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Valsartan, Losartan and Irbesartan use in the USA, UK, Canada and Denmark after the nitrosamine recalls: a descriptive cohort study

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ABSTRACT

Objectives To examine valsartan, losartan and irbesartan usage and switching patterns in the USA, UK, Canada and Denmark before and after July 2018, when the first Angiotensin-Receptor-Blocker (ARB) (valsartan) was recalled.

Design Retrospective cohort study.

Setting USA, Canadian administrative healthcare data, Danish National Prescription Registry and UK primary care electronic health records.

Participants Patients aged 18 years and older between January 2014 and December 2020.

Intervention Valsartan, losartan and irbesartan.

Main outcome Monthly percentages of individual ARB episodes, new users and switches to another ARB, ACE inhibitors (ACEI) or calcium channel blockers containing products.

Results We identified 10.8, 3.2, 1.8 and 1.2 million ARB users in the USA, UK, Canada and Denmark, respectively. Overall proportions of valsartan, losartan and irbesartan use were 18.4%, 67.9% and 5.2% in the USA; 3.1%, 48.3% and 10.2% in the UK, 16.3%, 11.4% and 18.3% in Canada, 1%, 93.5% and 0.6% in Denmark. In July 2018, we observed an immediate steep decline in the proportion of valsartan use in the USA and Canada. A similar trend was observed in Denmark; however, the decline was only minimal. We observed no change in trends of ARB use in the UK. Accompanying the valsartan decline was an increase in switching to other ARBs in the USA, Canada and Denmark. There was a small increase in switching to ACEI relative to the valsartan-to-other-ARBs switch. We also observed increased switching from other affected ARBs, losartan and irbesartan, to other ARBs throughout 2019, in the USA and Canada, although the usage trends in the USA remained unchanged.

Conclusion The first recall notice for valsartan resulted in substantial decline in usage due to increased switching to other ARBs. Subsequent notices for losartan and irbesartan were also associated with increased switching around the time of the recall, however, overall usage trends remained unchanged.
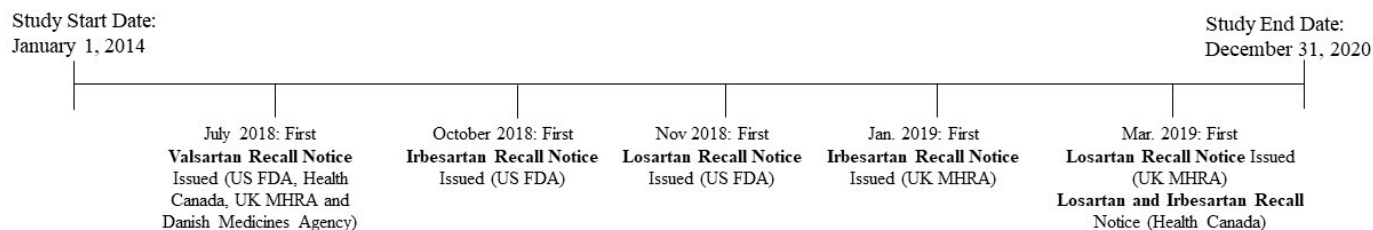
INTRODUCTION

In July 2018, several regulatory agencies around the world notified the public about

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study allowed for a comprehensive examination and comparison of switching patterns among Angiotensin-Receptor-Blocker (ARB) users in four different countries following the recall notice.
⇒ The study was limited by the inability to classify the affected ARB products into contaminated and uncontaminated categories.
⇒ We were unable to capture reasons for the increased switching immediately after recall of the affected products, although switching patterns prior to the notice were stable.

the presence of a potential carcinogenic impurity, N-nitrosodimethylamine (NDMA) in valsartan-containing products, due to changes in the manufacturing process at Zhejiang Huahai Pharmaceuticals as far back as 2012.[1–4] NDMA is one of several nitrosamine compounds considered a probable human carcinogen.[5] Regulatory agencies immediately began investigating and confirmed that nitrosamines in valsartan products were generated during the active pharmaceutical ingredient (API) chemical synthesis. Angiotensin-Receptor-Blockers (ARBs) with a tetrazole ring (candesartan, irbesartan, losartan, olmesartan, telmisartan and valsartan) were at risk since similar manufacturing processes were used in their API synthesis. Food and Drug Administration (FDA) further alerted the public to nitrosamine contamination in certain lots of irbesartan and losartan in October and November 2018, respectively. In the UK and Canada, recall notices were issued in January and March 2019 for losartan and irbesartan (figure 1). In the USA, more valsartan products (n=624) were recalled compared with

