BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (http://bmjopen.bmj.com).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

BMJ Open

Changes in Angiotensin-Receptor-Blocker utilization following nitrosamine contamination recalls in the US, UK, Canada, and Denmark

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-070985
Article Type:	Original research
Date Submitted by the Author:	13-Dec-2022
Complete List of Authors:	Eworuke, Efe; US Food and Drug Administration, Shinde, Mayura; Harvard Medical School and Harvard Pilgrim Health Care Institute, Department of Population Medicine Hou, Laura; Harvard Medical School and Harvard Pilgrim Health Care Institute, Department of Population Medicine Paterson, Michael; Canadian Network for Observational Drug Effect Studies (CNODES) Jensen, Peter Bjødstrup; University of Southern Denmark Maro, Judith; Harvard Medical School and Harvard Pilgrim Health Care Institute, Department of Population Medicine Rai, Ashish; Harvard Medical School and Harvard Pilgrim Health Care Institute, Department of Population Medicine Scarnecchia, Daniel; Harvard Medical School and Harvard Pilgrim Health Care Institute, Department of Population Medicine Pennap, Dinci; US Food and Drug Administration Woronow, Daniel; US Food and Drug Administration Ghosh, Rebecca; Clinical Practice Research Datalink, Medicines and Healthcare Products Regulatory Welburn, Stephen; Clinical Practice Research Datalink, Medicines and Healthcare Products Regulatory Pottegard, Anton; Odense Universitetshospital, Hospital Pharmacy; University of Southern Denmark, Department of Public Health, Clinical Pharmacology and Pharmacy Platt, Robert; Harvard Medical School and Harvard Pilgrim Health Care Institute, Department of Population Medicine Lee, Hana; US Food and Drug Administration Bradley, Marie; US Food and Drug Administration
Keywords:	Epidemiology < TROPICAL MEDICINE, Cardiac Epidemiology < CARDIOLOGY, Heart failure < CARDIOLOGY, Hypertension < CARDIOLOGY

SCHOLARONE™
Manuscripts

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

For peer review only

Changes in Angiotensin-Receptor-Blocker utilization following nitrosamine contamination recalls in the US, UK, Canada, and Denmark

Short Title: Impact of Nitrosamine Recall on ARB Trends

Authors: Efe Eworuke,[1] Mayura Shinde,[2] Laura Hou,[2] Michael Paterson,[3] Peter Jensen,[4] Judith C. Maro,[2] Ashish Rai,[2] Daniel Scarnecchia,[2] Dinci Pennap,[1] Daniel Woronow,[1] Rebecca E. Ghosh[5], Stephen Welburn[5], Anton Pottegård,[4] Robert W Platt,[3] Hana Lee,[1] Marie C Bradley[1]

Author Affiliations:

1. Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD, USA
2. Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, USA
3. Canadian Network for Observational Drug Effect Studies (CNODES), Montréal, QC, CA
4. University of Southern Denmark, Odense, DK
5. Clinical Practice Research Datalink, Medicines and Healthcare Products Regulatory Agency, UK

Corresponding author: Efe Eworuke

Division of Epidemiology II, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993

Telephone: 240-402-3972

Fax: 301-796-9850

Email: efe.eworuke@fda.hhs.gov; efeeworuke@gmail.com

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

For peer review only

Keywords: nitrosamine contamination, valsartan, angiotensin-receptor-blockers, sentinel system

Manuscript word count: 2,967 (max: 5000)

Abstract word count: 249 (max: 300)

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Abstract

Objectives: Accompanying the recall notices for nitrosamine-contaminated angiotensin-receptor blockers (ARBs) were published lists of uncontaminated products, allowing patients to continue their treatment. It is unknown how patients and providers responded to the recall notices.

Methods: Using data from US, Canadian administrative healthcare data, Danish National Prescription Registry and UK primary care electronic health records, we identified patients 18 years and older between January 2014 and December 2020 with an ARB dispensing. We calculated monthly percentages of individual ARB dispensings, new users and quarterly percentages of ARB switchers to other products before and after July 2018.

Results: We identified 10.8, 3.2, 1.8, and 1.2 million ARB users in the US, UK, Canada, and Denmark respectively. Losartan had the largest market share in the US (67.9%), Denmark (93.5%) and UK (48.3%), while candesartan (27.5%) and telmisartan (21.1%) were the prominent ARBs in Canada. In July 2018, we observed an immediate decline in valsartan use in the US, Canada, and Denmark. No change in trends of ARB use was observed in the UK. Accompanying the decline was an increase in switching to other ARBs. We also observed increased switching from other affected ARBs, losartan and irbesartan, to other ARBs throughout 2019, in the US and Canada, however, the utilization trends in the US remained unchanged.

Conclusion: The first recall notice for valsartan resulted in substantial decline in utilization due to increased switching to other ARBs. Subsequent notices for losartan and irbesartan were also associated with increased switching, however utilization trends remained unchanged.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

Introduction

In July 2018, several regulatory agencies around the world notified the public about 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 (ZHP) 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. ARBs with a tetrazole ring were at risk since similar manufacturing process were used in their API synthesis. Regulatory agencies further alerted the public to nitrosamine contamination in certain lots of irbesartan and losartan in October and November 2018, respectively. Since then, nitrosamine contamination has become a global topic of interest, affecting other therapeutic products, including metformin, ranitidine, rifampin/rifapentine and varenicline.[6]

Despite concerns about risk associated with use of contaminated nitrosamine products, FDA and the other regulatory agencies determined that the risk for cancer was extremely low and advised patients to continue recalled products until there was a replacement ARB or different treatment option.[7, 8] This was based on data from animal and other studies that showed that consuming up to 96 nanograms NDMA per day is considered reasonably safe.[7] Since cancer risk depends on both dose and years of exposure, it was determined that if 8,000 patients took the maximum recommended daily dose of valsartan (320mg daily) for four years, there may be one additional cancer case.[9] Interim limits for several nitrosamines and the maximum recommended daily dose for ARBs were published shortly after the recall notice. Lists of unaffected products were also published concurrently, allowing patients to potentially remain on their medications. However, it

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

is unclear how utilization 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 utilization, from 2014 through 2020 in four countries. Healthcare data from the US, four Canadian provinces, the UK and Denmark were converted to Sentinel's standardized common data model, allowing for the deployment of the same analysis in the four databases.

