Circulation

RESEARCH LETTER

Population Impact of Generic Valsartan Recall

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On July 9, 2018, Health Canada announced a voluntary recall of 6 generic valsartan products because a known carcinogen N-nitrosodimethylamine was detected.[1] In total, more than 22 countries, including the United States, initiated recalls. Despite an increase in drug recalls, few studies have evaluated their impact.[2,3] The valsartan recall of a frequently used oral medication for high prevalence chronic conditions, such as hypertension, provides an opportunity to examine the consequences of a drug recall by patients and health care systems.

We used a segmented regression analysis using multiple linked healthcare databases in Ontario, Canada, including the Ontario Drug Benefit prescription claims database to identify our cohort of recalled valsartan users and ascertain nonvalsartan medication use, the Ontario Registered Persons database for vital status, Canadian Institute for Health Information for discharge diagnoses for hospital admissions, baseline comorbidities, and clinical outcomes, National Ambulatory Care Reporting System database for emergency department (ED) visits, and the Statistics Canada census database for income datasets. These datasets were linked using unique encoded identifiers and analyzed at ICES. We included patients ≥65 years old who had been dispensed a supply of at least 1 recalled valsartan product that would cover the period up to and including the date of July 9, 2018, and were alive on this date.

We characterized changes in prescription patterns in recalled valsartan users before and after the July 9, 2018, recall date, the index date at which point 100% of patients in our cohort were taking a recalled valsartan product. We computed monthly rates of ED visits and hospitalizations for hypertension, heart failure, myocardial infarction, and stroke/transient ischemic attack as primary diagnoses from January 9, 2017, through January 9, 2019. We fit segmented regression models using 3 variables: baseline monthly change in the rate of the outcome before the recall, monthly change in rate after the recall, and an indicator variable representing an immediate jump in the rate at the time of the recall; all entered into the autoregressive model with identified lags using SAS version 9.3 (SAS Institute, Cary, NC). Data use in this study was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require Research Ethics Board review, but was approved by ICES' Privacy and Legal Office.

There were 55 461 patients in our sample. The mean age was 76.3±7.7 years, 41.5% were male, and 95.0% of patients had hypertension, while 5.0% had heart failure. The majority of patients changed to a nonvalsartan angiotensin-receptor-antagonist (73.8%) or a nonrecalled valsartan product (8.8%) within 1 month of the recall, with 84.4% of patients filling a new prescription for a likely alternative to their recalled valsartan. At 3 months, 10.7% of recalled valsartan users did not fill an alternative medication. (Figure)

Key Words: angiotensin receptor antagonists ■ drug recalls ■ drug utilization ■ health services research ■ hypertension

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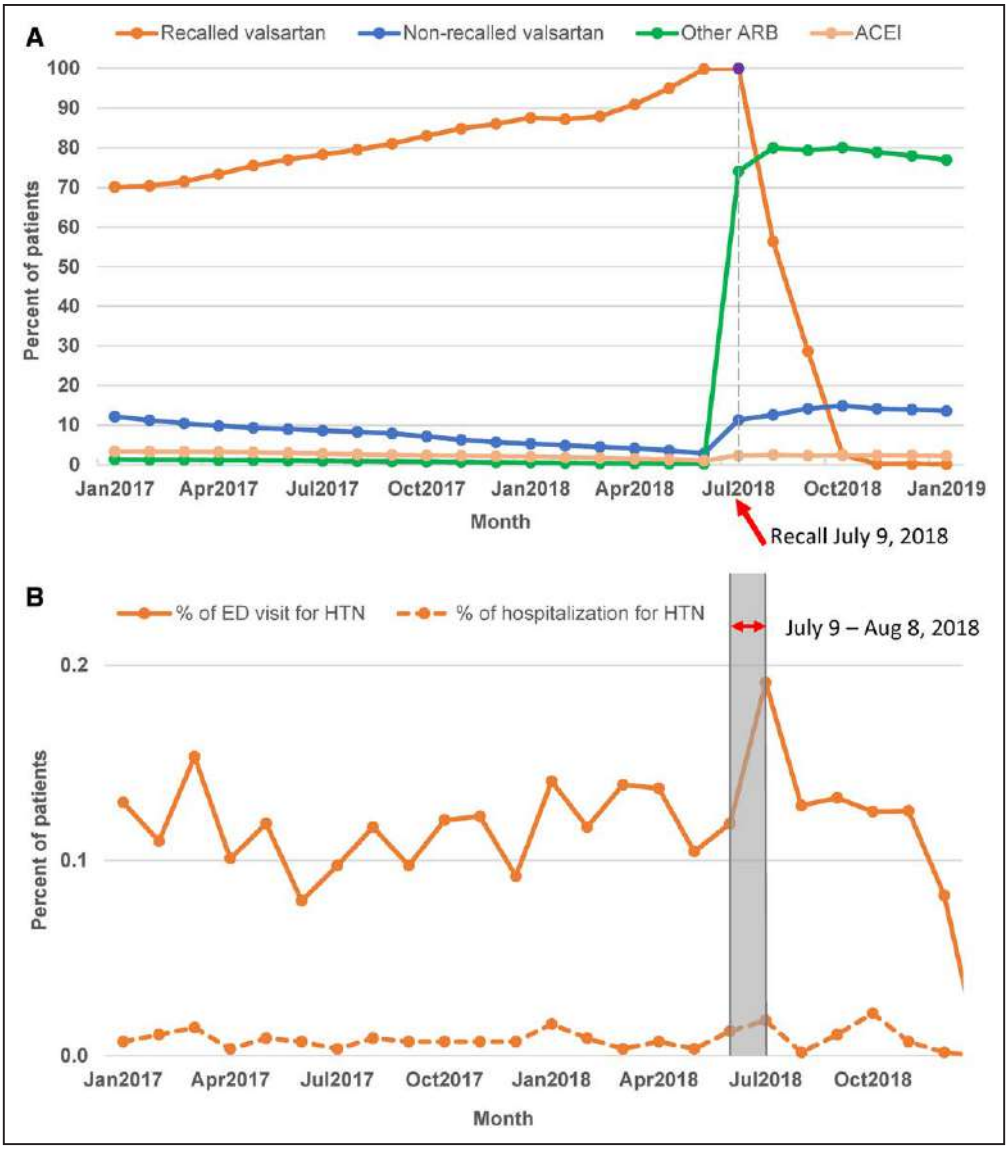

