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Burden of Changes in Pill Appearance for Patients Receiving Generic Cardiovascular Medications After Myocardial Infarction

Cohort and Nested Case–Control Studies

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Background: Generic prescription drugs made by different manufacturers may vary in color or shape, and switching among these drug products may interrupt medication use.

Objective: To determine whether nonpersistent use of generic drugs among patients with cardiovascular disease after myocardial infarction (MI) is associated with inconsistent appearance of their medications.

Design: Cohort and nested case–control studies.

Setting: Claims from a commercial health insurance database in the United States.

Patients: Patients discharged after hospitalization for MI between 2006 and 2011 who initiated treatment with a generic β-blocker, angiotensin-converting enzyme inhibitor, angiotensin II–receptor blocker, or statin. Case patients discontinued their index medication for at least 1 month; control patients continued treatment. Control patients were matched to case patients on therapeutic class, number of dispensings before nonpersistence, sex, and age.

Measurements: Rates of changes in pill color and shape during the year after MI were calculated. Next, 2 refills preceding nonpersistence were evaluated to determine whether pill color or shape had changed. Odds of discordance among case and control patients were compared using conditional logistic regression.

Results: A total of 29% of patients (3286 of 11 513) had a change in pill shape or color during the study. Statins had the most changes in appearance, whereas β-blockers had the fewest. A total of 4573 episodes of nonpersistence was matched to 19 881 control episodes. The odds of nonpersistence in case patients increased by 34% after a change in pill color (adjusted odds ratio, 1.34 [95% CI, 1.12 to 1.59]) and 66% after a change in pill shape (adjusted odds ratio, 1.66 [CI, 1.43 to 1.94]).

Limitation: Only 3 categories of drugs indicated after MI were evaluated, and clinical outcomes were not addressed.

Conclusion: Variation in the appearance of generic pills is associated with nonpersistent use of these essential drugs after MI among patients with cardiovascular disease.

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Generic drugs are essential to the treatment of cardiovascular disease. They are available in nearly every class of relevant medications—including antihypertensive, lipid-lowering, anticoagulant, antiplatelet, and antiarrhythmic agents—and are inexpensive for patients and payors (1). The U.S. Food and Drug Administration (FDA) certifies qualifying generic drugs as being interchangeable with their brand-name counterparts on the basis of bioequivalence testing (2).

Individual studies (3) and meta-analyses (4) show that patients who receive generic and brand-name drugs achieve equivalent clinical outcomes. Patients who reduce out-of-pocket spending by using generic drugs are more likely to adhere to their medication regimens (5, 6), which can improve cardiovascular outcomes (7, 8). Thus, most policymakers, physicians (9), and payors (which use tiered formularies that incentivize patients to fill prescriptions with generic drugs) encourage the use of generic drugs. The U.S. Government Accountability Office found that generic drugs contributed to more than $1 trillion in savings to the U.S. health care system in the past decade (10).

Generic drugs may be therapeutically interchangeable, but they are not required to look the same as their brand-name counterparts (11) or other generic versions of the same product (12), in part for historical reasons (13). Yet, pill appearance can be an important driver of patients' health care experience (14). Pill color mediates patients' clinical response to medication (15), and changes in pill appearance contribute to patient confusion and medical error (16, 17). Changes in the appearance of medications used to treat chronic conditions may lead to nonadherence and negative health outcomes (18, 19). We have shown that changes in pill color among otherwise bioequivalent antiepileptic drugs were associated with a nearly 30% increased odds of nonpersistent use of medication (20).

One half of patients with cardiovascular disease or its major risk factors adhere poorly to their prescribed medications (21), even in the year after myocardial infarction (MI) (22). Contributors include patient factors (23); providers (24); and routine aspects of health care delivery, such as medication burden (25). The association between nonadherence to cardiovascular medications and negative patient outcomes has been well-documented (26–28). To improve adherence to cardiovascular medications, investigators have eliminated drug copayments (29), enhanced the use of cardiac rehabilitation programs (30), and implemented direct patient education (31). However, even

effective interventions show incomplete results and these programs are costly, limiting their applicability.

We identified a cohort of patients who had an MI and followed their refill habits for 1 year to assess the effect of variations in the color and shape of the cardiovascular medications dispensed to them. We also assessed the relationship between such changes in pill appearance and patients' persistence to their prescribed regimens during this sensitive time.

Context

Generic medications are not required to have a similar appearance to brand-name medications or each other even though they are therapeutically interchangeable.

Contribution

Thirty percent of patients initiating treatment with a generic cardiovascular drug in 3 therapeutic classes after hospitalization for myocardial infarction had a change in medication shape or color. These changes were associated with nonpersistent use of the medications.

Caution

Clinical outcomes were not assessed.

Implication

Changes in the physical appearance of medications may be associated with gaps in patients' medication use.

—The Editors

METHODS

Research Design

We did 2 analyses of patients initiating treatment with β-blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II–receptor blockers (ARBs), or 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) after hospital discharge for MI. First, we did a cohort study to evaluate the incidence of changes in color and shape among the generic medications dispensed after MI. We then used a nested case–control design to determine whether the odds of nonpersistence increased after a change in pill appearance (**Figure**). Adherence and persistence are similar concepts; however, our study technically measured persistence, which is the time from initiation to discontinuation of therapy (32). The Institutional Review Board at Brigham and Women's Hospital (Boston, Massachusetts) approved these studies.