Methods

Data Sources

We analyzed 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 the appendix.

Study Cohorts

This retrospective cohort study was conducted using data from January 1, 2014, through December 31, 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 ARBs on the

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

For peer review only

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.

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), ACEI, CCB or ACEI/CCB combination drugs. We defined a switch as a dispensing of or a prescription for a switch product during an index ARB exposure episode. When no switch occurred, patients were censored at first occurrence of disenrollment, death, the end of the data provided by each data partner or product discontinuation.

Statistical Analysis

ARB utilization trends

We calculated the monthly percentage of individual ARB utilization as the number of dispensings or prescriptions for each individual ARB divided by all ARB dispensings or prescriptions occurring in 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.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

Switching Analysis

We computed the proportion of switching 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 utilization. We examined (1) the change in the monthly proportions (level change) of individual ARB utilization immediately after the recall notice (July 2018) and (2) the change in trend in the monthly proportions (trend change) of individual ARB utilization 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 utilized ARBs for each country. Additionally, we considered three sensitivity analyses: First, we treated July 2018-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). Lastly, we considered a randomly selected, false intervention date (July 2016) to investigate whether the level and trend change observed in the primary ITS and CITS 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 Inc., Cary, NC, USA. This Sentinel activity is a public health surveillance activity conducted under

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

the authority of the Food and Drug Administration and, accordingly, is not subject to Institutional Review Board oversight.[10-12]

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.

Results

During the study period, we identified 10,836,991; 3,270,823; 1,775,080; and 1,153,841 ARB users in the US, UK, Canada and Denmark, respectively. The two most frequently utilized ARBs were losartan (67.9%) and valsartan (18.4%) in the US, candesartan (27.5%) and telmisartan (21.1%) in Canada, and losartan (48.3%) and candesartan (34.2%) in the UK. In Denmark, 93.5% of the ARB episodes were for losartan (Table 1). Most ARB users were aged 65 years and older, although in Denmark, there was a high proportion of 45–64-year-old users compared to 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 US, Canada, and UK.

Table 1: Selected Demographic and Clinical Characteristics for all ARB users displayed by Country

Characteristics	US (%)	Canada (%)	Denmark (%)	UK (%)
Number of ARB users	10,836,991	798,231	492,229	578,652
Number of Episodes	22,406,719	1,775,080	1,153,841	3,270,823
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

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

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
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
Hyperlipidemia	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

NR: Not reported; *Clinical History collected 183 days before the index dispensing date
Proportions are calculated using the number of ARB episodes as the denominator.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

ARB Utilization Trends

The monthly trends for the percentage of individual ARB dispensings or prescriptions differed by country (Figure 1).

US

For the US, over time, losartan accounted for the largest share of ARB dispensings, followed by valsartan. After June 2018, a gradual decline for valsartan monthly proportions started from 11.8% (June 2018) to 7.4% (August 2018). The decline in valsartan dispensings was accompanied by a steep increase in losartan (63.8% to 95.2%), olmesartan (4.2% to 10.7%), and telmisartan (1.0% to 2.1%) dispensing (Figure 1). Visual trends are also supported by ITS analyses (Table 2), with significant level change for valsartan (-3.9%; $p<0.0001$) and losartan (11.0%; $p<0.0001$). 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 (STable 1).

Canada

For Canada, over time, candesartan accounted for the largest share of ARB dispensings, followed by telmisartan and irbesartan. Like the US, we also observed a steep decline for valsartan dispensings from June 2018 (10.9%) to August 2018 (7.3%) (Figure 1). An immediate, but not sustained increase for candesartan (20.4% to 105.6%), telmisartan (17.2% to 55%), irbesartan (13.5% to 36.7%), losartan (7.9% to 19.2%) and olmesartan (8.5% to 17.7%) was observed for only June to July 2018. Afterwards, the monthly trends for these products began to decline to pre-recall levels (Figure 1). ITS analyses (Table 2) confirmed significant level and trend changes

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

for valsartan (-3.5%; p<0.0001). Highly significant (p<0.0001) level change was also observed for candesartan (25%) and telmisartan (11.0%). Smaller but statistically significant changes were also observed for the other ARBs (Table 2). The level change for valsartan was significantly higher (i.e., larger decrease in use) than those for candesartan, telmisartan, and irbesartan (STable 1).

Denmark

For Denmark, losartan contributed over 90% of ARB dispensings with valsartan contributing around 1% of the total ARB dispensings. A small decline was observed for valsartan dispensings from June 2018 (1.7%) to August 2018 (1.3%), accompanied by slight immediate increase in losartan and candesartan dispensing (Figure 1). The observed trends for valsartan were non-significant (level change 0.18%; p =0.23) (Table 2). The level and trend changes for valsartan were mostly similar to those for candesartan, telmisartan, and irbesartan (STable 1).

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 1 and Table 2). The level and trend changes for valsartan were mostly similar to candesartan, losartan, and irbesartan (STable 1).

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

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

ARB	US		Canada		Denmark		UK	
	Level Change (%)	Trend Change (%)	Level Change (%)	Trend Change (%)	Level Change (%)	Trend Change (%)	Level Change (%)	Trend Change (%)
Valsartan	-3.9*	0.24*	-3.5*	0.18*	0.18 (0.23)	-0.0173 (0.09)	0.26 (0.07)	0.027 (0.0015)
Azilsartan	0.008 (0.7)	-0.005 (0.0002)	NA		NA		0.005 (0.02)	not reportable
Candesartan	0.6*	0.003 (0.31)	25.0*	0.067 (0.80)	0.58 (0.09)	0.02 (0.33)	0.14 (0.63)	-0.043 (0.015)
Irbesartan	4.0*	0.078*	6.3 (0.009)	0.091 (0.44)	0.17 (0.01)	-0.008 (0.07)	0.02 (0.89)	0.019 (0.032)
Losartan	11.0*	-0.35*	1.2 (0.091)	-0.025 (0.49)	0.8 (0.11)	0.07 (0.02)	0.34 (0.4)	-0.014 (0.56)
Olmesartan	4.5*	0.11*	0.33 (0.62)	-0.089 (0.009)	NA		0.23 (0.002)	0.019*
Telmisartan	1.7*	0.018 (0.12)	11.0*	-0.22 (0.015)	-0.09 (0.01)	0.0041 (0.09)	0.037 (0.57)	0.006 (0.10)

*p<0.0001

For peer review only

10.1136/bmjopen-2023-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Sensitivity ITS Analyses

Findings from the sensitivity analyses excluding the transition period (STable 2) and using equal time points prior to and after the intervention date (STable 3) 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 (STable 4).