Study Start Date:
January 1, 2014

Study End Date:
December 31, 2020

| July 2018: First **Valsartan Recall Notice** Issued (US FDA, Health Canada, UK MHRA and Danish Medicines Agency) | October 2018: First **Irbesartan Recall Notice** Issued (US FDA) | Nov 2018: First **Losartan Recall Notice** Issued (US FDA) | Jan. 2019: First **Irbesartan Recall Notice** Issued (UK MHRA) | Mar. 2019: First **Losartan Recall Notice** Issued (UK MHRA) **Losartan and Irbesartan Recall** Notice (Health Canada) |

Figure 1 Timeline of nitrosamine recalls issued in the USA, Canada, Denmark and the UK. FDA, Food and Drug Administration; MHRA, Medicines and Healthcare products Regulatory Agency.

losartan (n=500) and irbesartan (n=122) products. Similar trends were observed in the other countries. Since then, nitrosamine contamination has become a global topic of interest, affecting other therapeutic products, including metformin, ranitidine, rifampin/rifapentine and varenicline.[6]

FDA and the other regulatory agencies determined that the risk for cancer associated with the nitrosamine impurity was extremely low and advised patients to continue taking their medicine until there was a replacement ARB (either the same API or a different ARB) or different treatment option. This was based on data from animal and other studies that showed that consuming up to 96 ng NDMA per day is considered reasonably safe.[7] Since cancer risk depends on both dose and years of exposure, it was determined that if 8000 patients took the maximum recommended daily dose of valsartan (320 mg daily) for 4 years, there may be one additional cancer case. Interim limits for several nitrosamines and the maximum recommended daily dose for ARBs were published shortly after the recall notice. To enable patients to remain on their current API ARB, lists of contaminated ARB products were continually published and updated following the issuance of recall notices. However, it is unclear how usage trends were altered by these recalls. Regulatory communications and recalls are essential for safeguarding public health, and regulatory agencies are increasingly interested in the impact of their communications on drug adherence and use. Therefore, we sought to examine trends in ARB usage, from 2014 through 2020 in four countries. Healthcare data from the USA, four Canadian provinces, the UK and Denmark were converted to Sentinel's standardised common data model, allowing for the deployment of the same analysis in the four databases.

METHODS
Data sources
We analysed data from four countries: US data from the FDA's Sentinel System; data from the Canadian provinces of Manitoba, Nova Scotia, Ontario and Saskatchewan obtained by the Canadian Network for Observational Drug Effects (CNODES); Danish data from the Danish National Prescription Registry (DNPR) and the National Patient Register and the Clinical Practice Research Datalink (CPRD) provided data for the UK. Additional data source descriptions are provided in appendixonline supplemental appendix.

Study cohorts
This retrospective descriptive cohort study was conducted using data from 1 January 2014 through 31 December 2020, or the last date of available data. The prevalent user cohort included patients aged 18 years and older with a dispensing or prescription (CPRD and DNPR) of any of the eight available ARB products (azilsartan, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan) and excluded patients who had evidence of use of another ARB's on the index ARB dispensing date (index date). We also required patients to have medical and drug coverage in the 183 days prior to their index date. We identified an incident user cohort of patients with no ARB dispensing/prescription in the 183 days prior to index ARB dispensing date. For this study, we include both single ingredient and combination (ARB-combination and ACE inhibitors (ACEI)-combination) products.

Patient and public involvement
Due to the descriptive nature of the study and the use of retrospective administrative billing data, there was no patient engagement prior to conducting the study.

Exposure episodes and switching
We created exposure episodes based on the number of days of product supplied per dispensing or the number of days the product was prescribed by bridging together episodes less than 30 days apart and adding 30 days to the end of each episode. Further, we bridged together consecutive dispensings that had 33% overlap in days' supply. Patients could switch from any of the eight index ARBs to another ARB (non-index ARB) that is, switch to a different drug within the ARB class, ACEI, calcium channel blockers (CCB) or ACEI/CCB combination drugs. We did not consider a switch to a diuretic product, since this class of antihypertensives may be an initial or add-on therapy, making it challenging to consider a new dispensing of a diuretic, a switch. We defined a switch as a when dispensing or a prescription for a switch product occurred during an index ARB exposure episode. When no switch occurred, patients were censored at first occurrence of disenrolment, death, the end of the data provided by each data partner or product discontinuation.

