Circulation: Cardiovascular Quality and Outcomes

ORIGINAL ARTICLE

Impact of a Metoprolol Extended Release Shortage on Post-Myocardial Infarction β-Blocker Utilization, Adherence, and Rehospitalization

Katsiaryna Bykov, PharmD, ScD
Joshua J. Gagne, PharmD, ScD
Bo Wang, MD, PharmD
Niteesh K. Choudhry, MD, PhD

BACKGROUND: Shortages of chronic medications are an increasingly common problem, yet little is known about their impact on drug utilization and clinical outcomes. We evaluated the population-level impact of metoprolol extended release shortage that occurred in the United States in 2009 to 2010.

METHODS AND RESULTS: We conducted a population-based, time series analysis of 38 914 patients (mean age, 60 years; 69% men) discharged after hospitalization for myocardial infarction (MI) between January 2006 and November 2012 in a large commercial insurance database. The shortage period was defined as February 2009 to June 2010. Data before September 2008 was defined as preshortage period and data after June 2010 as postshortage period. Outcomes were proportion of patients who filled any long- or short-acting β-blocker within 30 days of discharge, adherence to β-blockers within the first year of therapy among patients who initiated β-blockers, and rates of 1-year rehospitalization for MI or unstable angina. Post-MI statin utilization and adherence were evaluated as control outcomes. During the preshortage period, 70% of patient filled a β-blocker, mean monthly adherence was 76%, and the average monthly rate of rehospitalization was 6.5 events per 100 person-years, as compared with β-blocker use of 62%, average adherence of 70%, and rehospitalization rate of 5.6 events per 100 person-years during the shortage. After accounting for the baseline (preshortage) trends, the shortage was associated with significant monthly reductions in postdischarge β-blocker use (–0.57% of patients [95% CI, –0.90 to –0.24] per month) and an immediate decrease in adherence (–4.58% days covered [95% CI, –6.12 to –3.04]). No negative impact on rates of rehospitalization, post-MI statin utilization, or statin adherence was observed. β-Blocker utilization began to increase after the resolution of the shortage.

CONCLUSIONS: The nationwide metoprolol extended release shortage in the United States was associated with fewer patients receiving any long- or short-acting β-blocker post-MI and lower adherence to β-blocker therapy for those who did receive it, but did not appear to appreciably affect clinical outcomes at the population level.

Key Words: medication adherence ■ metoprolol ■ myocardial infarction ■ United States

https://www.ahajournals.org/journal/circoutcomes

WHAT IS KNOWN

- Despite considerable attention and legislative efforts, drug shortage is an ongoing problem in the US healthcare system.
- A shortage of metoprolol extended release products occurred in the United States in 2009 and lasted ≈2 years.

WHAT THE STUDY ADDS

- This is the first study to assess the population-level impact of a chronic drug shortage on patient outcomes.
- In our cohort of 38914 commercially insured patients discharged after a myocardial infarction, metoprolol extended release shortage was associated with decreased post-myocardial infarction 30-day initiation of any β-blocker and decreased β-blocker adherence among those who started therapy.
- Healthcare providers need to be made aware of ongoing drug shortages and ensure that patients receive appropriate pharmacotherapy during these periods.

Drug shortages are a serious and chronic problem in the US healthcare system. Although there has been a decrease in the number of new drug shortages after the July 2012 enactment of the Food and Drug Administration Safety and Innovation Act, which required manufacturers to notify Food and Drug Administration of manufacturing interruptions and discontinuations at least 6 months in advance, the number of active and ongoing shortages remains high.[1–3] As of July 2018, there were 178 current drug shortages in the United States, affecting such common medications as atenolol, furosemide, and heparin.[4] A lot of attention has been given to shortages of cancer drugs or drugs used in acute care settings because of their immediate effect on patients and health care systems.[2,5–7] However, shortages affecting widely used chronic medications are also common; the impact of such shortages on patient care and clinical outcomes is unknown.

β-Blockers are part of the standard of care for patients with acute myocardial infarction (MI).[8,9] In 2009, a nationwide shortage of metoprolol succinate extended release (metoprolol ER) tablets, that was caused by production interruptions at 2 drug manufacturers and lasted for ≈2 years, began affecting the drug supply.[10] In September 2008, Sandoz recalled all of its metoprolol ER products and then in January 2009, KV Pharmaceuticals recalled all of its generic metoprolol ER tablets, as part of a wider recall of its products for quality problems.[11,12] At the time of recall, these products represented the majority of the metoprolol ER market. And, although dosing errors resulting from patients switching from metoprolol ER products to immediate-release versions were reported,[10] the impact of this shortage on patient outcomes at the population level is not known.

The goal of this study was to assess the impact of the metoprolol ER shortage on post-MI β-blocker use, longer-term adherence, and clinical outcomes in a large population of patients discharged after hospitalization for acute MI.

METHODS

The analytic methods and study protocol are available from the corresponding author on a request from other researchers for the purposes of reproducing the results. The study data cannot be made available to other researchers because of the terms specified in the Data Use Agreement.

Data

We used Optum Clinformatics ® Data Mart (Eden Prairie, MN), which is a nationwide US commercial health insurance database with an approximate cross-sectional size of 12 to 13 million and longitudinal information on all reimbursed medical services and outpatient drug dispensings. Patient data were deidentified, and the study was approved by the Brigham and Women's Hospital Institutional Review Board.