Trends for Incident ARB users

In the US, 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 2). 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% to 73.2%); olmesartan (3.0% to 4.6%) and irbesartan (0.8% to 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 users increased (20.5% to 23.2% and 18.3% to 19.6%, respectively) during the same period. No changes to the rate of any incident ARB users were observed in Denmark and UK (Figure 2).

Switching

In the US and Canada, there was an immediate increase, from Q2-2018 (April-June) to Q3-2018 (July-August), in the proportions of valsartan episodes that switched to a non-index ARB, ACEI or CCB (US: 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 3). Other notable switching patterns were

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

observed for the other ARBs. In the US, 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 3). 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 3).

Patients on valsartan were more likely switched to other ARBs than to ACEIs or CCBs (SFigure 1-4). In the US, from Q2 to Q3 2018, there was increased switching from valsartan to a non-index ARB (0.6% to 42.8%), but only a small increase for ACEI (0.7% to 1.3%) and a decrease in switching to CCB (6.3% to 4.9%) (SFigure 1). In Canada and Denmark (SFigure 2-3), similar trends were observed for valsartan; increased switching to a non-index ARB (Canada: 0.3% to 52.6%; Denmark: 0.9% to 10.4%); or to ACEI (Canada: 0.5% to 1.8%; Denmark:1.1% to 1.4%) but decreased switching to CCB (Canada: 5.4% to 3.2%; Denmark: 4.8% to 3.6%). Switching trends in the UK were negligible (SFigure 4). Generally, patients on valsartan were switched to the most frequently used ARB in the respective country, following the recall notice. In the US, the majority of valsartan episodes were switched to losartan, followed by irbesartan and olmesartan (SFigure 5). In Canada, most valsartan episodes were switched to candesartan, followed by telmisartan, irbesartan and olmesartan (SFigure 6) and in Denmark, majority of valsartan episodes were switched to losartan (SFigure 7). Switching patterns for valsartan were negligible (SFigure 8). For other affected ARBs (losartan and irbesartan) switching to other ARBs was also observed around the time of recall notices for these products.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

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, long-term exposure at allowable or higher levels may increase the risk of some cancers.[13, 14] For valsartan and the other affected ARBs that remained on the market, regulatory agencies agreed that level of nitrosamine impurity identified corresponded to published allowable interim limits and should not increase the risk of cancer. Because these products are used to prevent serious conditions such as stroke, heart failure or myocardial infraction, regulatory agencies recommended that patients should not abruptly stop their medications and provided lists of non-affected drug products to allow patients to remain on treatment. Despite availability of non-affected drug products, our study revealed that the immediate response was to switch patients from affected ARBs to other ARBs. 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 US and Canada compared to Denmark and the UK, and a slight increase in switching to ACEI was also observed in the US and Canada. This is likely because the US and Canada had a higher proportion of valsartan users compared to 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 to 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 health care professionals were assured that there would be no shortage in supply, and they could continue prescribing as normal.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

An interesting finding was the lower proportion of switching for losartan and irbesartan to other ARBs compared to 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 US, Denmark and UK, there were only negligible changes to the overall utilization trends for losartan after the recall notice issued in November 2018. Some switching from losartan to other ARBs was observed in the US and UK, but there was no change to the losartan utilization trends. In Canada, increased switching from losartan to olmesartan, candesartan and telmisartan resulted in a decline in losartan utilization. Irbesartan utilization 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 utilization of ARB following recall notices related to nitrosamine contamination across four countries. Previous studies[15, 16] conducted closer to the time of the recall may not have included sufficient observation time needed to examine the full impact. This also is the first international collaboration utilizing data from the FDA Sentinel System, CNODES, the U.K CPRD and the Danish prescription registry. All data were converted to Sentinel's standardized common data model, allowing for the deployment of an identical analytic program 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 utilization were due to the recall notices. For prescribing data, we are unable to confirm that patients filled or received the products in the prescription.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

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 dispensings 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 utilization waned over time.

Summary

What is already known about this subject Some product lots of three Angiotensin-Receptor-Blockers (ARBs), valsartan, losartan and irbesartan were found to be contaminated with nitrosamine.

What does this study add? In this retrospective cohort study of over 10 million ARB users, we observed substantial decline in the use valsartan-containing products following the first recall notice, which was accompanied by increased switching to another ARB. For subsequent notices, we also observed increased switching to other ARBS with losartan and irbesartan, although there was no change in the overall use trends.

How might this impact on clinical practice? Our study revealed that many patients abruptly switched to an alternative ARB despite availability of uncontaminated drug products.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Acknowledgements, sources of funding & disclosures

A) Acknowledgments: Many thanks are due to those who participated in this project: The Canadian Network for Observational Drug Effect Studies (CNODES), a collaborating centre of the Drug Safety and Effectiveness Network (DSEN), is funded by the Canadian Institutes of Health Research (CIHR; Grant # DSE-146021). This study was made possible through data-sharing agreements between the CNODES member research centres and the respective provincial governments of Manitoba, Nova Scotia, Ontario, and Saskatchewan. The opinions, results, and conclusions are those of the authors; no endorsement by the provincial governments, data stewards, Health Canada or CIHR is intended or should be inferred.

