry et al. NEJM 2011; 365: 2088-2097

Lowering copayments decreased major vascular events

MI FREEE

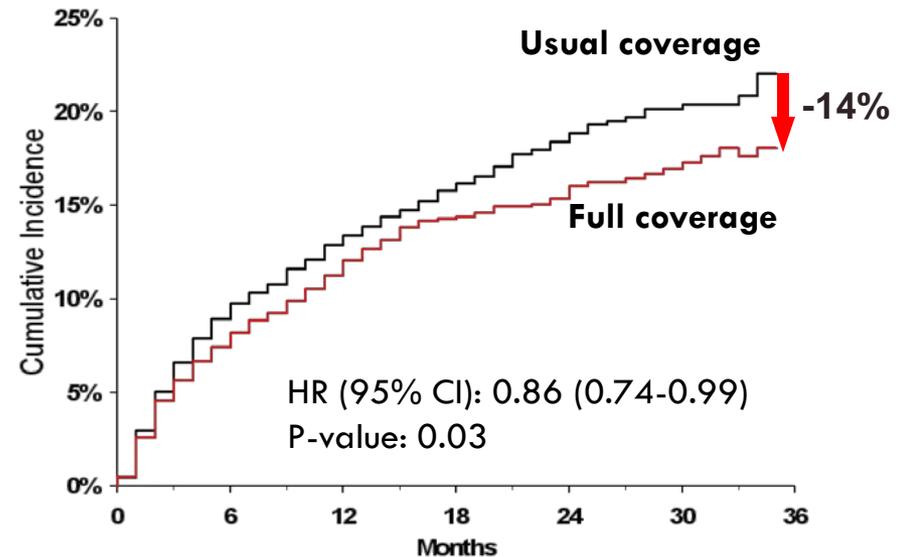
Major vascular event or revascularization

	Full coverage	Usual coverage
Rate/100 py	17.6	18.8



Major vascular events

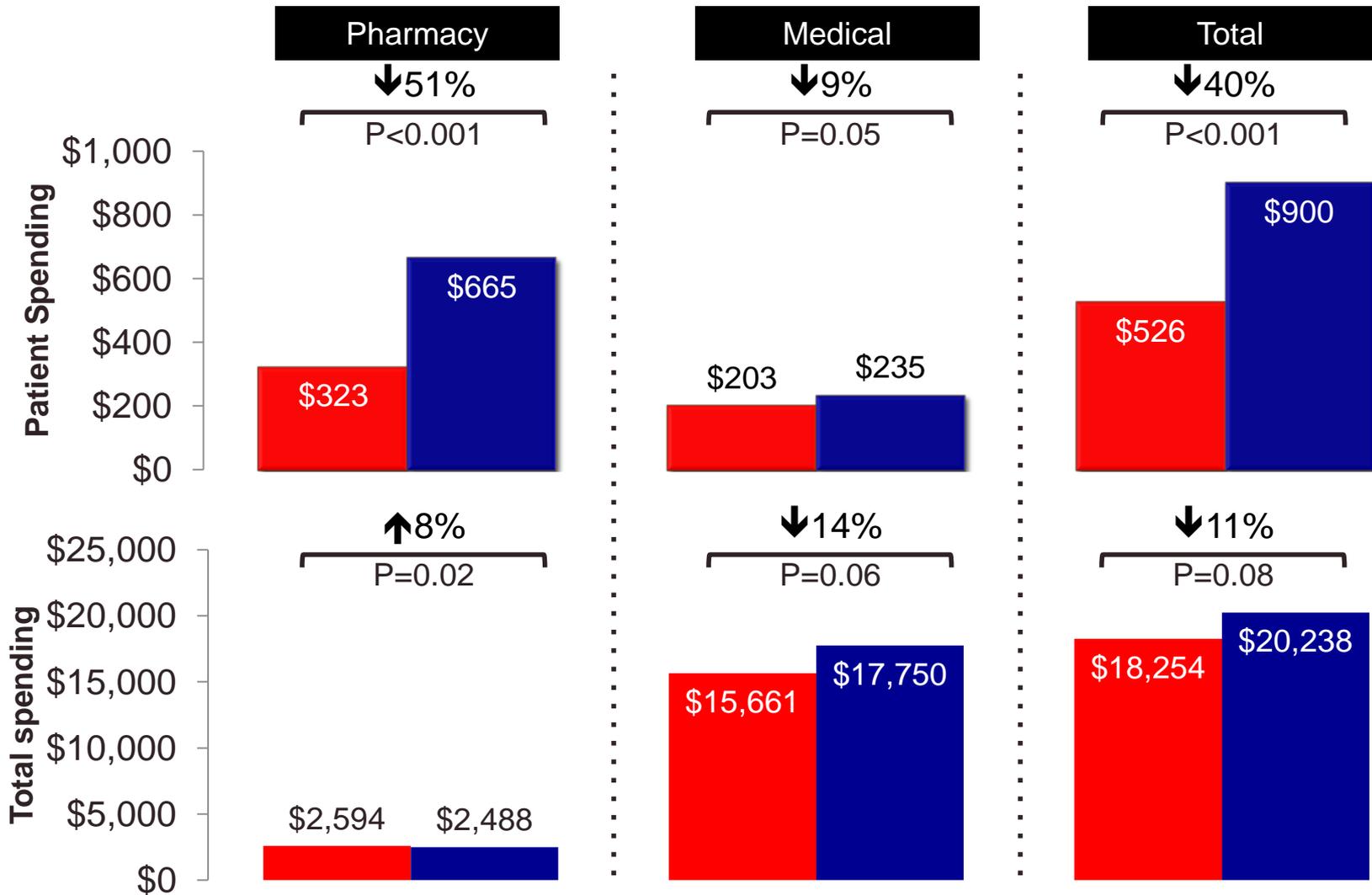
	Full coverage	Usual coverage
Rate/100 py	11.0	12.8