STATISTICAL ANALYSIS
ARB usage trends
We calculated the monthly percentage of individual ARB usage as the number of the specific ARB episodes that spanned a given month divided by any ARB episodes that spanned the same month. We also calculated the monthly percentage of new ARB users as the number of new users for each individual ARB divided by the total new ARB users, in each month.

Switching analysis
We computed the proportion of switching defined as the number of the index ARB episodes that resulted in a switch to either a non-index ARB, ACEI or CCB, divided by the total number of index ARB episodes, for each quarter. We also examined the distribution of the non-index ARB products after the switch from three affected ARBs (valsartan, losartan and irbesartan).

Interrupted time series analysis
We conducted interrupted time series (ITS) analysis of the monthly panel data for each individual ARB to examine the impact of the recall notice on each ARB usage. We examined (1) the change in the monthly proportions (level change) of individual ARB usage immediately after the recall notice (July 2018) and (2) the change in trend in the monthly proportions (trend change) of individual ARB usage before and after the recall notice. We also performed a controlled ITS (CITS) analysis looking at the difference in levels and trends between valsartan (reference) and the top three frequently used ARBs for each country. Additionally, we considered three sensitivity analyses: first, we treated July 2018 to October 2018 as a transition period for the effect of the recall to take place and excluded this period from the primary analyses. Second, due to differences in the number of available time points for each data source, we selected the same number of time points before and after the recall notice for all data sources, spanning September 2016 to May 2020 (22-time points before and after July 2018). Finally, we considered a randomly selected, false intervention date (July 2016) to investigate whether the level and trend change observed in the primary ITS analyses were because of the recall notice or due to seasonal trend changes. The ITS analyses were conducted using SAS autoregressive procedure (PROC AUTOREG) SAS Studio, 2012–2020, SAS Institute, Cary, North Carolina, USA. All data are deidentified and this study was conducted as a public health surveillance activity under the authority of the FDA and, accordingly, is not subject to Institutional Review Board oversight.[8–10]

RESULTS
During the study period, we identified 10 836 991; 3 270 823; 1 775 080; and 1 153 841 ARB users in the USA, UK, Canada and Denmark, respectively. The overall proportions of valsartan, losartan and irbesartan use were 18.4%, 67.9% and 5.2% in the USA; 3.1%, 48.3% and 10.2% in the UK, 16.3%, 11.4% and 18.3% in Canada, 1%, 93.5% and 0.6% in Denmark (table 1). Most ARB users were aged 65 years and older, although in Denmark, there was a high proportion of 45–64 years old users compared with the other countries. Generally, there was a higher proportion of female users than male users across all countries. Prominent co-morbid conditions among ARB users were hypertension and diabetes in the USA, Canada and the UK.

ARB usage trends
The monthly trends for the percentage of individual ARB usage differed by country (figure 2).

USA
For the USA, over time, losartan accounted for the largest share of ARB episodes, followed by valsartan. After June 2018, a gradual decline for valsartan monthly proportions started from 21% (June 2018) to 11% (November 2018). The decline in valsartan episodes was accompanied by an increase in losartan (67%–72%), olmesartan (5%–6%) and olmesartan (4%–6%) episodes for the same time period (figure 2). Visual trends are also supported by ITS analyses (table 2), with significant level change for valsartan (−6.4%) and losartan (2.9%). Smaller but statistically significant increases in level changes were also observed for olmesartan, telmisartan, irbesartan and candesartan. CITS analyses confirmed that the decrease in valsartan use after the recall (changes in both level and trend) was significantly lower than those of losartan, olmesartan and irbesartan (online supplemental table 1).

Canada
For Canada, over time, candesartan and valsartan accounted for the largest share of ARB episodes, followed by telmisartan and irbesartan. Like the USA, we also observed a decline in valsartan use from June 2018 (21%) to November 2018 (9%) (figure 2). A sustained increase in candesartan use (20%–23%), telmisartan (18%–20%) and irbesartan (16%–17%) was observed for the same period. ITS analyses (table 2) confirmed significant level and trend changes for valsartan (−8%). Significant level change was observed for telmisartan, olmesartan and losartan (table 2). The level change for valsartan was significantly higher (ie, larger decrease in use) than those for candesartan, telmisartan and irbesartan (online supplemental table 1).

Denmark
For Denmark, losartan contributed over 90% of ARB episodes with valsartan contributing around 1% of the total ARB episodes. There was a small but significant change in the level of valsartan use (−0.04%; p=0.04) accompanied by an increased use in losartan (0.13%; p=0.02) (table 1). The level and trend changes for valsartan was significantly higher (ie, larger decrease in use) compared with candesartan, telmisartan and irbesartan (online supplemental table 1).