U.S. Data Partners who provided data used in the analysis: CVS Health Clinical Trial Services, an affiliate of Aetna, a CVS Health Company, Blue Bell, PA; Duke University School of Medicine, Department of Population Health Sciences, Durham, NC, through the Centers for Medicare and Medicaid Services which provided data; HealthCore/Anthem, Wilmington, DE; Humana Healthcare Research Inc., Louisville, KY; Northern California, Division of Research, Oakland, CA; OptumInsight Life Sciences Inc., Boston, MA; Vanderbilt University Medical Center, Department of Health Policy, Nashville, TN, through the TennCare Division of the Tennessee Department of Finance & Administration which provided data.

B) Source of Funding: This project was supported by Task Order 75F40119F19002 under Master Agreement 75F40119D10037 from the US Food and Drug Administration (FDA).

C) Disclosures: The views expressed in this publication are those of the authors and do not necessarily reflect the official policy of the US Food and Drug Administration or Health Canada or the UK Medicines and Healthcare products Regulatory Agency.

D) Conflicts of Interest: The authors declare no conflicts of interest.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

E) Contributionship: All authors contributed to the design, conduct of the study, drafting and final editing of the manuscript.

F) Data Sharing: All data used in the analyses remain confidential and cannot be shared publicly.

G) Ethics statement: All data are deidentified and this study was conducted as a public health surveillance activity and was not subject to ethics or IRB approval.

Supplemental Material

Supplemental Tables STables1-4

Supplemental Figures SFigures1-8

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

References

1. FDA announces voluntary recall of several medicines containing valsartan following detection of an impurity. 2018. Accessed May 26, 2022. https://www.fda.gov/news-events/press-announcements/fda-announces-voluntary-recall-several-medicines-containing-valsartan-following-detection-impurity

2. EMA reviewing medicines containing valsartan from Zhejiang Huahai following detection of an impurity: some valsartan medicines being recalled across the EU. 2018. Accessed May 26, 2022. https://www.ema.europa.eu/en/news/ema-reviewing-medicines-containing-valsartan-zhejiang-huahai-following-detection-impurity-some

3. Several drugs containing valsartan being recalled due to contamination with a potential carcinogen. 2018. Accessed May 26, 2022. https://recalls-rappels.canada.ca/en/alert-recall/several-drugs-containing-valsartan-being-recalled-due-contamination-potential

4. Blood pressure and heart medication recalled from Pharmacie. 2018. Accessed May 26, 2022. https://www.gov.uk/government/news/blood-pressure-and-heart-medication-recalled-from-pharmacies

5. International Agency for Research on Cancer. *IARC monographs on the evaluation of carcinogenic risks to humans. Overall evaluations of carcinogenicity: an updating of IARC Monographs*. Vol. 1-42. 1987.

6. US Food and Drug Administration. Information about Nitrosamine Impurities in Medications. Accessed June 18, 2022, 2022. https://www.fda.gov/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications

7. Update - Analysis of N-nitrosodimethylamine (NDMA) Levels in Recalled Valsartan in the US. 2018. Accessed June 1 2022. https://www.fda.gov/drugs/drug-safety-and-

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan#6297781d0e2e7

8. Pottegård A, Kristensen KB, Ernst MT, Johansen NB, Quartarolo P, Hallas J. Use of N-nitrosodimethylamine (NDMA) contaminated valsartan products and risk of cancer: Danish nationwide cohort study. *BMJ*. 2018;362:k3851. doi:10.1136/bmj.k3851

9. US Food and Drug Administration. Laboratory analysis of valsartan products. Accessed May 26, 2022, 2022. https://www.fda.gov/drugs/drug-safety-and-availability/laboratory-analysis-valsartan-products

10. Basic HHS Policy for Protection of Human Research Subjects, Title 45 82 FR 7259, 7273 1-23 (2017). https://www.fda.gov/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications

11. Federal Policy for the Protection of Human Subjects. In: Office for Human Research Protections (OHRP) Department of Health and Human Services. 82 FR 71492017. p. 126.

12. Rosati K JN, Soliz M, Evans BJ. . Sentinel Initiative Principles and Policies: HIPAA and Common Rule Compliance in the Sentinel Initiative. 2018.

13. Peto R, Gray R, Brantom P, Grasso P. Effects on 4080 Rats of Chronic Ingestion of N-Nitrosodiethylamine or N-Nitrosodimethylamine: A Detailed Dose-Response Study1. *Cancer Research*. 1991;51(23_Part_2):6415-6451.

14. Peto R, Gray R, Brantom P, Grasso P. Dose and time relationships for tumor induction in the liver and esophagus of 4080 inbred rats by chronic ingestion of N-nitrosodiethylamine or N-nitrosodimethylamine. *Cancer Res*. Dec 1 1991;51(23 Pt 2):6452-69.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

For peer review only

15. Desai RJ, Sarpatwari A, Gautam N, Lii J, Fischer MA, Gagne JJ. Changes in Utilization of Generic Angiotensin Receptor Blockers Following Product Recalls in the United States. *JAMA*. 2020;323(1):87. doi:10.1001/jama.2019.17521

16. Rudolph UM, Enners S, Kieble M, et al. Impact of angiotensin receptor blocker product recalls on antihypertensive prescribing in Germany. *Journal of Human Hypertension*. 2021;35(10):903-911. doi:10.1038/s41371-020-00425-z

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Figure Legends

Figure 1. Monthly ARB utilization trends between January 2014 and end of available data or December 2020 by country. Data callouts represent the month-year, monthly percentage (%) for valsartan only.