Patients

In each month from January 2006 to November 2012, we identified patients discharged from hospitalizations after MI. Following a validated algorithm,[13] we defined MI hospitalizations as those lasting at least 3 days with *International Classification of Diseases, Ninth Revision,* Clinical Modification codes of 410.x0 or 410.x1 as a primary or secondary diagnosis. If patients had multiple MI hospitalizations during the study period, we used only the first one as the index hospitalization. Patients were required to have at least 6 months of continuous health plan enrollment before the index MI hospitalization. This period was used to assess medication use before the index hospitalization and coexisting illnesses (see Table I in the Data Supplement for definitions).

Outcomes

We measured 3 outcomes after MI hospital discharge: (1) use of any long- or short-acting β-blocker within 30 days after discharge; (2) adherence to β-blockers within the first year of therapy among patients who initiated β-blockers; and (3) rehospitalization for either MI or unstable angina within 1 year.

To define postdischarge β-blocker use, we determined the proportion of patients who filled a prescription for any oral long- or short-acting β-blocker (metoprolol succinate, metoprolol tartrate, acebutolol, atenolol, betaxolol, bisoprolol, carvedilol, labetalol, nadolol, penbutolol, propranolol, timolol) within 30 days after being discharged from their index hospitalization. In our primary analysis, we evaluated 30-day initiation of any β-blocker. We also examined the initiation trends for specific β-blockers: metoprolol ER products that

were affected by shortage, metoprolol ER not affected by shortage, immediate-release metoprolol tartrate, atenolol, or carvedilol.

Adherence was calculated for each month of the first year of therapy as proportion of days covered (PDC) among patients who filled a β-blocker within 30 days after discharge. PDC is a valid and widely used measure of long-term adherence.[14] Starting from the date of the first postdischarge dispensing and using the days supply variable in the pharmacy claims data, we determined whether patients had a β-blocker pill available on each day during the 12 months of their follow-up. We included all β-blockers defined above in the adherence analysis so that if patients switched from one β-blocker to another during follow-up, both contributed to the PDC calculation. If patients died or lost insurance eligibility during the follow-up year, we censored them at that time. We did not censor patients if they experienced another MI or angina hospitalization, but we excised days spent in the hospital from the calculation. To evaluate whether the shortage disproportionally affected patients who were started on a subsequently recalled metoprolol ER product, we stratified patients discharged during the year before the second recall according to their initial β-blocker dispensing (whether it was for a metoprolol ER product that was subsequently recalled or not) and examined adherence trends within these 2 groups separately.

The primary clinical outcome of rehospitalization was defined as any inpatient stay for MI (using the same definition as for cohort entry) or unstable angina (primary *International Classification of Diseases, Ninth Revision*, discharge code 411.1x with a hospitalization lasting at least 3 days but not longer than 180 days). Patients were followed for the duration of 1 year until the first occurrence of an event, death, or loss of insurance eligibility, whichever came first.

As control outcomes, we also evaluated post-MI statin use (a prescription filled within 30 days after a discharge) and adherence to statins among those who filled the initial prescription. These outcomes were evaluated within the same cohort of post-MI patients, and the same definitions were applied.

Statistical Analysis

The study period was divided into monthly periods. We plotted and evaluated post-MI β-blocker use according to the month of each patient's index hospital discharge. However, because adherence and rehospitalization for MI or angina were evaluated for 1 year of follow-up and patients could contribute observation time to both preshortage and shortage periods, we evaluated monthly adherence and rehospitalization rates according to a calendar month. Thus, monthly adherence was an average adherence among all patients under observation during that month, and rehospitalization rates were calculated by dividing the number of events that occurred during a calendar month by the amount of person-time contributed by patients under follow-up.

To evaluate the impact of shortages on our study outcomes, we conducted an interrupted time series analysis using segmented linear regression.[15,16] Since the first manufacturer recalled all of its metoprolol ER products in late September 2008 and the second manufacturer announced the recall at the end of January 2009, we used October 2008 through January 2009 as a transition period and excluded it from the analysis. As a result, the shortage period was defined as February 2009 through June 2010, the preshortage period was defined as January 2007 through September 2008, and the postshortage period was defined as July 2010 through November 2012 in the analysis of drug use and July 2010 through December 2011 for adherence and clinical outcomes. The year 2012 was not included in the analysis of adherence, and rehospitalization rates to ensure that the distribution of time since the index MI for patients under follow-up at each month remained relatively stable throughout the study. The linear regression model included a linear term for time in months from the start of the preshortage period (January 2007), a binary indicator for the first change point (February 2009), a linear term for time after the first change point (February 2009–June 2010), a binary indicator for the second change point (July 2010), and a linear term for time after July 2010:

$$Y_t = \beta_0 + \beta_1 \times \text{time}_t + \beta_2 \times \text{change point1}_t + \beta_3 \times \text{time after change point1}_t + \beta_4 \times \text{change point2}_t + \beta_5 \times \text{time after change point2}_t + e_t$$

The Durbin-Watson test was used to assess for autocorrelation, including seasonal autocorrelation (correlations between error terms separated by multiples of 12 months). The final model included a first-order autoregression term.