Table 1 Selected demographic and clinical characteristics for all Angiotensin-Receptor-Blockers displayed by country

Characteristics	USA (%)	Canada (%)	Denmark (%)	UK (%)
Number of ARB users	10 836 991	1 775 080	1 153 841	3 270 823
Number of episodes*	22 406 719	798 231	492 229	578 652
Individual ARB episodes				
Azilsartan	0.6	–	–	0.005
Candesartan	0.9	27.5	4.8	34.2
Eprosartan	0.006	–	–	0.4
Irbesartan	5.2	18.3	0.6	10.2
Losartan	67.9	11.4	93.5	48.3
Olmesartan	8.6	12.2	–	2.3
Telmisartan	2.2	21.1	0.4	1.9
Valsartan	18.4	16.3	1.0	3.1
Age				
18–44 years	5.5	3.5	5.6	3.6
45–64 years	25.8	17.6	39.1	32.8
≥65 years	68.7	78.9	55.3	63.7
Gender				
Female	55.9	54.5	51.4	53.5
Male	44.1	45.5	48.6	46.5
Race				
American Indian or Alaska Native	0.3	NR	NR	NR
Asian	2.4	NR	NR	NR
Black or African American	10.0	NR	NR	NR
Native Hawaiian or Other Pacific Islander	0.2	NR	NR	NR
White	56.7	NR	NR	NR
Unknown	30.3	NR	NR	NR
Ethnicity		NR	NR	NR
Hispanic origin	2.3	NR	NR	NR
Clinical history†				
Angina	17.4	3.4	NR	0.8
Atrial fibrillation	10.9	5.6	NR	2.4
Diabetes	36.6	25.0	NR	13.2
Heart failure	12.3	4.1	NR	1.6
Hyperlipidaemia	57.2	4.7	NR	0.9
Hypertension	86.1	46.1	NR	25.3
Myocardial infarction	2.2	1.1	NR	0.7
Renal disorders	20.7	5.4	NR	2.8
Stroke	4.7	1.8	NR	1.6

*An ARB episode occurs when ARB dispensings are bridged together ensuring continuous exposure to an ARB. The number of days of product supplied per dispensing or the number of days the product was prescribed by bridging together episodes less than 30 days apart and adding 30 days to the end of each episode.
†Clinical History collected 183 days before the index date.
NR, not reported.

UK

For the UK, candesartan and losartan accounted for over 80% of the ARB prescriptions, with valsartan contributing around 3% of the total ARB prescriptions. No visual or statistically significant changes were observed for valsartan and the other ARBs (figure 2 and table 2). The level and trend changes for valsartan were mostly similar to candesartan, losartan and irbesartan (online supplemental table 1).