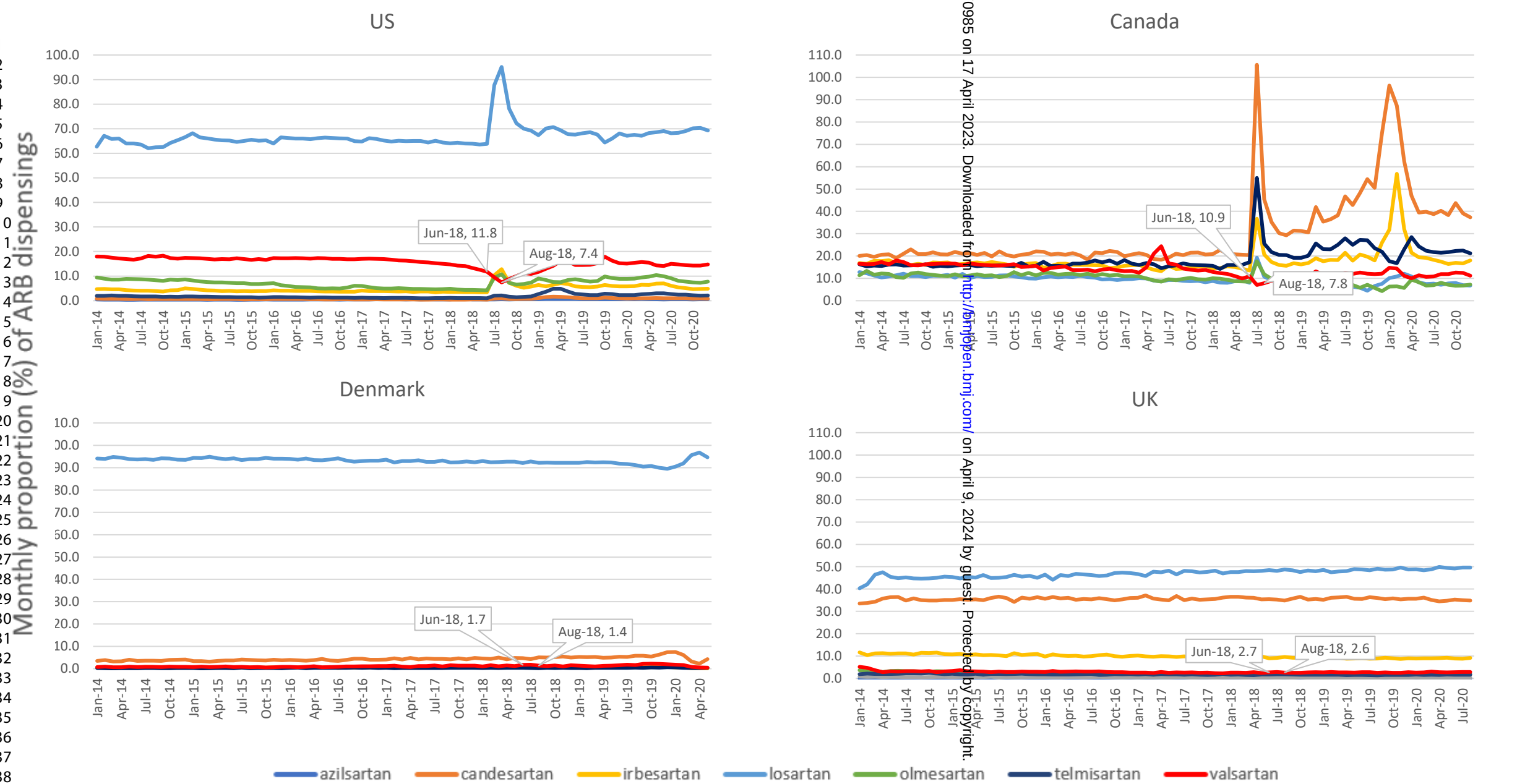
Figure 2. Trends for incident ARB users between January 2014 and end of available data or December 2020 by country. Data callouts represent the month-year, monthly proportion (%) for valsartan only.

Figure 3. Quarterly proportions (represented as percentages) for individual ARB episodes switching to non-index ARB, ACEI or CCB, stratified by country. Data callouts represent the month-year, monthly percentage (%) for valsartan only.

For peer review only

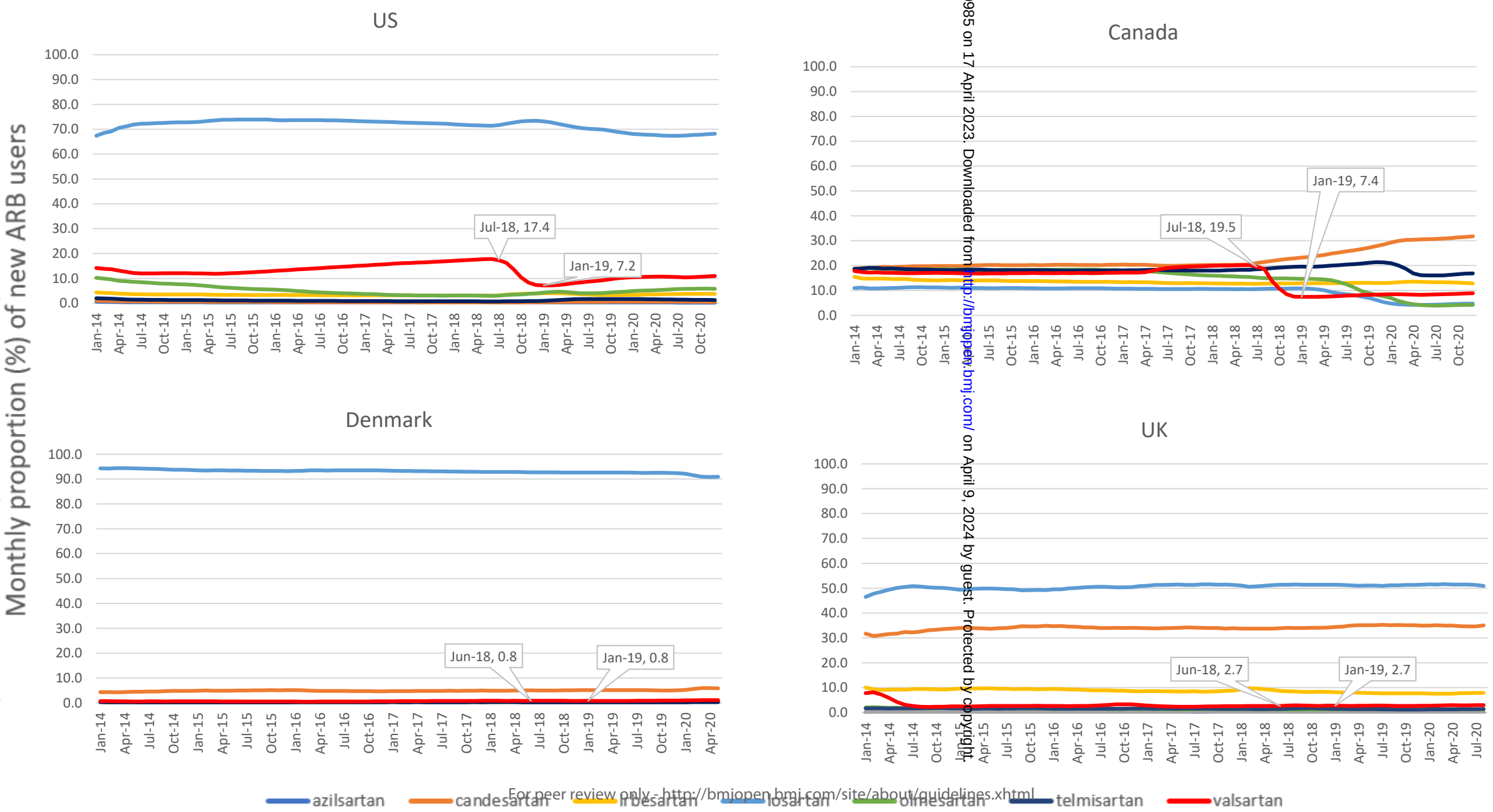
BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml



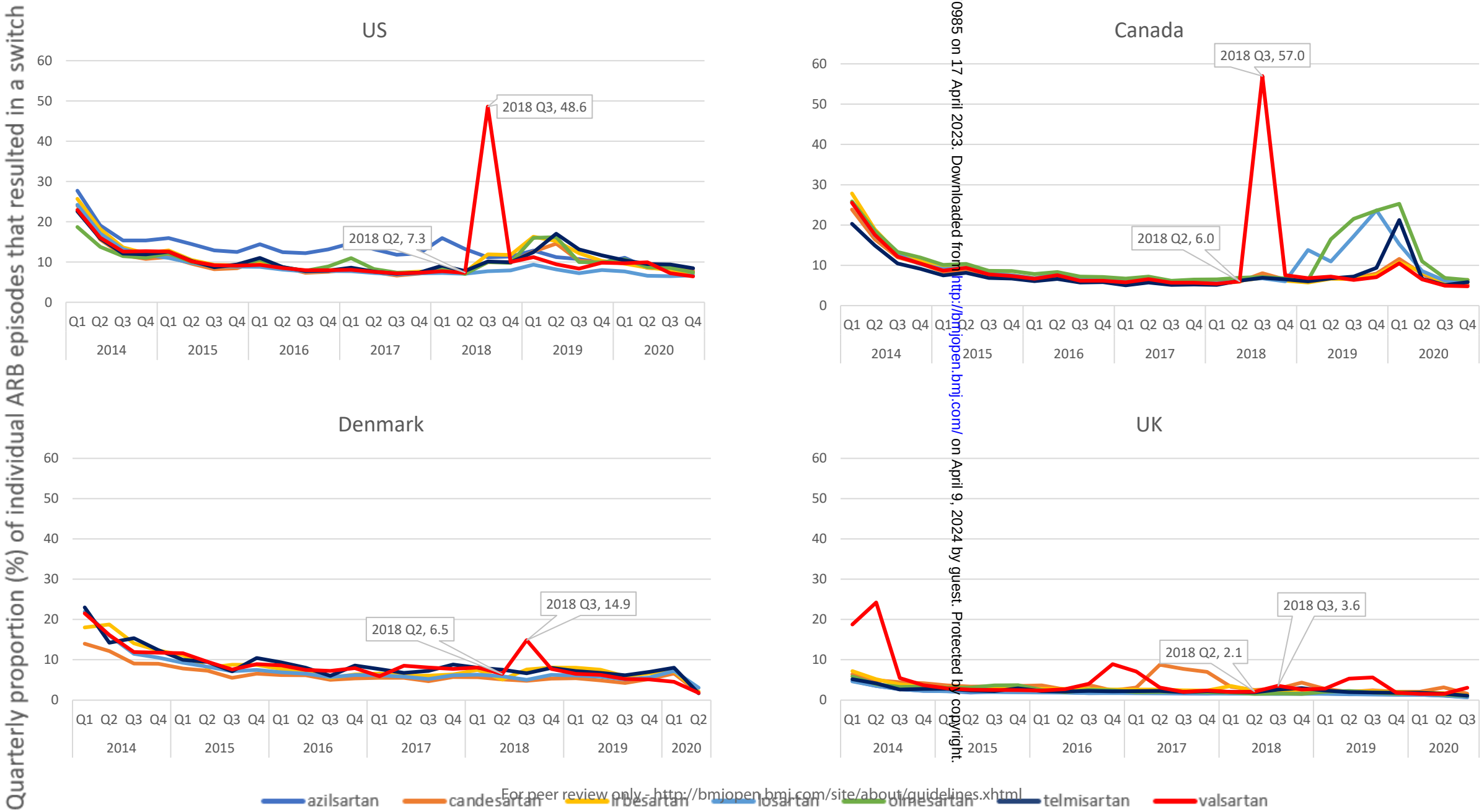
For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.



For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.



For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

Impact of angiotensin-receptor-blocker (ARB) recalls due to nitrosamine contamination on ARB utilization in the U.S., Canada, Denmark and the U.K.

Authors: Efe Eworuke,[1] Mayura Shinde,[2] Laura Hou,[2] J. Michael Paterson,[3] Peter Jensen,[4] Judy Maro,[2] Ashish Rai,[2] Daniel Scarnecchia,[2] Dinci Pennap,[1] Daniel Woronow,[1] Rebecca Ghosh[5], Stephen Welburn[5], Anton Pottegard,[4] Robert W Platt[3], Hana Lee,[1] Marie C Bradley[1]

Author Affiliations:

1. Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD, USA
2. Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, USA
3. Canadian Network for Observational Drug Effect Studies (CNODES), Montréal, QC, CA
4. University of Southern Denmark, Odense, DK
5. Medicines and Healthcare Products Regulatory Agency, UK

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

Appendix A. Description of Data Sources

Sentinel (US Data Source)

Sentinel comprises electronic health care data from a distributed network of 18 US based data partners including Medicare. These data partners, mostly commercial health insurers and integrated delivery care networks, convert their data into a common data model. The data domains include patient demographics, enrollment, inpatient, outpatient, and emergency room diagnoses and procedures and outpatient pharmacy dispensing based on National Drug Codes (NDCs).