Adherence was evaluated using individual-level data and generalized estimating equations that adjusted for the fact that repeated measured were made on each patient. β-Blocker 30-day initiation and rehospitalization rates were evaluated using aggregate monthly data and SAS proc autoreg command that fitted a regression line through the monthly aggregated data points. As sensitivity analyses, we also evaluated β-blocker initiation using logistic regression and rehospitalization rates using Poisson regression. Nonlinear trends before shortage and during the shortage were evaluated by adding quadratic term for time.

To assess whether the composition of the study population remained constant over time, we compared the baseline characteristics of patients who were discharged during the shortage period to characteristics of patients who were discharged before and after the shortage. Covariates with a standardized difference >0.1 were considered imbalanced and were added as aggregate monthly values to the final model for the rehospitalization outcome.

Secondary Analyses

We conducted a sensitivity analysis shifting the end of the shortage period to April 2010. We also performed subgroup analyses of β-blocker initiation and adherence according to β-blocker use before index MI hospitalization.

Analyses were performed with SAS version 9.4 statistical software (SAS Institute).

RESULTS

Patients

Between January 2006 and November 2012, we identified 38 914 eligible patients who were discharged from

Table 1. Characteristics of Patients Discharged After an MI During the Study Period (January 2006–November 2012)

Characteristic*	Preshortage Jan 2006–Sept 2008 (n=16 599)	Shortage Oct 2008–Jun 2010 (n=10 477)	Postshortage Jul 2010–Nov 2012 (n=11 838)
Age, y, mean (SD)	59.7 (11.5)	60.8 (12.0)	60.0 (11.6)
Male sex	11 360 (68.4)	7069 (67.5)	8228 (69.5)
Procedure on index hospitalization			
Coronary artery bypass grafting	2662 (16.0)	1647 (15.7)	1899 (16.0)
Stent	7446 (44.9)	4428 (42.3)	5198 (44.0)
Coexisting illness			
Congestive heart failure	1603 (9.7)	1030 (9.8)	1051 (8.9)
Coronary artery disease	3793 (22.9)	2281 (21.8)	2622 (22.2)
Hypertension	7620 (45.9)	5130 (49.0)	5819 (49.2)
Diabetes mellitus	5569 (33.6)	3800 (36.3)	4333 (36.6)
Chronic obstructive pulmonary disease	3046 (18.4)	1905 (18.2)	2025 (17.1)
Prior myocardial infarction	196 (1.2)	99 (0.9)	116 (1.0)
Atrial fibrillation	211 (1.3)	91 (0.9)	106 (0.9)
Ontario acute MI mortality score, mean (SD)†	1.91 (1.4)	2.08 (1.4)‡	2.06 (1.4)
Medication use before index hospitalization			
Angiotensin receptor blocker or ACE inhibitor	5213 (31.4)	3337 (31.9)	3580 (30.2)
β-Blockers	4470 (26.9)	2705 (25.9)	2755 (23.3)
Calcium channel blockers	2342 (14.1)	1559 (14.9)	1665 (14.1)
Thiazide diuretics	1154 (7.0)	694 (6.6)	731 (6.2)
Loop diuretics	1757 (10.6)	1169 (11.2)	1311 (11.1)
Potassium sparing agents/aldosterone antagonists	726 (4.4)	423 (4.0)	464 (3.9)
Statins	4458 (26.9)	2995 (28.6)	3839 (32.4)
Nonstatin lipid-lowering drugs	1941 (11.7)	1172 (11.2)	1166 (9.9)
Nonsteroidal anti inflammatory drugs	2001 (12.1)	1266 (12.1)	1446 (12.2)
Proton pump inhibitors	1946 (11.7)	960 (9.2)	897 (7.6)
Antiarrhythmic	323 (2.0)	260 (2.5)	347 (2.9)
Warfarin	745 (4.5)	504 (4.8)	526 (4.4)
Antiplatelet medications	1633 (9.8)	1095 (10.5)	1306 (11.0)
Medication use after the MI (within 30 d)			
Angiotensin receptor blocker or ACE inhibitor	8527 (51.4)	4929 (47.1)	5351 (45.2)
β-Blocker	11 618 (70.0)	6597 (63.0)	7076 (59.8)
Statin	10 211 (61.5)	6273 (59.8)	7645 (64.6)
Nonstatin lipid-lowering drugs	2153 (13.0)	1019 (9.7)	821 (6.9)
Antiplatelet medications	9454 (57.0)	5655 (54.0)	6515 (55.0)
Other antihypertensive medications	4957 (29.9)	3272 (31.2)	3743 (31.6)

ACE indicates angiotensin-converting enzyme; and MI, myocardial infarction.

*Data are expressed as number (%) of patients unless otherwise noted.

†Ontario acute MI mortality score predicts 30-day and 1-year mortality and is calculated based on published weights according to age, sex, and presence of 9 clinical conditions.[17]

‡Standardized difference between the groups >0.1.

a hospital after MI. The average age was 60 years and 69% were men. Baseline characteristics were comparable across the study periods (Table 1), except for the Ontario acute MI mortality prediction score.[17] On average, patients who were discharged during the shortage period had a higher mortality score as compared with patients discharged before the shortage. A quarter of the patients had filled a β-blocker prescription before their index MI hospitalization.