Data Synthesis and Analysis

Data Sources

We collected medical and pharmacy data from the UnitedHealth research database, a commercial insurance database covering more than 14 million persons annually. The database describes all participants, their demographic information, and the enrollment status of their health plan and includes inpatient and outpatient medical encounters (coded using the International Classification of Diseases, Ninth Revision, Clinical Modification, and Current Procedural Terminology, Fourth Edition) and filling prescriptions, including the National Drug Code numbers, quantity dispensed, and days' supply. Data were available from January 2006 through June 2012. We then linked pharmacy claims data by National Drug Code number to FDB MedKnowledge (formerly the First Databank National Drug Data File), which contains information on formulation (for example, capsule, tablet, or suspension), dose, color, and shape.

Cohort Identification

The study cohort consisted of patients aged 18 years or older discharged after MI (index hospitalization) between 1 July 2006 and 31 June 2011 who newly initiated treatment with a generic version of a β-blocker, ACEI, ARB, or statin within 90 days of discharge. A diagnosis of MI was identified by a principal or secondary discharge diagnosis code 410.x2 with a 3- to 180-day length of stay. Previous research showed that this algorithm had a high positive predictive value (97%), sensitivity (96%), and specificity (99%) for MI (33). Patients were required to have at least 6 months of continuous insurance enrollment before discharge and at least 12 months of continuous enrollment after discharge.

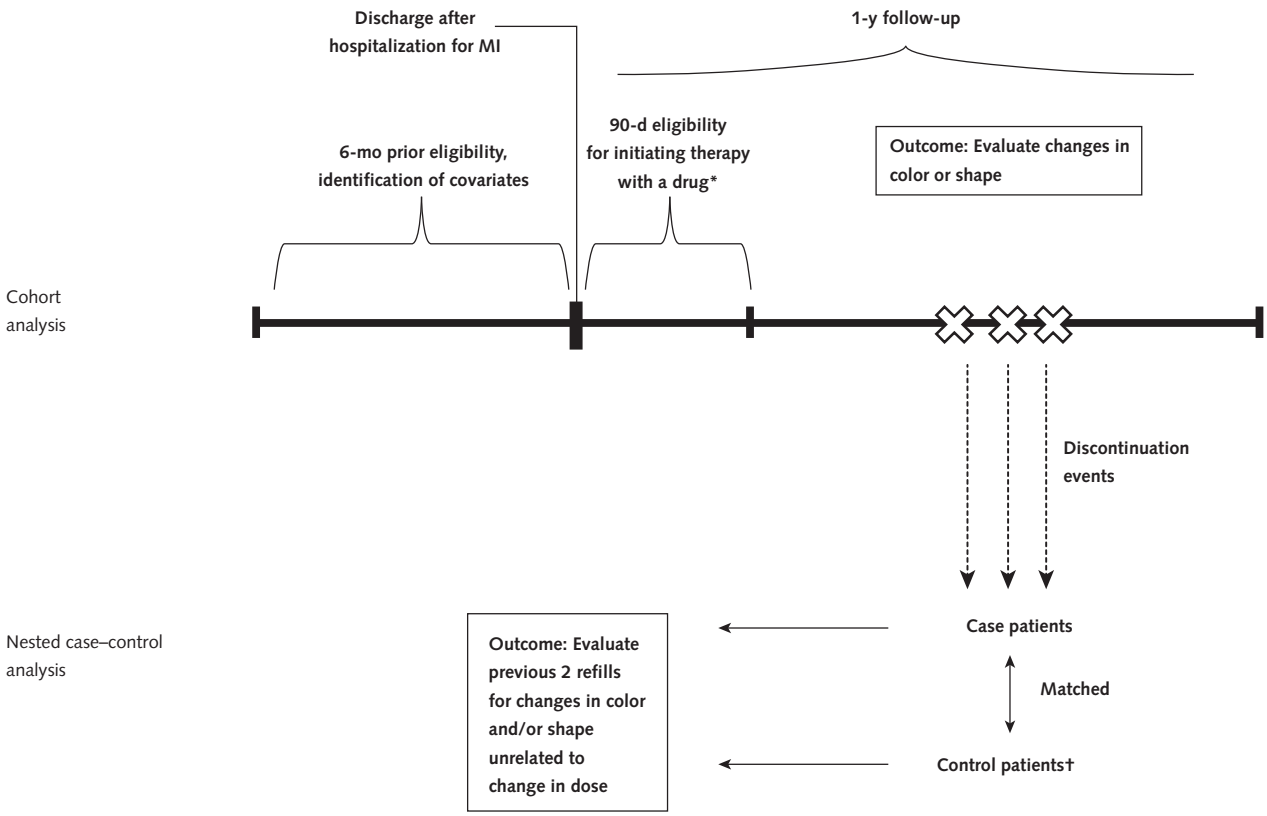
We required that dispensed medications be in pill form (tablet or capsule) and have at least 2 generic versions available on the U.S. market (**Appendix Table 1**, available at www.annals.org, shows the list of eligible medications and when this second criterion was met). A prescription was "newly initiated" if no prescriptions were filled for any drug in the same therapeutic class in the 6 months before treatment initiation. For patients who initiated treatment with more than 1 therapeutic drug class, each eligible episode of treatment initiation was evaluated separately; thus, patients could have up to 3 cohort entries.