Sensitivity ITS analyses

Excluding the transition period (online supplemental table 2) strengthened the valsartan decline in the USA (from −6.4% to 10%), Canada (−8% to −12.2%) and in
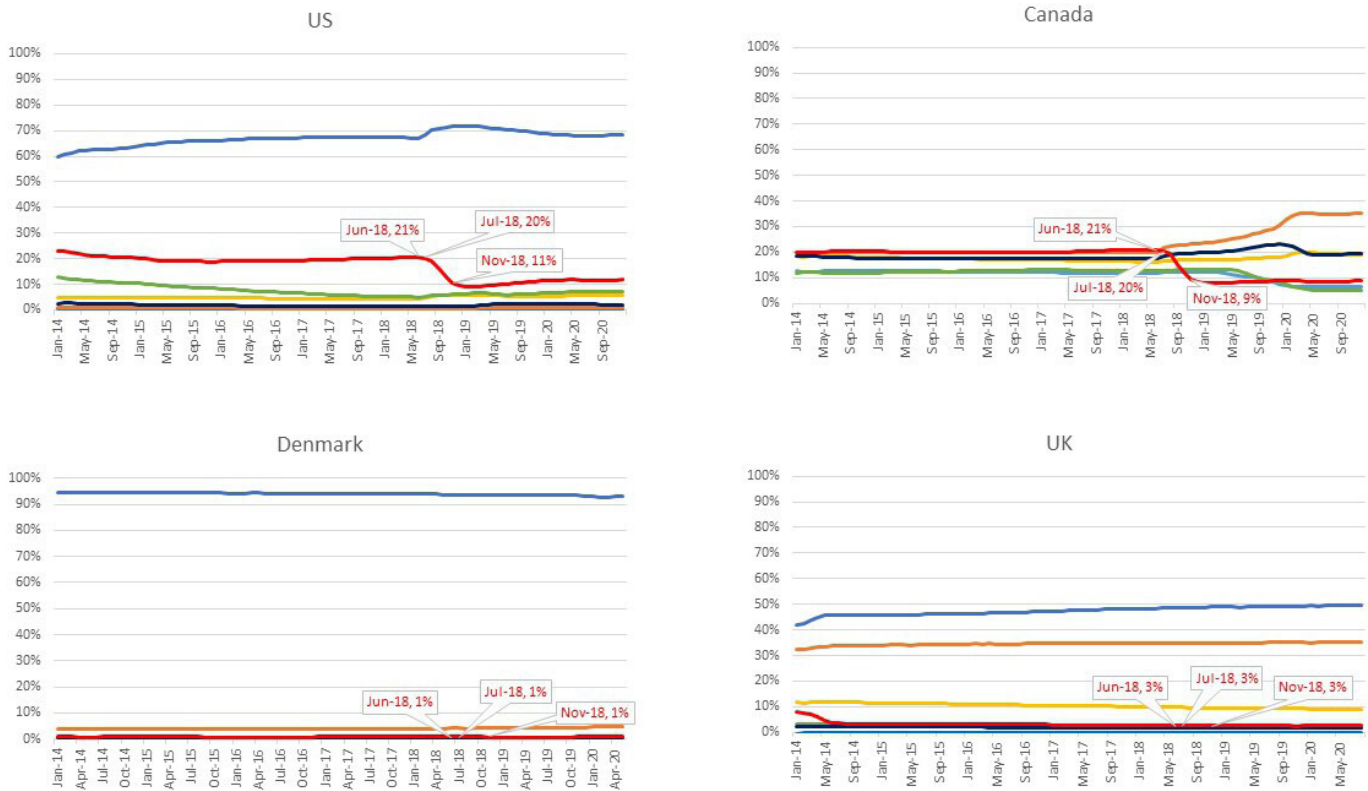
Figure 2 Monthly Angiotensin-Receptor-Blockers use trends between January 2014 and end of available data or December 2020 by country. Monthly ARB proportions represent the number of individual ARB episodes that span the month divided by the total number of any ARB episodes that span the same month. Data callouts represent the month-year, monthly percentage (%) for valsartan only.

Denmark (−0.04% to −0.1%). Using equal time points prior to and after the intervention date (online supplemental tables 3a and 3b) were consistent with the primary findings. The level changes observed using the random negative control period was no longer significant or in the opposite direction (online supplemental table 4).
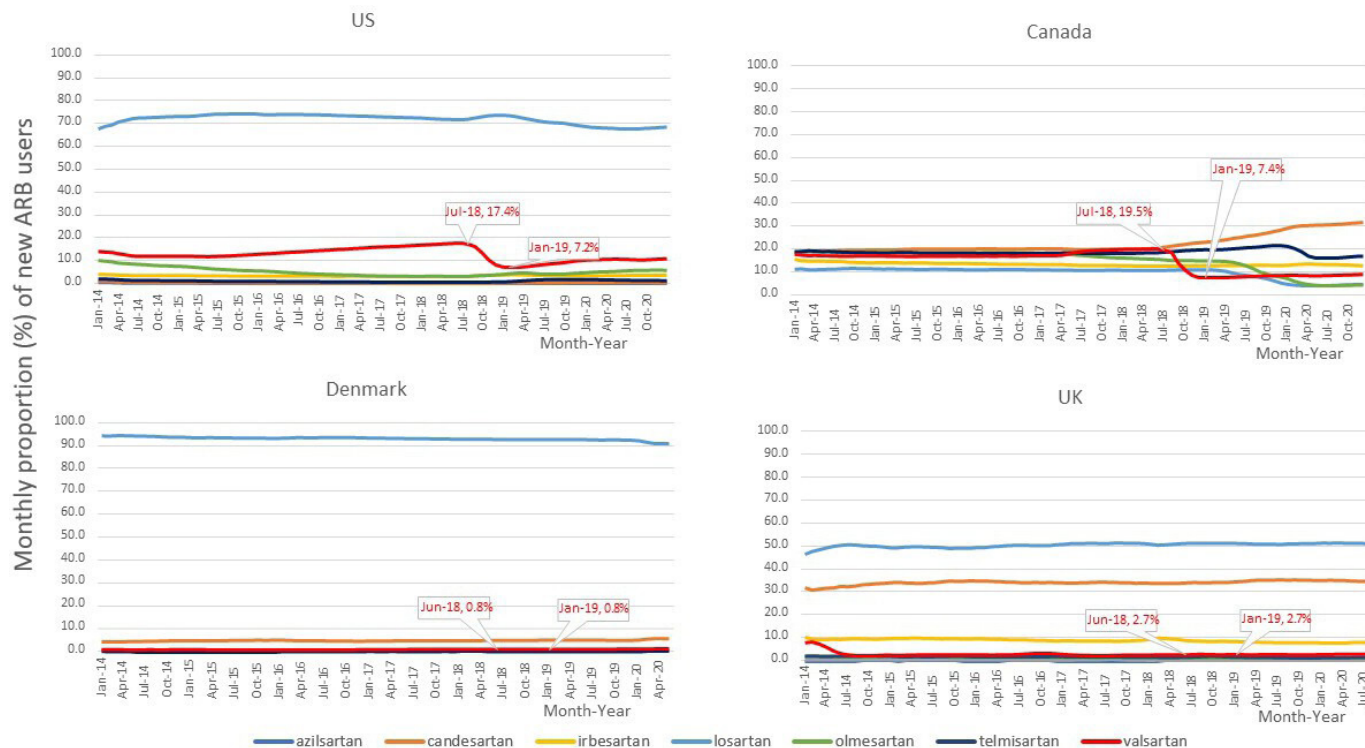
Trends for incident ARB users

