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.
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. As of July 2018, there were 178 current drug shortages in the United States, affecting such common medications as atenolol, furosemide, and heparin. 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. 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). 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. In September 2008, Sandoz recalled all of its metoprolol extended release products occurred in the United States in 2009 and lasted ≈2 years.

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.

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 38,914 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.

In each month from January 2006 to November 2012, we identified patients discharged from hospitalizations after MI. Following a validated algorithm, 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 switching from metoprolol ER products to immediate-release versions were reported, the impact of this shortage on patient outcomes at the population level is not known.
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. 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. 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:

\[ Y_t = \beta_0 + \beta_1 \times \text{time}_t + \beta_2 \times \text{change point}_1 + \beta_3 \times \text{change point}_2 + \beta_4 \times \text{time after change point}_1 + \beta_5 \times \text{change point}_2 + \beta_6 \times \text{time after change point}_2 + \epsilon_t \]

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
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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. 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.
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...
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-

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

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

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.
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

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.
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 2005.14 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 cannot 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

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