Patients were followed for 12 months after MI discharge and were censored if they were hospitalized for a subsequent MI, switched to a different drug in the same therapeutic class, or discontinued treatment with the index medication. Discontinuation was defined as a gap of 31 days or longer after the end of the days supplied in the last fill.

Covariates

We extracted the following information from the database: demographic characteristics (age at index hospital discharge and sex), characteristics of index hospitalization (whether a patient had coronary artery bypass grafting, placement of a percutaneous coronary stent, or percutaneous coronary angioplasty), coexisting illnesses (such as congestive heart failure, chronic obstructive pulmonary disease, diabetes, and previous MI or stroke), prior medication use (ACEIs, ARBs, β-blockers, statins, clopidogrel,

Figure. **Organization of cohort and nested case–control studies.**



MI = myocardial infarction.
* No history in the prior 6 mo of receiving any drugs in the same therapeutic class.
† Control patients were selected from members of the cohort who were receiving the same class of drugs as case patients; were still under observation when case patients discontinued their index medication; and were further matched on age (±5 y), sex, and the number of dispensings of the index medication.

and warfarin), and use of health care services (the number of distinct medications filled, hospitalizations, inpatient days, and physician visits). The latter 3 categories were assessed during the 6 months before the index hospitalization for MI. In the absence of recorded diagnosis or procedure code, the covariate value was 0.

Cohort Study of the Effect of Pill Appearance

We expressed rates of changes in color and shape during follow-up as the number of changes (defined as a refill discordant in color or shape) divided by the total number of filled prescriptions. We calculated these rates for each therapeutic class separately and overall. We further distinguished whether changes in medication color or shape between refills were related to changes in dose strength.

For the overall calculation, we combined all treatment episodes and determined the rates of nonpersistence on the patient level, with treatment episode as the unit of analysis. We compared patients with at least 1 change in pill appearance unrelated to change in dose with patients who did not have such changes by using chi-square and *t* tests, as appropriate. We further explored the associations between rates of change with the covariates by fitting a generalized estimating equation with logit link function and binary distributed errors. We adjusted for all covariates in the analysis.

Nested Case–Control Analysis

To evaluate the association between changes in pill appearance and medication discontinuation, we identified members of the cohort who discontinued treatment with each index medication (case patients). The 31-day gap required for discontinuation was shortened to 7 days and extended to 60 days in sensitivity analyses. Because we censored members of the cohort when they discontinued treatment with an index medication, they could not have had more than 1 episode of nonpersistence for a given drug. However, we followed members of the cohort for each therapeutic class separately and they could have nonpersistent use of more than 1 index medication. The date when a cohort member became nonpersistent was the "outcome date." Because we evaluated color or shape dis-

cordance in the dispensings before discontinuation, case patients had a minimum of 3 dispensings (1 index fill and 2 refills) of the same drug.

Control patients were members of the cohort who filled prescriptions for the same therapeutic class as case patients and who were still under observation when case patients discontinued treatment with their index medication (incidence density sampling). We matched control patients to case patients on the basis of the number of dispensings filled after their MI, sex, and age (within 5 years), including a maximum of 5 control patients per case patient. Before their episodes of nonpersistence, case patients could be control patients. We assigned control patients the outcome date of the matched case patient.

For each episode in which case and control patients were identified, we evaluated the 2 refills before the outcome date and determined whether these refills matched (concordant) or did not match (discordant) each other in color or shape. We considered only appearance changes unrelated to variations in strength of the prescribed medication.

Odds ratios (ORs) defined the association between nonpersistence and discordance in color or shape or both. We used a conditional logistic regression model with case–control status as an outcome or dependent variable and change in color or shape or both as an independent variable. An adjusted model included prespecified baseline covariates of age; index year; revascularization procedure during the index MI; combined comorbidity score (34); use of ACEIs or ARBs, β-blockers, and statins; and number of distinct medications filled (all assessed during the baseline period).

We used a combined comorbidity score to reduce the overall number of covariates in the model. In sensitivity analyses, we subsequently added 2 key covariates evaluated during follow-up: whether the 2 refills assessed for discordance in color or shape were filled in the same pharmacy and whether the patient used a mail-order pharmacy before the episode of nonpersistence (SAS, version 9.3, SAS Institute, Cary, North Carolina).

Role of the Funding Source

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RESULTS

Patient Characteristics

We identified 11 513 persons who initiated treatment with a generic prescription drug in 1 of the cardiovascular drug classes of interest (β-blockers, ACEIs or ARBs, and statins) within 90 days of discharge after hospitalization for MI (**Appendix Figure**, available at www.annals.org). The cohort primarily comprised men at an average age of 57.7 years, nearly all of whom had commercial insurance (**Appendix Table 2**, available at www.annals.org). A total of 5419 patients (47.1%) newly filled a prescription in 1 of the study medication groups, 4322 (37.5%) newly filled prescriptions in 2 drug classes, and 1772 (15.4%) newly filled prescriptions in all 3 classes in the 90 days after discharge. Most patients began treatment with a generic β-blocker (8683 [75.4%]), fewer began treatment with a generic ACEI or ARB (6083 [52.8%]), and the fewest began treatment with a generic statin (4613 [40.0%]).