Postdischarge β-Blocker Filling

Overall, nearly two-thirds of patients (n=25 291; 65%) filled a prescription for a β-blocker within 30 days after

discharge from their index hospitalization. During the preshortage period, 70% of patients filled a β-blocker prescription after hospital discharge as compared with 62% of patients during the shortage period. Figure 1 shows the rates of post-MI β-blocker 30-day use, overall and by a β-blocker type, during the study period. During the 3 months before the first recall (September 2008), 98% of patients who filled a metoprolol ER prescription were dispensed a generic product, and 82% of them received a product that was subsequently recalled. The overall rates of post-MI β-blocker use were decreasing by a small but statistically significant amount (Table 2; *P*-value for baseline trend=0.03). Immediately after the recall of the second manufacturer's product, metoprolol ER use started to decrease to a nadir of 11% in June 2010 despite the increase in use of the brand metoprolol ER and generic metoprolol ER products from manufacturers not subject to recalls (Figure 1). Moreover, despite an increase in the use of other β-blockers—metoprolol tartrate, atenolol, and carvedilol (from 50% during the preshortage period to 53% during the shortage period with a peak of 63% in March 2009)—we observed an overall reduction in postdischarge β-blocker use during the shortage period (Table 2; *P*-value for trend during the shortage period=0.001). The use of β-blockers started to increase after the spring of 2010—there was a significant level increase in July 2010, followed by a steady monthly increase during the postshortage period (*P*<0.001).

The rate of post-MI statin filling was relatively constant throughout the study period, with no detectable level or slope change corresponding to the metoprolol ER shortage, and a slight increase in utilization rates during the postshortage period (Figure 2; Table II in the Data Supplement).

Longer-Term Medication Adherence

Rates of β-blocker adherence among those who filled a prescription within 30 days of post-MI discharge were stable during the preshortage period, with an average monthly PDC of 76% (Figure 3; Table 2). The shortage was associated with an immediate decrease in adherence (–4.58% of days covered; *P*<0.0001) and no significant change in the slope (Table 2), corresponding to a mean observed monthly PDC of 70% during the shortage period.

We observed no negative impact of metoprolol ER shortage on adherence to statins; there was a small (0.17% per month) increase in slope during the shortage period (*P*=0.017), followed by decrease (–0.26% per month) during the postshortage period (Figure 3; Table II in the Data Supplement).

Patients with a history of β-blocker use at baseline had better adherence after MI than patients who did not have a β-blocker fill during the 6-month period preceding their MI hospitalization; however, the absolute decrease in adherence during the shortage was similar between these 2 groups (Table III in the Data Supplement). Among patients discharged in 2008, those with the initial β-blocker dispensing of a metoprolol ER product that was subsequently recalled had better adherence before the shortage but a more pronounced decrease in adherence after the second recall, as compared with patients who were started on other β-blockers (Figure II in the Data Supplement).

Rehospitalization

Within 1 year of discharge from the index hospitalization, 1723 (4.4%) patients were rehospitalized for MI or

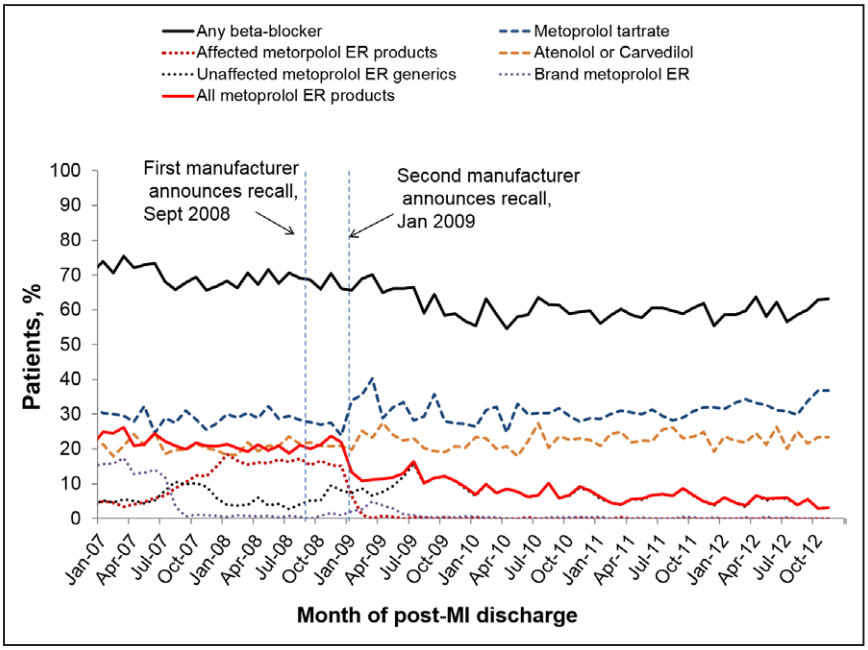

Figure 1. Post–myocardial infarction (MI) β-blocker initiation, overall and by specific β-blocker group, January 2007 to November 2012.
Initiation was evaluated within 30 d of discharge after an MI. ER indicates extended release.