In the USA, the monthly percentages of valsartan users steadily increased from January 2014 to a peak rate (17.4%) in June 2018. Immediately after the recall notice,

we observe a steady decline to the lowest rate in January 2019 (7.2%) (figure 3). Incident valsartan use started to increase after January 2019 but did not reach the peak rate observed before the recall notice. An accompanying increase in new users of losartan (71.4%–73.2%); olmesartan (3.0%–4.6%) and irbesartan (0.8%–1.1%) was observed from June 2018 to January 2019. In Canada, the monthly proportion new users of valsartan also steadily declined from 19.5% to 7.4%, from June 2018 to January 2019, while the rate for candesartan and telmisartan new

Table 2 Change in usage trend following issuance of recall notice stratified by country (results from interrupted time series analysis)

ARB	USA		Canada		Denmark		UK	
	Level change (%)	Trend change (%)	Level change (%)	Trend change (%)	Level change (%)	Trend change (%)	Level change (%)	Trend change (%)
Valsartan	−6.4[*]	−0.05 (0.2)	−8.0[*]	−0.2[*]	−0.04 (0.04)	0.0	0.61 (0.08)	0.04 (0.03)
Azilsartan	0.0	0.0	NA				0.0	0.0
Candesartan	0.1[*]	0.02[*]	0.2 (0.6)	0.6[*]	−0.01 (0.8)	0.03[*]	−0.4 (0.001)	−0.01 (0.09)
Irbesartan	1.2[*]	0.01 (0.01)	0.06 (0.7)	0.2[*]	−0.01 (0.2)	0.0	−0.09 (0.004)	0.01[*]
Losartan	2.9[*]	−0.25[*]	1.7[*]	−0.3[*]	0.13 (0.02)	−0.03[*]	0.0	−0.05[*]
Olmesartan	1.4[*]	0.2[*]	2.1[*]	−0.4[*]	NA		0.16[*]	0.02[*]
Telmisartan	0.5[*]	0.05[*]	2.9[*]	0.01 (0.7)	−0.01 (0.4)	0.0	0.04[*]	0.0

ARB: Angiotensin-Receptor-Blocker
[*]p<0.0001.

Figure 3 Trends for incident Angiotensin-Receptor-Blocker use between January 2014 and end of available data or December 2020 by country. Monthly proportions of incident ARB users represent the number of users who newly initiated an individual ARB in the month divided by the total number of users who newly initiated any ARB in the same month. Data callouts represent the month-year, monthly proportion (%) for valsartan only.