Burden of Changes in Pill Shape and Color

Overall, cohort members had a median of 10 pharmacy dispensings of all index drugs (interquartile range, 4 to 14 dispensings) during the year after hospitalization for MI. More than one quarter (3286 [28.5%]) had a change in shape or color unrelated to a change in dose for these drugs in the first year after their hospitalization. Approximately one fifth (2214 [19.2%]) had at least 1 change in the color of their generic cardiovascular medication, and slightly more (2532 [22.0%]) had at least 1 change in shape (**Table 1**).

Cohort members who had at least 1 change in color or shape unrelated to dose change had a median of 1 change

Table 1. **Rates of Changes in Pill Appearance Among Cohort Members Prescribed Generic Medications After MI**

Variable	Number	Color Change, *n* (%)		Shape Change, *n* (%)		Any Change, *n* (%)	
		Related to Medication Strength	Unrelated to Medication Strength	Related to Medication Strength	Unrelated to Medication Strength	Related to Medication Strength	Unrelated to Medication Strength
Patients*	11 513	1645 (14.3)	2214 (19.2)	1042 (9.1)	2532 (22.0)	2129 (18.5)	3286 (28.5)
ACEI or ARB	6083	675 (11.1)	964 (15.8)	303 (5.0)	999 (16.4)	821 (13.5)	1392 (22.9)
β-Blocker	8683	490 (5.6)	437 (5.0)	402 (4.6)	1086 (12.5)	801 (9.2)	1313 (15.1)
Statin	4613	591 (12.8)	1070 (23.2)	385 (8.3)	776 (16.8)	710 (15.4)	1186 (25.7)
All treatment initiation episodes	19 379	1756 (9.1)	2471 (12.8)	1090 (5.6)	2861 (14.8)	2332 (12.0)	3891 (20.1)

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II–receptor blocker; MI = myocardial infarction.
* For patients who initiated treatment with >1 therapeutic drug class, each episode of initiation is counted separately.

Table 2. **Characteristics of Case and Control Episodes**

Variable	Case Group (*n* = 4573)	Control Group (*n* = 19 881)
General characteristics		
Mean age (SD), *y*	56.1 (10.4)	56.2 (9.9)
Men, *n (%)*	3284 (71.8)	14 370 (72.3)
Mean total cohort entries (SD), *n*	2.00 (0.7)	2.04 (0.8)*
Patients with 1 cohort entry, *n (%)*	1229 (26.9)	5144 (25.9)
Patients with 2 cohort entries, *n (%)*	2113 (46.2)	8763 (44.1)*
Patients with 3 cohort entries, *n (%)*	1231 (26.9)	5974 (30.1)*
Mean distinct nonindex drugs from MI discharge to outcome date (SD), *n*	7.8 (4.8)	7.7 (5.2)
Pharmacy-related characteristics		
Mean copay of index drug (SD), *$*	7.57 (5.7)	7.51 (5.4)
Use of mail-order pharmacy before outcome, *n (%)*	441 (9.6)	1004 (5.1)*
Change in pharmacy during the last 2 refills before outcome, *n (%)*	472 (10.3)	1335 (6.7)*
Characteristics of index hospitalization, *n (%)*		
Revascularization	3566 (78.0)	16 335 (82.2)*
Year		
2006–2007	1046 (22.9)	4639 (23.3)
2008	1132 (24.8)	4848 (24.4)
2009	933 (20.4)	3999 (20.1)
2010–2011	1462 (32.0)	6395 (32.2)
Coexisting illnesses†		
Congestive heart failure, *n (%)*	173 (3.8)	567 (2.9)*
Chronic obstructive pulmonary disease, *n (%)*	208 (4.6)	697 (3.5)*
Diabetes, *n (%)*	817 (17.9)	3476 (17.5)
Prior MI, *n (%)*	436 (9.5)	1742 (8.8)
Mean combined comorbidity score (SD)	0.3 (1.3)	0.2 (1.1)*
Prior use of nonindex study drugs, *n (%)*†		
ACEI or ARB	598 (13.1)	2724 (13.7)
β-Blocker	348 (7.6)	1407 (7.1)
Statin	664 (14.5)	3023 (15.2)
Clopidogrel	163 (3.6)	518 (2.6)*
Warfarin	95 (2.1)	339 (1.7)
Mean health care utilization (SD), *n*†		
Distinct drugs	8.4 (11.8)	9.4 (12.7)*
Hospital admissions	0.09 (0.43)	0.06 (0.35)*
Hospital days	0.6 (7.2)	0.4 (4.6)*
Physician visits	3.3 (7.3)	3.0 (6.0)*

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II–receptor blocker; MI = myocardial infarction.
* $P < 0.050$.
† Assessed on the basis of filled prescriptions and available diagnoses and procedures during the 6 mo preceding the index hospitalization.

in color or shape (interquartile range, 1 to 2 changes) during follow-up. The odds of a change in color or shape in cohort members who filled prescriptions in all 3 generic drug classes were more than 5 times greater than those of cohort members receiving generic β-blockers, which was the class with the fewest changes in pill appearance (adjusted OR, 5.14 [95% CI, 4.39 to 6.01]) (**Appendix Table 3**, available at www.annals.org).