Table 2. Impact of Metoprolol ER Shortage on Post-MI β-Blocker Initiation, Adherence, and Subsequent Clinical Outcomes

	β-Blocker Initiation, % Post-MI Patients	β-Blocker Adherence, % Days Covered	MI/Unstable Angina, Events/100 py	MI/Unstable Angina, Adjusted for Mortality Score, Events/100 py
	Change per Month (95% CI)			
Baseline trend (pre-shortage)	−0.22 (−0.41, −0.03)	−0.06 (−0.14, 0.02)	0.07 (−0.02, 0.16)	0.07 (−0.03, 0.16)
Level change in February 2009	1.39 (−2.10, 4.89)	−4.58 (−6.12, −3.04)	−0.72 (−2.37, 0.94)	−0.72 (−2.39, 0.96)
Change in monthly trend during shortage	−0.57 (−0.90, −0.24)	−0.10 (−0.25, 0.04)	−0.16 (−0.31, −0.004)	−0.16 (−0.32, −0.002)
Level change in July 2010	4.20 (0.98, 7.41)	0.37 (−0.84, 1.58)	0.06 (−1.63, 1.75)	0.06 (−1.72, 1.83)
Change in monthly trend after the shortage	0.81 (0.52, 1.10)	0.09 (−0.11, 0.28)	0.11 (−0.06, 0.28)	0.11 (−0.06, 0.28)

Adherence was evaluated among patients who filled a β-blocker within 30 days after MI discharge. Preshortage period included January 2007 to September 2008; shortage period included February 2009 to June 2010; after the shortage period included July 2010 to November 2012 for β-blocker initiation and July 2010 to December 2011 for adherence and MI/unstable angina rehospitalization; level refers to the immediate impact. Mortality score is Ontario acute myocardial infarction score that predicts 30-day and 1-year mortality.[17] ER indicates extended release; MI, myocardial infarction; and py, person-years.

unstable angina; 4.9% of patients who were discharged between January 2006 and September 2008, 4.4% of patients who were discharged during the shortage period (February 2009–June 2010), and 3.8% of patients who were discharged in the postshortage period (July 2010–November 2012). The average monthly rehospitalization rate was 6.5 events per 100 person-years during the preshortage period, 5.6 events per 100 person-years during the shortage period, and 5.1 events per 100 person-years during the postshortage period. The results of the time series analysis are presented in Table 2 (see Figure I in the Data Supplement for the trend). Controlling for changes in patients' Ontario MI mortality prediction scores did not affect the results (Table 2).

Sensitivity Analyses

Restricting the shortage period to February 2009 to April 2010 period did not substantially change the findings (Table IV in the Data Supplement). Evaluating β-blocker initiation using logistic regression and rehospitalization using a Poisson model provided the estimates that were concordant with findings from the main analyses (Tables V and VI in the Data Supplement). Investigations of nonlinear patterns suggested that changes may have followed a curvilinear trend (Table VII in the Data Supplement); however, except for the outcome of rehospitalization, where the rates were no longer decreasing during the shortage period, there was no substantial impact on the findings.

DISCUSSION

In this large cohort of patients who were discharged after hospitalization for MI, we observed an association between a nationwide metoprolol ER shortage and lower post-MI β-blocker utilization and long-term adher-

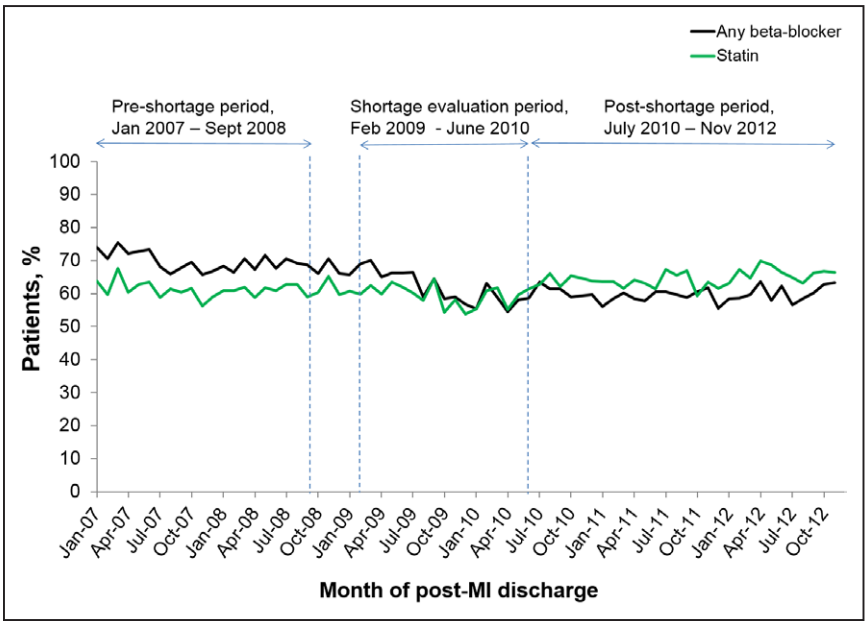

Figure 2. Trends in post–myocardial infarction (MI) β-blocker and statin initiation, January 2007 to November 2012.
Initiation was evaluated within 30 d of discharge after an MI.