users increased (20.5%–23.2% and 18.3%–19.6%, respectively) during the same period. No changes to the rate of any incident ARB users were observed in Denmark and the UK (figure 3).
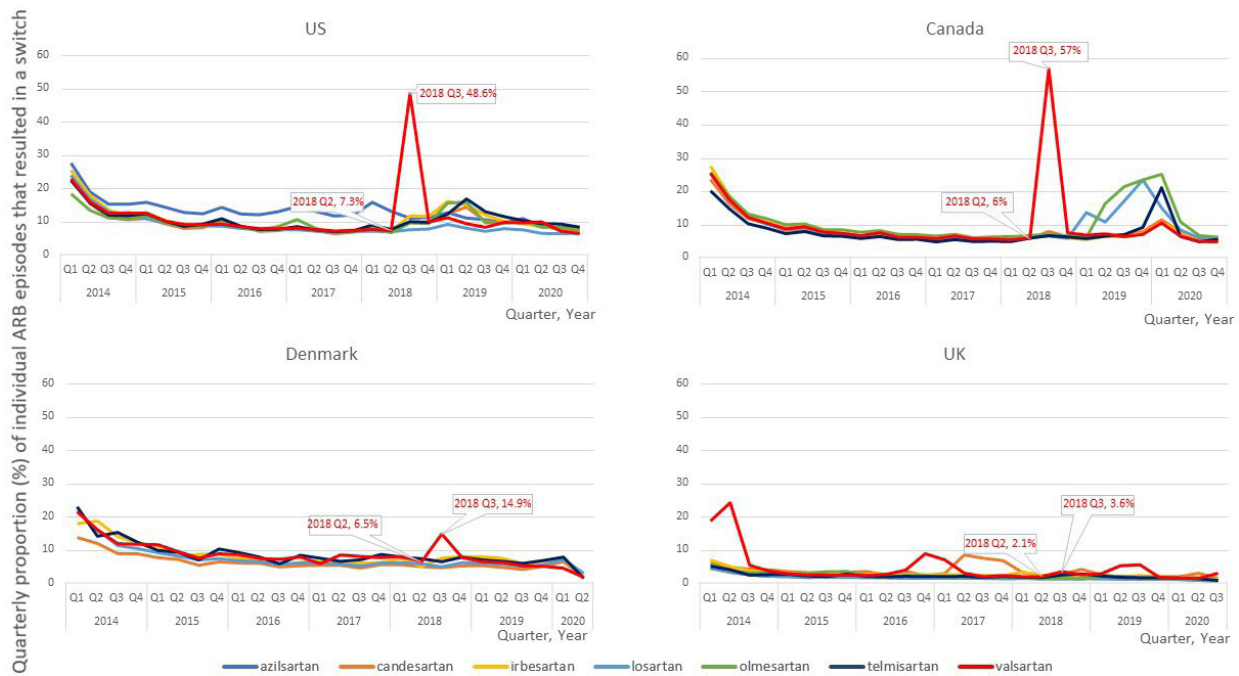
Switching

In the USA and Canada, there was an immediate increase, from Q2-2018 (April to June) to Q3-2018 (July to August), in the proportions of valsartan episodes that switched to a non-index ARB, ACEI or CCB (USA: 7.3% (Q2-2018) to 48.6% (Q3-2018); Canada: 6.0% to 56.9%). A similar but smaller increase was also observed in Denmark (from 6.5% (Q2-2018) to 14.9% (Q3-2018)) but no trend changes were observed in the UK (figure 4). Other notable switching patterns were observed for the other ARBs. In the USA, we observed slight increases in the quarterly proportion of olmesartan (Q1 and Q2-2019), irbesartan (Q1 and Q2-2019) and telmisartan (Q2 and Q3-2019) episodes that resulted in switching (figure 4). In Canada, we observed increased switching for losartan between Q1 and Q4-2019, olmesartan between Q2-2019 and Q1-2020 and for telmisartan between Q4-2019 and Q1-2020 (figure 4).

Patients on valsartan were more likely switched to other ARBs than to ACEIs or CCBs (online supplemental figures 1–4). In the USA, from Q2 to Q3 2018, there was increased switching from valsartan to a non-index ARB (0.6%–42.8%), but only a small increase for ACEI (0.7%–1.3%) and a decrease in switching to CCB (6.3%–4.9%)

(online supplemental figure 1). In Canada and Denmark (online supplemental figures 2 and 3), similar trends were observed for valsartan; increased switching to a non-index ARB (Canada: 0.3%–52.6%; Denmark: 0.9%–10.4%); or to ACEI (Canada: 0.5%–1.8%; Denmark:1.1%–1.4%) but decreased switching to CCB (Canada: 5.4%–3.2%; Denmark: 4.8%–3.6%). Switching trends in the UK were negligible (online supplemental figure 4). Generally, patients on valsartan were switched to the most frequently used ARB in the respective country, following the recall notice. In the USA, the majority of valsartan episodes were switched to losartan, followed by irbesartan and olmesartan (online supplemental figure 5). In Canada, most valsartan episodes were switched to candesartan, followed by telmisartan, irbesartan and olmesartan (online supplemental figure 6); in Denmark, majority of valsartan episodes were switched to losartan (online supplemental figure 7) and in the UK there was negligible switching in Q3-2018 (online supplemental figure 8). For other affected ARBs (losartan and irbesartan) switching to other ARBs were also observed around the time of recall notices for these products.