Because cohort members could be prescribed drugs from more than 1 class in our study, the 11 513 patients in the cohort accounted for 19 379 treatment episodes (**Table 1**). One fifth of these episodes (3891 [20.1%]) involved at least 1 change in pill appearance unrelated to dose change. Although only 3 generic statins were available, these drugs had the most changes in pill color and shape, whereas β-blockers had the fewest.

Characteristics of Case and Control Patients

We identified 4573 episodes of nonpersistent cardiovascular medication use (among 3666 case patients), which we matched to 19 881 episodes of drug continuation (among 6519 control patients) (**Table 2**). Case and control groups had similar rates of coexisting illnesses, medication use before hospitalization, and health care utilization and an average of approximately 9 different drugs filled in the 6 months before index hospitalization.

Association of Changes in Pill Appearance With Nonpersistence

Discordance in color and shape preceded instances of nonpersistence significantly more often than concordance did. A total of 177 (3.9%) instances of nonpersistence involved color discordance, 242 (5.3%) involved shape discordance, and 110 (2.4%) involved color and shape discordance. Discordance in color or shape occurred before approximately 1 in every 14 episodes of nonpersistence among case patients (309 of 4573 [6.8%]) (**Table 3**).

After age, year, combined comorbidity score, revascularization procedure during the index hospitalization, number of drugs received before the index hospitalization, and prior use of nonindex study drugs were adjusted for, the OR for nonpersistence after a change in color or shape was 1.49 (CI, 1.30 to 1.71). Case patients had a 34% increase in the odds of discordance in pill color preceding an episode of nonpersistence (adjusted OR, 1.34 [CI, 1.12 to 1.59]) and a 66% increase in the odds of nonpersistence after a change in shape (adjusted OR, 1.66 [CI, 1.43 to 1.94]).

Adding indicators for a change in pharmacy that occurred with the change in physical appearance of a medication or the use of a mail-order pharmacy immediately before nonpersistence did not change the statistically significant associations with nonpersistence in the primary analysis except for color alone (**Table 3**). A sensitivity analysis in which we stratified patients by pharmacy change during the 2 fills before nonpersistence confirmed these results (**Appendix Table 4**, available at www.annals.org). Shortening our definition of the period of nonpersistence (to 7 days) or lengthening it (to 60 days) did not change the statistical significance of the associations identified in our primary analysis (**Appendix Table 5**, available at www.annals.org).

DISCUSSION

We found that a substantial fraction of patients with cardiovascular disease faces changes in the appearance of essential medications after MI. Patients in our sample who subsequently discontinued treatment with their cardiovas-

Table 3. **Association Between Nonpersistence and Color/Shape Discordance in Medications After MI**

Change	Discordance Among Case Group (n = 4573), n (%)	Discordance Among Control Group (n = 19 881), n (%)	OR (95% CI)	Adjusted OR (95% CI)*	Adjusted OR for Pharmacy Change (95% CI)†	Adjusted OR for Use of a Mail-Order Pharmacy (95% CI)‡
Color	177 (3.9)	587 (3.0)	1.34 (1.13–1.59)	1.34 (1.12–1.59)	1.10 (0.91–1.32)	1.16 (0.97–1.39)
Shape	242 (5.3)	644 (3.2)	1.67 (1.43–1.95)	1.66 (1.43–1.94)	1.41 (1.19–1.66)	1.38 (1.18–1.62)
Color or shape	309 (6.8)	922 (4.6)	1.50 (1.31–1.71)	1.49 (1.30–1.71)	1.25 (1.08–1.45)	1.25 (1.09–1.44)
Color and shape	110 (2.4)	309 (1.6)	1.58 (1.27–1.98)	1.58 (1.27–1.98)	1.32 (1.05–1.66)	1.37 (1.09–1.72)

MI = myocardial infarction; OR = odds ratio.
* Adjusted for age, year, combined comorbidity score, revascularization procedure during the index hospitalization for MI, prior use of nonindex study drugs, and number of distinct drugs used during baseline (all drug use was assessed during the 6 mo preceding the index hospitalization for MI).
† Adjusted for all covariates in the primary adjusted OR model and an additional covariate for change in pharmacy defined by evaluating the 2 refills before the outcome date (the same refills used to assess pill appearance) to determine whether these refills were linked to the same (concordant) or a different (discordant) pharmacy identification number.
‡ Adjusted for all covariates in the primary adjusted OR model and an additional covariate defined by having the last prescription before an outcome date filled through a mail-order pharmacy.

cular medications had a nearly 30% greater odds of having had a change in pill color or shape preceding the discontinuation.

The association between changes in pill appearance and nonpersistent use of essential cardiovascular medications has important implications for public health. After patients have a first MI, evidence-based guidelines mandate treatment with an array of long-term medications. A change in the color or shape of those medications—which we have shown is common during the first year of care after MI—may contribute to patients' stopping treatment with their medications. This factor will increase morbidity and mortality and health care spending overall because of preventable complications and disease recurrence. The associations revealed in our study explain a substantial part of suboptimal outcomes after MI.

These results suggest several possible policy interventions relevant to patients, physicians, and regulators. Changes in appearance can cause patients to lose confidence in the safety or effectiveness of their prescription drugs or lead to confusion that contributes to dangerous errors, such as duplication of medications (35). Subsequent conversations with providers about these changes may lead to extended gaps in patients' use of medications. Cardiologists and other prescribers of cardiovascular medications should proactively warn patients about the potential for these changes and their lack of clinical import, especially in light of the growing prevalence of use of generic drugs.