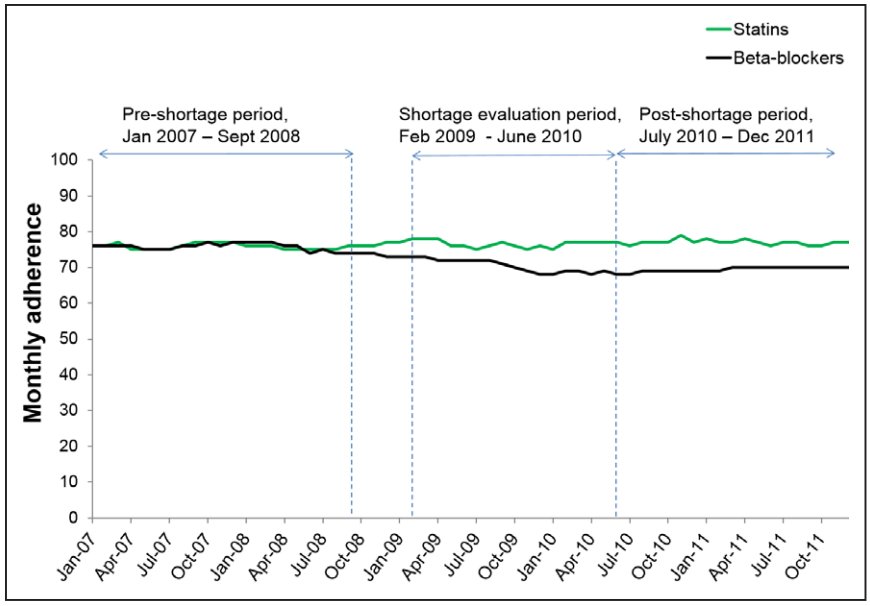

Figure 3. Trends in medication adherence among patients initiating either β-blockers or statins within 30 d after a post–myocardial infarction (MI) discharge, January 2007 to December 2011.
Adherence was evaluated among patients who filled a prescription within 30 d of post-MI discharge. Patients were followed for 1 y, and monthly adherence was calculated as percent of days covered by dispensed medications among patients who were under follow-up during that month.

ence. These results were observed despite an increase in use of other β-blockers, including generic metoprolol ER products that were not affected by recalls and a transient increase in brand metoprolol ER utilization. We did not observe a negative impact of the shortage on 1-year MI or unstable angina rehospitalization rates.

Drug shortages are a common problem in the United States that seems to persist despite legislative efforts and considerable attention from the media, Food and Drug Administration, and professional organizations. Although the number of new drug shortages reported per year has been declining, existing shortages have been slow to resolve and the number of ongoing shortages remains high, placing a substantial burden on patients and the healthcare system.[1–3] Currently, >170 drugs are in short supply, including atenolol, a commonly used β-blocker. The multisource atenolol shortage was announced at the end of July 2017, and despite the drug being made by multiple pharmaceutical companies, as of February 2018, no resolution dates have been announced.

The biggest concern about shortages stems from their potential for adverse clinical effects. A recent study of a 2011 norepinephrine shortage showed a 3.7% increase in in-hospital mortality among patients with septic shock during the shortage period despite the increase in use of other vasopressors.[7] However, for most shortages, data describing potential patient-related outcomes are limited to case reports or survey data,[18,19] which have little utility in risk quantification. The population impacts of shortages of oral medications used for chronic management of medical conditions, in particular, have not been evaluated. Although rarely as acute as shortages of injectable medications, shortages of chronic medications can affect millions of patients, especially if prolonged. They are also more likely to remain invisible to treating providers as they are usually managed by pharmacies. And although many hospitals have strategies in place to ensure treatment continuity during drug shortages,[20] parallel strategies are less common in outpatient setting. Change in formulations (eg, metoprolol succinate to metoprolol tartrate) and therapeutic substitution (eg, metoprolol to atenolol) usually requires a physician authorization and a new prescription, which may be a barrier to treatment continuity. To our knowledge, ours is the first study to evaluate the impact of an outpatient drug shortage on long-term patient outcomes, using a population-based cohort with complete ascertainment of drug utilization and longitudinal follow-up.

Although we observed a decrease in β-blocker utilization and adherence during the shortage, there did not appear to be a negative effect on MI/angina rehospitalization rates in our cohort. There are several potential explanations for why the reduction in β-blocker use and adherence that we observed did not translate into adverse clinical consequences. First, although US guidelines recommend using β-blockers for all patients with acute MI,[8,9] the evidence of clinical benefit associated with the use of these drugs in this context is inconsistent, with some studies suggesting that the benefits are small, if any, in asymptomatic patients or patients free of heart failure.[21–23] Only 10% of patients in our study had either a diagnosis of heart failure or a dispensing of loop diuretics in the 6 months before their index MI. Thus, it is possible that patients who did not fill post-MI β-blocker prescriptions would not have benefited from such therapy. Second, even among patients who stood to benefit from β-blockers, it is possible that a larger reduction in β-blocker use and adherence than we observed would have been needed to produce a clinically meaningful impact on the rate of

subsequent cardiovascular events. Although the average monthly adherence declined during the shortage, it never dropped <68%, an 8%-absolute reduction from the average monthly adherence during the preshortage period.