CNODES (Canada Data Source)

CNODES is a collaborating center of the Canadian Drug Safety and Effectiveness Network. CNODES team members have access to linked healthcare and prescription drug records from seven provincial databases across Canada, including the four that contributed to this study; Saskatchewan, Manitoba, Ontario, and Nova Scotia; the first provinces to transform their data into the Sentinel Common Data Model. · CNODES uses a distributed network like that in the Sentinel system and includes the same data domains. Outpatient prescription drug dispensings are identified using Health Canada Drug Identification Numbers (DINs).

Danish National Prescription Registry (Denmark Data Source)

The Danish National Prescription Registry (DNPR), one of the Danish national registries collects detailed information on prescriptions redeemed in Denmark since 1995. Prescription medicines are offered to Danish residents under a reimbursement scheme which allows for a patient co-payment until the out-of-pocket expenditure is reached. The DNPR receives data recorded in the electronic dispensing systems of community pharmacies and includes information on the patient, the drug dispensed (fill date, composition and amount of drug), the prescriber and dispensing pharmacy.

CPRD (UK Data Source)

The UK CPRD is a computerized database of anonymized longitudinal patient records from primary care linked to a range of other health related data. It collects data from around 674 general practices in the UK, covers about 8.5% of the population and is broadly representative in terms of age, sex and geography. Demographic information, lifestyle data, prescription details, clinical events and diagnoses, preventive care, specialist referrals, and hospital admissions and their major outcomes are all recorded in the database.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

STable 1. Comparative Interrupted Time Series Analysis

Variable	Estimate (%)	P-value	Comparator ARB
UK			
Level change	0.4	0.298	Candesartan
Trend change	0.1	0.002	
Level change	0.6	0.243	Losartan
Trend change	0.0	0.166	
Level change	0.3	0.209	Irbesartan
Trend change	0.0	0.511	
US			
Level change	-14.8	<.0001	Losartan
Trend change	0.6	<.0001	
Level change	-8.4	<.0001	Olmesartan
Trend change	0.1	0.0004	
Level change	-8.3	<.0001	Irbesartan
Trend change	0.3	<.0001	
Denmark			
Level change	-0.4	0.1548	Candesartan
Trend change	0.0	0.822	
Level change	0.3	0.0548	Telmisartan
Trend change	0.0	0.0239	
Level change	0.0	0.8829	Irbesartan
Trend change	0.0	0.2777	
Canada			
Level change	-29.0	<.0001	Candesartan
Trend change	0.1	0.6811	
Level change	-14.3	<.0001	Telmisartan
Trend change	0.4	0.0003	
Level change	-9.8	0.0001	Irbesartan
Trend change	0.1	0.4758	

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

STable 2. Interrupted Time Series Analysis excluding the transition period

	US		**Canada**		**Denmark**		**UK**	
	Level Change	Trend Change	Level Change	Trend Change	Level Change	Trend Change	Level Change	Trend Change
Valsartan	-1.4 (0.012)	0.14*	-1.9 (0.03)	0.11 (0.03)	0.20 (0.23)	-0.019 (0.15)	0.29 (0.06)	0.026 (0.015)
Azilsartan	0.042 (0.16)	-0.007*					-0.0046 (0.04)	not reportable
Candesartan	0.77*	-0.006 (0.067)	19.0*	0.44 (0.079)	0.95 (0.01)	-0.051 (0.08)	0.006 (0.98)	-0.0061 (0.006)
Irbesartan	0.028*	-0.009 (0.38)	4.8 (0.043)	0.19 (0.16)	0.2 (0.006)	-0.013 (0.02)	-0.076 (0.64)	0.018 (0.11)
Losartan	3.0*	0.0093 (0.79)	-1.1 (0.038)	0.09 (0.002)	-1.2 (0.03)	0.12 (0.004)	-0.28 (0.5)	not reportable
Olmesartan	4.3*	0.13*	-2.2*	0.027 (0.33)			0.22 (0.009)	0.0019 (0.0004)
Telmisartan	2.0*	-0.014 (0.25)	6.5*	-0.011 (0.83)	-0.075 (0.061)	0.0048 (0.12)	-0.062 (0.36)	0.012 (0.009)

For peer review only

STable 3. Interrupted Time Series Analysis using equal time points before and after the intervention date

	US		Canada		Denmark		UK	
	Level Change	Trend Change	Level Change	Trend Change	Level Change	Trend Change	Level Change	Trend Change
Valsartan	-3.6*	0.5*	-3.5 (0.018)	0.34 (0.003)	0.09 (0.7)	-0.02 (0.21)	0.15 (0.078)	0.012 (0.07)
Azilsartan	-0.03 (0.53)	-0.003 (0.41)					-0.004 (0.11)	not reportable
Candesartan	0.54*	0.0091 (0.30)	18.0 (0.06)	0.95 (0.18)	0.05 (0.27)	-0.017 (0.65)	-0.094 (0.79)	-0.029 (0.28)
Irbesartan	4.5*	-0.09 (0.08)	2.4 (0.55)	0.52 (0.09)	0.17 (0.04)	-0.008 (0.19)	0.014 (0.93)	0.022 (0.09)
Losartan	15.0*	-0.57 (0.004)	1.6 (0.23)	-0.013 (0.89)	-0.76 (0.3)	0.069 (0.2)	-0.29 (0.33)	-0.010 (0.66)
Olmesartan	3.4*	0.13 (0.0005)	2.3 (0.026)	-0.13 (0.12)			0.47 (0.3)	0.011 (0.02)
Telmisartan	1.3 (0.002)	0.032 (0.29)	12.0 (0.0004)	-0.18 (0.46)	-0.06 (0.14)	0.062 (0.07)	0.38 (0.6)	0.002 (0.7)