Pharmacies have experimented with tools intended to promote knowledge about changes to generic pills and that drugs that appear different may be clinically identical. Some affix labels that describe the pills and alert patients to changes (36). Unfortunately, warning stickers on pill bottles are often numerous (37) and are often ignored (38). The value of this intervention could be studied further, and pharmacies could supplement the stickers with verbal information or other written educational material.

This study is particularly relevant to FDA policymakers. Reducing variability in appearance among chemically identical medications could help promote adherence. The agency has maintained that it does not regulate "aesthetic factors" of pharmaceutical products (39). The FDA's stance may also be related to fears that it would infringe on intellectual property rights—also called "trade dress"—that some manufacturers have claimed in their pill shapes and colors, but the U.S. Supreme Court recently made clear that trade dress does not affix to functional attributes of products (13). Our demonstration of a link between pill appearance and nonpersistence shows that variation in color and shape among otherwise pharmaceutically identical generic drugs is clinically relevant.

In principle, the FDA could require new generic applicants to make the shape and color of their pills conform to the brand-name reference listed drug. Formal rulemaking or legislative changes to the Federal Food, Drug, and Cosmetic Act should not be necessary. Federal law gives the FDA the authority to reject applications for generic drugs where "the composition of the drug is unsafe under such conditions because of . . . the manner in which the inactive ingredients are included," which would cover the appearance of the pill (40). For example, in December 2013, the FDA released a long-awaited draft guidance in which it recommended that manufacturers of generic drugs consider the effect on patients of the physical attributes of their drugs when developing future products (41). In light of the growing literature supporting the functionality of pill appearance, the FDA could extend this guidance to encourage generic manufacturers to adopt consistent physical attributes for bioequivalent products.

We also found that variables related to the pharmacy interacted with the association between changes in the appearance of pills containing cardiovascular drugs and nonpersistence. This finding was not surprising. When patients switch pharmacies or use mail-order pharmacies, they may be more likely to receive medication from different suppliers that varies in shape or color. Reducing use of multiple pharmacies may also temper the association between changes to the appearance of generic drugs and nonpersistence, perhaps by reducing the likelihood that patients will receive generic drugs from different manufacturers. The

growth of "pharmacy homes," in which patients receive coordinated longitudinal medical and pharmaceutical care from the same group of providers, incorporates such a strategy (42). Further study is needed of the relationship among changes in pharmacies, changes in the appearance of pills containing generic drugs, and patient nonpersistence.

Our study has limitations. Our evaluation of only 3 classes of cardiovascular drugs after MI limits its generalizability. However, our data support the results from our earlier study in antiepileptic drugs (20), which showed that changes in pill color were associated with nonpersistence. We also lacked certain data points on patients, such as socioeconomic status or enrollment in automatic refill programs, that we could therefore not adjust for in the model. Finally, we examined the association between changes in pill appearance and nonpersistent use of medications, not clinical outcomes related to cardiovascular disease, although many studies have linked nonpersistence and clinical outcomes.

Of interest, the effect size of the association between nonpersistence and changes in shape was higher than that between nonpersistence and changes in color in this study and in our prior study of antiepileptic drugs. Shape changes may exert a stronger effect because the visual acuity needed to distinguish pill colors may be diminished among patients—particularly elderly ones—with chronic diseases, whereas differences in pill shapes are more readily perceived or involve the sense of touch as well as vision. Patients also may get used to swallowing pills of a particular shape and prefer to avoid changes to that shape.

Cardiovascular disease is the leading cause of death in the United States (43), and the period after MI is a key time when proper medication use can lead to positive health outcomes for patients. Our study shows the association between changes in pill appearance during that time and nonpersistence with these essential medications.

Could a relatively simple intervention—ensuring similar pill appearance among generic prescription drugs—help promote patient adherence to drugs after MI, reducing complications and associated costs? Until the FDA or manufacturers of generic drugs take the initiative to make consistent pill shape or color an industry standard, it is incumbent on prescribers and pharmacists to take steps to warn patients about the diversity of the shapes and colors of the pills containing their generic cardiovascular drugs to reduce the burden of these changes on the public health.

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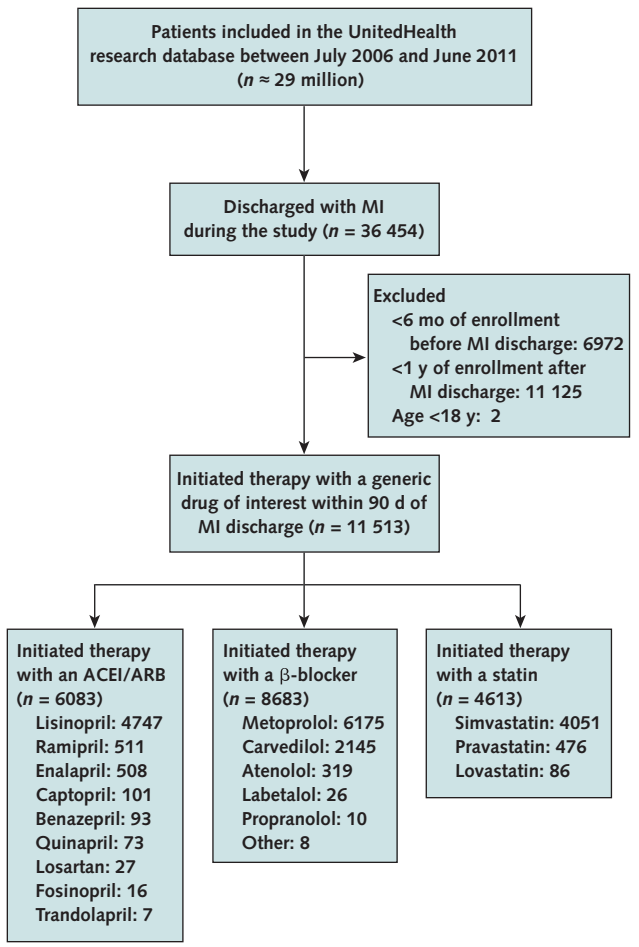
Appendix Table 1. **Study Drugs Leading to Inclusion in Cohort**