Third, the recalls that led to metoprolol ER shortage were caused by manufacturing issues. To the extent that manufacturing issues might have led to patients receiving subtherapeutic doses before recalls, the higher rates we observed during the preshortage period could be at least partially explained by ineffective metoprolol ER tablets, a hypothesis not directly verifiable in our data, but worth exploring in future studies. Finally, other changes in the treatment of MI at the time of the shortage could have mitigated the impact of decreased β-blocker use. The incidence of MI, and particularly ST-elevation MI, has been decreasing steadily since 2005.[24] We are unaware of any interventions or changes in the treatment of MI that could have differentially impacted patients during the time of metoprolol ER shortage. However, confounding by simultaneously occurring changes, including a greater use of $4 generic β-blockers that would not be captured in insurance claims,[25] cannot be completely ruled out.

A few additional limitations should be noted. Because of administrative nature of the data, we could only evaluate outcomes severe enough to warrant a hospitalization. Thus, the results may not be generalizable to less severe angina symptoms or worsening of health that are treated in outpatient settings. In addition, the study population comprised commercially insured patients with an average age of 60 years, and the findings may not be generalizable to other populations, including older patients who may have higher rates of MI and unstable angina, or uninsured patients, who may be less likely to buy a more expensive substitute. Some data on β-blocker use may be missing if patients opted to use $4 generics or a similar low cost program, paid for their medications out-of-pocket, or had secondary coverage for prescription medications. Unless the use of these programs in our study population changed during the shortage period as compared with either pre- or postshortage periods, this type of missingness should not have affected our findings.

Last, although interrupted time series design with a control group is the strongest quasiexperimental method to evaluate changes because of interventions, as with any nonrandomized data, confounding can not be completely ruled out. In a time series design, however, potential confounding is limited to factors related to the outcome that change at the time of the intervention.[15] We evaluated patient characteristics in our cohort before, during, and after the shortage and did not observe any significant changes. Neither are we aware of any changes in post-MI treatment, prescription coverage, or adherence interventions that were occurring during the metoprolol ER 2009 to 2010 shortage. Nevertheless, confounding because of changing patient characteristics or simultaneously occurring interventions is possible.

CONCLUSIONS

The nationwide metoprolol ER shortage in the United States was associated with fewer patients receiving any post-MI β-blocker and lower adherence to β-blocker therapy for those who did receive it; however, no population-level impact on 1-year MI or angina rehospitalization was observed in this cohort of patients. Given the impact that the shortage had on β-blocker initiation and adherence and the persistent nature of drug shortages in the United States, more attention should be given to shortages of common chronic medications and their impact on patients. In particular, patients, physicians, and pharmacists need to be aware of the ongoing shortages and work together to ensure that patients continue to receive appropriate treatment.

ARTICLE INFORMATION

Received November 21, 2017; accepted September 5, 2018.

The Data Supplement is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCOUTCOMES.117.004096.

Correspondence

Katsiaryna Bykov, PharmD, ScD, Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital and Harvard Medical School, 1620 Tremont St, Suite 3030, Boston, MA 02120. Email kbykov@partners.org

Affiliations

Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine (K.B., J.J.G., B.W., N.K.C.) and Center for Healthcare Delivery Sciences (N.K.C.), Brigham and Women's Hospital and Harvard Medical School, Boston, MA. Departments of Epidemiology (J.J.G.) and Health Policy and Management (N.K.C.), Harvard T.H. Chan School of Public Health, Boston, MA. Department of Medicine, Stanford University School of Medicine, CA (B.W.).

Disclosures

K. Bykov has received support from Harvard T.H. Chan School of Public Health (partially supported by an unrestricted training grant from Takeda). J.J. Gagne was a Principal Investigator of a grant from Novartis Pharmaceuticals Corporation and a grant from Eli Lilly and company, both to Brigham and Women's Hospital for unrelated work. J.J. Gagne is a consultant to Aetion, Inc and to Optum, Inc for unrelated work. The other authors report no conflicts.

REFERENCES

1. Fox ER, Sweet BV, Jensen V. Drug shortages: a complex health care crisis. *Mayo Clin Proc*. 2014;89:361–373. doi: 10.1016/j.mayocp.2013.11.014
2. Chen SI, Fox ER, Hall MK, Ross JS, Bucholz EM, Krumholz HM, Venkatesh AK. Despite federal legislation, shortages of drugs used in acute care settings remain persistent and prolonged. *Health Aff (Millwood)*. 2016;35:798–804. doi: 10.1377/hlthaff.2015.1157
3. United States Government Accountability Office. Drug Shortages: Public Health Threat Continues, Despite Efforts to Help Ensure Product Availability. 2014. http://www.gao.gov/products/GAO-14–194. Accessed June 5, 2017.