Figure. Medication utilization, emergency department (ED) visits and hospitalizations for primary diagnosis of hypertension before and after July 9, 2018, valsartan recall.

A, Percentage of patients dispensed recalled valsartan, nonrecalled valsartan, other ARB, and ACEI monthly before and after the valsartan recall index date of July 9, 2018. **B**, Percentage of patients with ED visits and hospitalizations for a primary diagnosis of hypertension monthly before and after the valsartan recall index date of July 9, 2018. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; and HTN, hypertension.

Before the recall, 0.11% of the cohort had ED visits for hypertension per month, with no monthly change in the rate of ED visits for hypertension before the recall (P=0.68). After the recall, there was an immediate increase in ED visits for hypertension to 0.17%/month (P=0.02), with a declining temporal trend after the recall (P=0.04). (Figure) There was no change in the rate of hospitalizations for hypertension (immediate level: P=0.18; postrecall trend: P=0.78). Although there were no immediate changes in ED visits (P=0.32) or hospitalizations (P=0.50) for stroke/transient ischemic attack, there was an increasing postrecall temporal trend in ED visits of 6% (P=0.020) and hospitalizations of 8% (P=0.037). There were no immediate or sustained postrecall changes in ED visits or hospitalizations for myocardial infarction or heart failure (P≥0.16 for each).

We found that prescriptions dispensed for recalled valsartan sharply decreased immediately after the recall date. However, there was an incomplete replacement of valsartan with alternative products, with 1 in 10 patients not receiving an alternative antihypertensive agent. Moreover, we observed an immediate increase in ED visits for hypertension and a delayed increase in ED visits and hospitalizations for stroke/transient ischemic attack following the recall. It is uncertain whether the increased ED visits reflect excess healthcare utilization by patients seeking replacement prescriptions for their recalled valsartan, or encounters for loss of hypertension control. However, these findings highlight

the potential burden and risks associated with recalls of chronic oral medications used by large populations.[4]

While government agencies issued advisories to continue taking medications until contacting their prescribers, there is a high potential for misunderstanding by patients, particularly given the mass media news that may have heightened the alarm regarding the potential negative consequences of the recalled products on their health.[1,2,5] Patients may have been willing to risk the short term potential of uncontrolled hypertension to avoid ingesting a potential carcinogen. The increase in ED visits for hypertension in our primarily hypertensive sample suggests that the lack of replacement of recalled valsartan was associated with increased healthcare utilization and may have been associated with adverse unintended clinical effects of uncontrolled hypertension in the setting of the valsartan recall. Limitations of our study include the use of administrative data, which does not include patient-stated reasons for ED visits or hospitalizations, and lack of a control group.

ARTICLE INFORMATION

Data sharing: The dataset from this study is held securely in coded form at ICES. While data sharing agreements prohibit ICES from making the dataset publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at www.ices.on.ca/DAS.

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