Drug	Study Date When Multisource Generic Drug Became Available*
ACEIs	
Benazepril	July 2006
Captopril	July 2006
Enalapril	July 2006
Fosinopril	July 2006
Lisinopril	July 2006
Moexipril	July 2006
Perindopril	December 2009
Quinapril	July 2006
Ramipril capsule	July 2008
Trandolapril	July 2007
ARBs	
Losartan	November 2010
Olmesartan	October 2009
β-Blockers	
Acebutolol	July 2006
Atenolol	July 2006
Betaxolol	July 2006
Bisoprolol	July 2006
Metoprolol tartrate	July 2006
Nadolol	July 2006
Pindolol	July 2006
Propranolol	July 2006
Timolol tablet	July 2006
Labetalol	July 2006
Carvedilol	October 2007
Metoprolol succinate	
25 mg	April 2008
50 mg	June 2008
100 mg	May 2010
200 mg	May 2010
Statins	
Lovastatin	July 2006
Pravastatin	November 2006
Simvastatin	July 2006

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II–receptor blocker.
* Month when at least 2 generic versions became available on the U.S. market. Patients were eligible to enter the cohort only if treatment with the medications was initiated after the date specified. The data set started in July 2006, so any drugs with preexisting multisource generic availability are listed with that date.

Appendix Figure. **Study flow diagram.**



ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II–receptor blocker; MI = myocardial infarction.

Appendix Table 2. Baseline Characteristics for Overall Cohort

Variable	Overall Cohort (n = 11 513)	Patients Who Had a Change in Pill Shape or Color (n = 3286)	Patients Who Did Not Have a Change in Pill Shape or Color (n = 8227)
General characteristics			
Mean age (SD), *y*	57.7 (10.7)	57.8 (10.5)	57.7 (10.8)
Men, *n (%)*	8305 (72.1)	2460 (74.9)	5845 (71.1)*
Patients with 1 cohort entry, *n (%)*	5419 (47.1)	1036 (31.5)	4383 (53.3)*
Patients with 2 cohort entries, *n (%)*	4322 (37.5)	1460 (44.4)	2862 (34.8)*
ACEI/ARB plus β-blocker	2363 (20.5)	743 (22.6)	1620 (19.7)*
ACEI/ARB plus statin	503 (4.4)	207 (6.3)	296 (3.6)*
β-Blocker plus statin	1456 (12.6)	510 (15.5)	946 (11.5)*
Patients with 3 cohort entries, *n (%)*	1772 (15.4)	790 (24.0)	982 (11.9)*
Index drug filled at mail-order pharmacy, *n (%)*	209 (1.8)	40 (1.2)	169 (2.1)*
Type of insurance, *n (%)*			
Commercial	11 465 (99.6)	3276 (99.7)	8189 (99.5)
Medicare	48 (0.4)	10 (0.3)	38 (0.5)
Characteristics of index hospitalization, *n (%)*			
Event			
Coronary artery bypass graft	2107 (18.3)	601 (18.3)	1506 (18.3)
Stent placement	6067 (52.7)	1882 (57.3)	4185 (50.9)*
Percutaneous transluminal coronary angioplasty	6895 (59.9)	2116 (64.4)	4779 (58.1)*
Year			
2006–2007	2949 (25.6)	825 (25.1)	2124 (25.8)
2008	2709 (23.5)	923 (28.1)	1786 (21.7)*
2009	2453 (21.3)	603 (18.4)	1850 (22.5)*
2010–2011	3402 (29.5)	935 (28.5)	2467 (30.0)
Coexisting illnesses, *n (%)*†			
Congestive heart failure	539 (4.7)	114 (3.5)	425 (5.2)*
Chronic obstructive pulmonary disease	592 (5.1)	147 (4.5)	445 (5.4)*
Diabetes	2449 (21.3)	573 (17.4)	1876 (22.8)*
Prior MI	1103 (9.6)	285 (8.7)	818 (9.9)*
Prior use of nonindex study drugs and other drugs, *n (%)*†			
ACEI or ARB	2229 (19.4)	501 (15.3)	1728 (21.0)*
β-Blocker	1337 (11.6)	374 (11.4)	963 (11.7)
Statin	2389 (20.8)	537 (16.3)	1852 (22.5)*
Clopidogrel	589 (5.1)	114 (3.5)	475 (5.8)*
Warfarin	326 (2.8)	85 (2.6)	241 (2.9)
Mean health care utilization (SD), *n*†			
Distinct drugs	10.42 (12.9)	8.99 (11.9)	10.99 (13.2)*
Hospital admissions	0.1 (0.4)	0.07 (0.3)	0.11 (0.5)*
Hospital days	0.72 (10.7)	0.54 (8.3)	0.8 (11.5)
Physician visits	3.82 (7.8)	3.27 (6.9)	4.04 (8.1)*

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II–receptor blocker; MI = myocardial infarction.
* $P < 0.050$.
† Assessed on the basis of all filled prescriptions and available diagnoses and procedures during the 6 mo preceding the index hospitalization.