4. American Society of Health-System Pharmacists. Drug Shortages: Current Drug Shortages. 2018. https://www.ashp.org/Drug-Shortages/Current-Shortages/Drug-Shortages-List?page=CurrentShortages. Accessed July 1, 2018.
5. Decamp M, Joffe S, Fernandez CV, Faden RR, Unguru Y; Working Group on Chemotherapy Drug Shortages in Pediatric Oncology. Chemotherapy drug shortages in pediatric oncology: a consensus statement. *Pediatrics*. 2014;133:e716–e724. doi: 10.1542/peds.2013-2946
6. Gatesman ML, Smith TJ. The shortage of essential chemotherapy drugs in the United States. *N Engl J Med*. 2011;365:1653–1655. doi: 10.1056/NEJMp1109772
7. Vail E, Gershengorn HB, Hua M, Walkey AJ, Rubenfeld G, Wunsch H. Association between US norepinephrine shortage and mortality among patients with septic shock. *JAMA*. 2017;317:1433–1442. doi: 10.1001/jama.2017.2841
8. O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX, Anderson JL, Jacobs AK, Halperin JL, Albert NM, Brindis RG, Creager MA, DeMets D, Guyton RA, Hochman JS, Kovacs RJ, Kushner FG, Ohman EM, Stevenson WG, Yancy CW; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;127:e362–e425. doi: 10.1161/CIR.0b013e3182742cf6
9. Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Jr, Ganiats TG, Holmes DR Jr, Jaffe AS, Jneid H, Kelly RF, Kontos MC, Levine GN, Liebson PR, Mukherjee D, Peterson ED, Sabatine MS, Smalling RW, Zieman SJ, Members AATF. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;130:e344–e426.
10. American Society of Health-System Pharmacists (ASHP). Metoprolol Succinate Extended Release Tablets. 2011. http://www.ashp.org/menu/DrugShortages/ResolvedShortages/Bulletin.aspx?id=507. Accessed July 4, 2016.
11. Biospace. ETHEX Corporation (KVa) Issues Nationwide Voluntary Recall of Products. 2009. http://www.biospace.com/News/ethex-corporation-issues-nationwide-voluntary/124256. Accessed June 3, 2017.
12. The United States Department of Justice. United States Files Suit Against Missouri-Based Pharmaceutical to Block Manufacturing and Shipping of Unapproved Drugs. 2009. https://www.justice.gov/opa/pr/united-states-files-suit-against-missouri-based-pharmaceutical-block-manufacturing-and. Accessed July 3, 2017.
13. Kiyota Y, Schneeweiss S, Glynn RJ, Cannuscio CC, Avorn J, Solomon DH. Accuracy of Medicare claims-based diagnosis of acute myocardial infarction: estimating positive predictive value on the basis of review of hospital records. *Am Heart J*. 2004;148:99–104. doi: 10.1016/j.ahj.2004.02.013
14. Karve S, Cleves MA, Helm M, Hudson TJ, West DS, Martin BC. Prospective validation of eight different adherence measures for use with administrative claims data among patients with schizophrenia. *Value Health*. 2009;12:989–995. doi: 10.1111/j.1524-4733.2009.00543.x
15. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. *J Clin Pharm Ther*. 2002;27:299–309.
16. Gillings D, Makuc D, Siegel E. Analysis of interrupted time series mortality trends: an example to evaluate regionalized perinatal care. *Am J Public Health*. 1981;71:38–46.
17. Tu JV, Austin PC, Walld R, Roos L, Agras J, McDonald KM. Development and validation of the Ontario acute myocardial infarction mortality prediction rules. *J Am Coll Cardiol*. 2001;37:992–997.
18. Institute for Safe Medication Practices. A shortage of Everything Except Errors: Harm Associated With Drug Shortages. 2012. https://www.ismp.org/resources/shortage-everything-except-errors-harm-associated-drug-shortages. Accessed September 6, 2018.
19. Institute for Safe Medication Practices. Drug Shortages: National Survey Reveals High Level of Frustration, Low Level of Safety. 2010. http://www.ismp.org/newsletters/acutecare/articles/20100923.asp. Accessed June 5, 2017.
20. Fox ER, Birt A, James KB, Kokko H, Salverson S, Soflin DL. ASHP Guidelines on managing drug product shortages in hospitals and health systems. *Am J Health Syst Pharm*. 2009;66:1399–1406.
21. Huang BT, Huang FY, Zuo ZL, Liao YB, Heng Y, Wang PJ, Gui YY, Xia TL, Xin ZM, Liu W, Zhang C, Chen SJ, Pu XB, Chen M, Huang DJ. Meta-analysis of relation between oral β-blocker therapy and outcomes in patients with acute myocardial infarction who underwent percutaneous coronary intervention. *Am J Cardiol*. 2015;115:1529–1538. doi: 10.1016/j.amjcard.2015.02.057
22. Dondo TB, Hall M, West RM, Jernberg T, Lindahl B, Bueno H, Danchin N, Deanfield JE, Hemingway H, Fox KAA, Timmis AD, Gale CP. β-blockers and mortality after acute myocardial infarction in patients without heart failure or ventricular dysfunction. *J Am Coll Cardiol*. 2017;69:2710–2720. doi: 10.1016/j.jacc.2017.03.578
23. Bangalore S, Steg G, Deedwania P, Crowley K, Eagle KA, Goto S, Ohman EM, Cannon CP, Smith SC, Zeymer U, Hoffman EB, Messerli FH, Bhatt DL; REACH Registry Investigators. β-Blocker use and clinical outcomes in stable outpatients with and without coronary artery disease. *JAMA*. 2012;308:1340–1349. doi: 10.1001/jama.2012.12559
24. Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. *N Engl J Med*. 2010;362:2155–2165. doi: 10.1056/NEJMoa0908610
25. Choudhry NK, Shrank WH. Four-dollar generics–increased accessibility, impaired quality assurance. *N Engl J Med*. 2010;363:1885–1887. doi: 10.1056/NEJMp1006189