Patient costs decreased without increasing insurer spending

MI FREEE: CV SPENDING

Full coverage
Usual coverage



Claims and Randomization “Lag”

RESEARCH CHALLENGES: MI FREEE

AETNA BENEFICIARIES DISCHARGED AFTER ACUTE MI

Based on discharge claims submitted by hospitals (specificity 99%)

- Submission of claims by hospitals to insurers may take up to 3 months
- Resource intensive to identify eligible patients frequently
 - We identified patients every 2 weeks
- Even after identification, patients must be randomized and contacted

study group assignment occurred a mean of 49 days post-MI

cluster randomized
by plan sponsor

Threats to sample size

RESEARCH CHALLENGES: MI FREEE

ISSUE	DESCRIPTION	MITIGATION STRATEGY
Plan sponsor opt-outs	<ul style="list-style-type: none"> Plan sponsors must allow their beneficiaries to participate → some unwilling to “experiment” 	<ul style="list-style-type: none"> Used an “opt out” approach → required high-level support from Aetna Multipayer collaboratives could be a promising strategy
Insurance “churn”	<ul style="list-style-type: none"> Large turn-over of patients in commercial insurance markets Threaten follow-up time and eligible pool of subjects 	<ul style="list-style-type: none"> Incorporate loss to follow-up in power calculations Could focus on more stably insured workers (?generalizability)
Patient willingness to participate	<ul style="list-style-type: none"> Patients may be skeptical of interventions done by insurers Occurred even with “free drugs” 	<ul style="list-style-type: none"> Carefully scripted outreach and responses to “FAQ”s

Co-intervention

RESEARCH CHALLENGES: MI FREEE

- Insurance systems undergo changes on a very frequent basis
- Could confound the exposure-outcome relationship that is of interest
- Potential strategies:
 - Randomization
 - Pre-assignment stratification for known/anticipated changes
 - Post-trial adjustment for unanticipated (but still measurable) changes

Benefit
changes/open
enrollment

Coverage
changes for
preventive
health
services

Formulary
shifts

Disease
management
programs

Implications and lessons for large simple clinical trials

MI FREEE



- **MI FREEE demonstrates the ability to conduct clinically and policy-relevant studies in real-world settings**
 - Model for new studies being evaluating other strategies to improve adherence to evidence-based medications
 - Many other comparative effectiveness, safety and other types of trials could follow a similar strategy

- **Aetna will begin reducing copayments for post-MI secondary prevention medications in January 2013**
 - Demonstrates the willingness of payers to act rapidly on the results of a large simple insurance trial