Appendix Table 3. Potential Predictors of Changes in Color or Shape

Characteristic	Adjusted OR (95% CI)*
Age	1.01 (1.00–1.01)
Men	1.14 (1.03–1.26)
Year of discharge from hospitalization for MI†	
2008	1.20 (1.07–1.35)
2009	0.73 (0.64–0.83)
2010–2011	0.82 (0.73–0.93)
Cohort entry‡	
Statin only	1.69 (1.36–2.09)
ACEI/ARB only	1.88 (1.56–2.27)
ACEI/ARB plus β-blocker	2.83 (2.44–3.27)
ACEI/ARB plus statin	4.13 (3.27–5.21)
β-Blocker plus statin	3.28 (2.81–3.84)
Patients with 3 cohort entries	5.14 (4.39–6.01)
Index drug filled at mail-order pharmacy	0.53 (0.37–0.75)
Commercial insurance§	1.54 (0.74–3.20)
Congestive heart failure	0.82 (0.65–1.03)
Chronic obstructive pulmonary disease	0.99 (0.80–1.22)
Diabetes	0.88 (0.78–0.99)
Prior MI	0.93 (0.80–1.09)
Baseline use of ACEI/ARB	1.23 (1.07–1.42)
Baseline use of β-blocker	1.17 (0.98–1.40)
Baseline use of statin	1.14 (1.00–1.30)
Baseline use of clopidogrel	0.80 (0.64–1.01)
Baseline use of warfarin	1.13 (0.86–1.48)
Number of distinct drugs filled during the baseline period	1.00 (0.99–1.00)
Number of hospital admissions during the baseline period	0.87 (0.75–1.00)
Number of hospital days during the baseline period	1.00 (1.00–1.00)
Number of physician visits during the baseline period	1.00 (0.99–1.01)

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II–receptor blocker; MI = myocardial infarction; OR = odds ratio.
* All predictors presented were forced into the model without selection.
† 2006–2007 was the reference group.
‡ β-Blockers were the reference group.
§ Versus Medicare.

Appendix Table 4. Association Between Nonpersistence and Color/Shape Discordance in Medications After MI, Stratifying the Cohort on the Basis of Pharmacy Change During the Past 2 Refills Before the Outcome Date

Variable	All*	Change in Pharmacy†	No Change in Pharmacy†
Case episodes, *n*	4573	464	4100
Control episodes, *n*	19 881	2075	19 059
Adjusted OR for change in color (95% CI)	1.10 (0.91–1.32)	1.22 (0.93–1.59)	1.16 (0.89–1.50)
Adjusted OR for change in shape (95% CI)	1.41 (1.19–1.66)	1.39 (1.10–1.76)	1.66 (1.33–2.07)
Adjusted OR for change in color or shape (95% CI)	1.25 (1.08–1.45)	1.30 (1.04–1.63)	1.40 (1.15–1.71)
Adjusted OR for change in color and shape (95% CI)	1.32 (1.05–1.66)	1.41 (1.03–1.93)	1.47 (1.05–2.06)

OR = odds ratio; MI = myocardial infarction.
* From **Table 3.** The ORs in this column were also adjusted for the pharmacy change covariate.
† The ORs in these columns were adjusted for age, year, combined comorbidity score, revascularization procedure during the index hospitalization for MI, prior use of nonindex study drugs, and the number of distinct drugs used during baseline (all drug use was assessed during the 6 mo preceding the index hospitalization). In addition to matching criteria specified in the Methods section, case and control patients were matched on pharmacy change (yes/no) during the past 2 refills. Nine case patients were excluded from this sensitivity analysis because no matching control patients were found for them.

Appendix Table 5. **Associations Between Nonpersistence and Color/Shape Discordance in Medications After MI, Using 7- or 60-Day Nonpersistence Periods**

Change	Discordance Among Case Group, *n (%)*	Discordance Among Control Group, *n (%)*	OR (95% CI)
7-d nonpersistence period			
Total	4994	21 970	
Color	200 (4.0)	686 (3.1)	1.28 (1.09–1.51)
Shape	247 (5.0)	753 (3.4)	1.45 (1.25–1.68)
Color or shape	336 (6.7)	1070 (4.9)	1.40 (1.23–1.59)
Color and shape	111 (2.2)	369 (1.7)	1.32 (1.06–1.63)
60-d nonpersistence period			
Total	4260	18 540	
Color	181 (4.3)	535 (2.9)	1.49 (1.25–1.78)
Shape	240 (5.6)	630 (3.4)	1.69 (1.45–1.98)
Color or shape	309 (7.3)	894 (4.8)	1.53 (1.34–1.75)
Color and shape	112 (2.6)	271 (1.5)	1.85 (1.47–2.32)

MI = myocardial infarction; OR = odds ratio.