DISCUSSION

After the discovery of NDMA in the valsartan API, additional nitrosamines were found in other ARB products. Based on animal studies, these nitrosamine impurities are considered safe when present up to certain allowable limits. However,

Figure 4 Quarterly proportions (represented as percentages) for individual ARB episodes switching to non-index Angiotensin-Receptor-Blockers (ARBs), Angiotensin-Converting-Enzyme inhibitors (ACEIs) or calcium channel blockers, stratified by country. Data callouts represent the quarter-year, monthly percentage (%) for valsartan only.

long-term exposure at allowable or higher levels may increase the risk of some cancers.[11 12] For valsartan, losartan and irbesartan regulatory agencies agreed that the level of nitrosamine impurity identified corresponded to published allowable interim limits and should not increase the risk of cancer. As these products are used to prevent and manage serious conditions such as stroke, heart failure or myocardial infarction, regulatory agencies recommended that patients should not abruptly stop their medications and provided lists of contaminated products to allow patients determine whether their medication was affected and switch to an uncontaminated product of the same API. Despite availability of uncontaminated products, our study revealed that the immediate response was to switch patients from affected ARBs to a different ARB API. Often the ARB of choice was the predominantly used ARB in the respective country.

We observed the highest rates of switching from valsartan to another ARB in the USA and Canada compared with Denmark and the UK, and a slight increase in switching to ACEI was also observed in the USA and Canada. This is likely because the USA and Canada had a higher proportion of valsartan users compared with Denmark and the UK. It is also possible that this change in use trends may be related to differences in approaches to communications by the agencies in North America compared with the other regions. The lack of change observed in the UK is also not unexpected as there was only a selective recall of some ARB products affected by the nitrosamine contamination and the UK had adequate supply of alternative unaffected losartan containing products. Therefore, UK healthcare professionals were assured that there

would be no shortage in supply, and they could continue prescribing as normal.

An interesting finding was the lower proportion of switching for losartan and irbesartan to other ARBs compared with valsartan switches following the recall notices for these ARBs. A comparable number of valsartan and losartan (624 vs 500) products were published under the recall list although the losartan recall notices occurred later in 2018. Despite the widespread use of losartan in the USA, Denmark and the UK, there were only negligible changes to the overall usage trends for losartan after the recall notice issued in November 2018. Some switching from losartan to other ARBs was observed in the USA and UK, but there was no change to the losartan usage trends. In Canada, increased switching from losartan to olmesartan, candesartan and telmisartan resulted in a decline in losartan usage. The gradual increase in candesartan and irbesartan usage between April 2019 and January 2020 is likely the result of the increased switching from losartan to these products. Irbesartan usage trends were unaffected by the increased switching to other ARBs during Q1 to Q4-2019 in all countries.

To date, our study is the largest with sufficient observation time to evaluate the usage of ARB following recall notices related to nitrosamine contamination across four countries. Previous studies[13 14] conducted closer to the time of the recall may not have included sufficient observation time needed to examine the full impact of the recall notice, since these notices were published periodically into 2019. This also is the first international collaboration utilising data from the FDA Sentinel System, CNODES,

the UK CPRD and the Danish prescription registry. All data were converted to Sentinel's standardised common data model, allowing for the deployment of an identical analytic programme across the four data sources. Comprehensive dispensing and prescribing data from four different countries allowed an international comparison of global trends after recall notices from multiple regulatory agencies.

Our study also has limitations. We were unable to capture reasons for switching, although the use of a control period prior to the recall notice provides some assurance that the changes in ARB usage were due to the recall notices. For prescribing data, we are unable to confirm that patients filled or received the products in the prescription. The study was also limited by the inability to classify the affected ARB products into contaminated and uncontaminated categories.

CONCLUSION

Despite availability of uncontaminated ARB products at the time of the recall, data from three out of four countries revealed a substantial decline in valsartan use following the first notices in 2018. Switching from valsartan to the predominantly dispensed ARB in each country appears to be responsible for the decline. The impact of subsequent notices on ARB usage waned over time.

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