For peer review only

10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

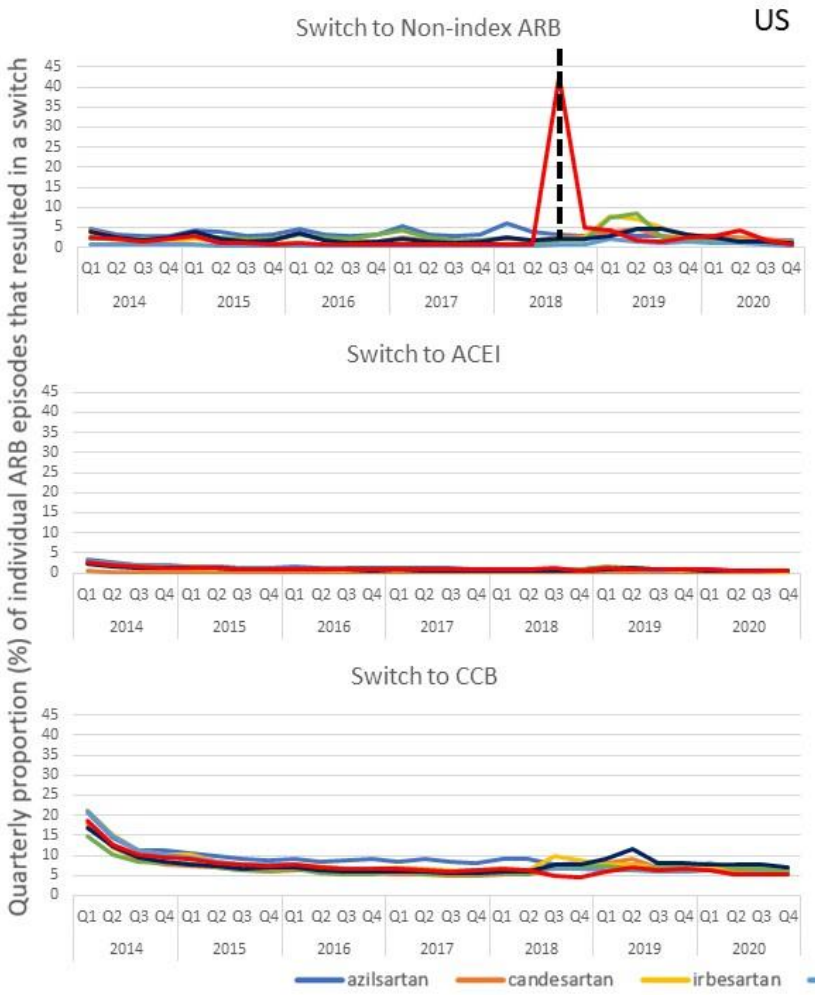
STable 4. Interrupted Time Series analysis using control time period (September 2014-May 2018) with intervention date, July 2016.

	US		Canada		Denmark		UK	
	Level Change	Trend Change	Level Change	Trend Change	Level Change	Trend Change	Level Change	Trend Change
Valsartan	1.2*	-0.16*	0.82 (0.54)	0.009 (0.93)	0.22 (0.03)	0.019 (0.017)	-0.12 (0.26)	-0.01 (0.18)
Azilsartan	0.048 (0.24)	0.0043 (0.18)					-0.003 (0.35)	not reportable
Candesartan	-0.065 (0.002)	-0.003 (0.088)	-0.68 (0.24)	0.027 (0.54)	0.13 (0.44)	0.018 (0.16)	-0.44 (0.2)	-0.028 (0.31)
Irbesartan	-0.034 (0.77)	not reportable	-0.3 (0.34)	-0.008 (0.79)	-0.14 (0.013)	-0.007 (0.1)	0.22 (0.3)	0.021 (0.2)
Losartan	0.35 (0.52)	-0.17 (0.0002)	-0.029 (0.9)	-0.063 (0.006)	-0.36 (0.1)	-0.015 (0.4)	0.24 (0.5)	0.018 (0.5)
Olmesartan	-0.16 (0.41)	0.1*	-0.15 (0.69)	-0.16*			0.039 (0.64)	0.018 (0.009)
Telmisartan	-0.044(0.24)	0.007 (0.11)	1.4 (0.001)	-0.11 (0.0013)	0.025 (0.54)	-0.006 (0.04)	0.075 (0.4)	0.008 (0.2)

For peer review only

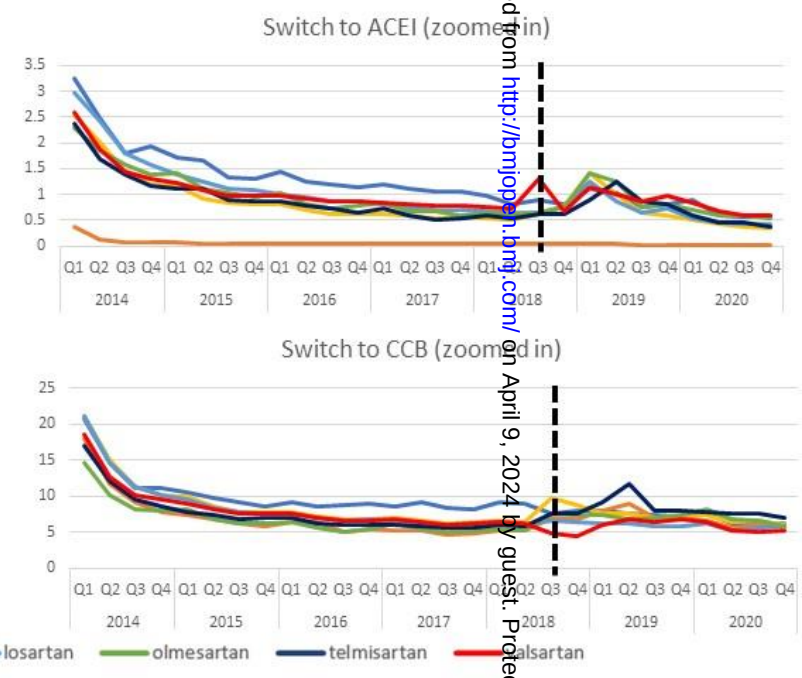
10.1136/bmjopen-2023-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

SFigure 1. Quarterly proportions (represented as percentages) for individual ARB episodes switching to non-index ARB, ACEI or CCB (individually) for US data.



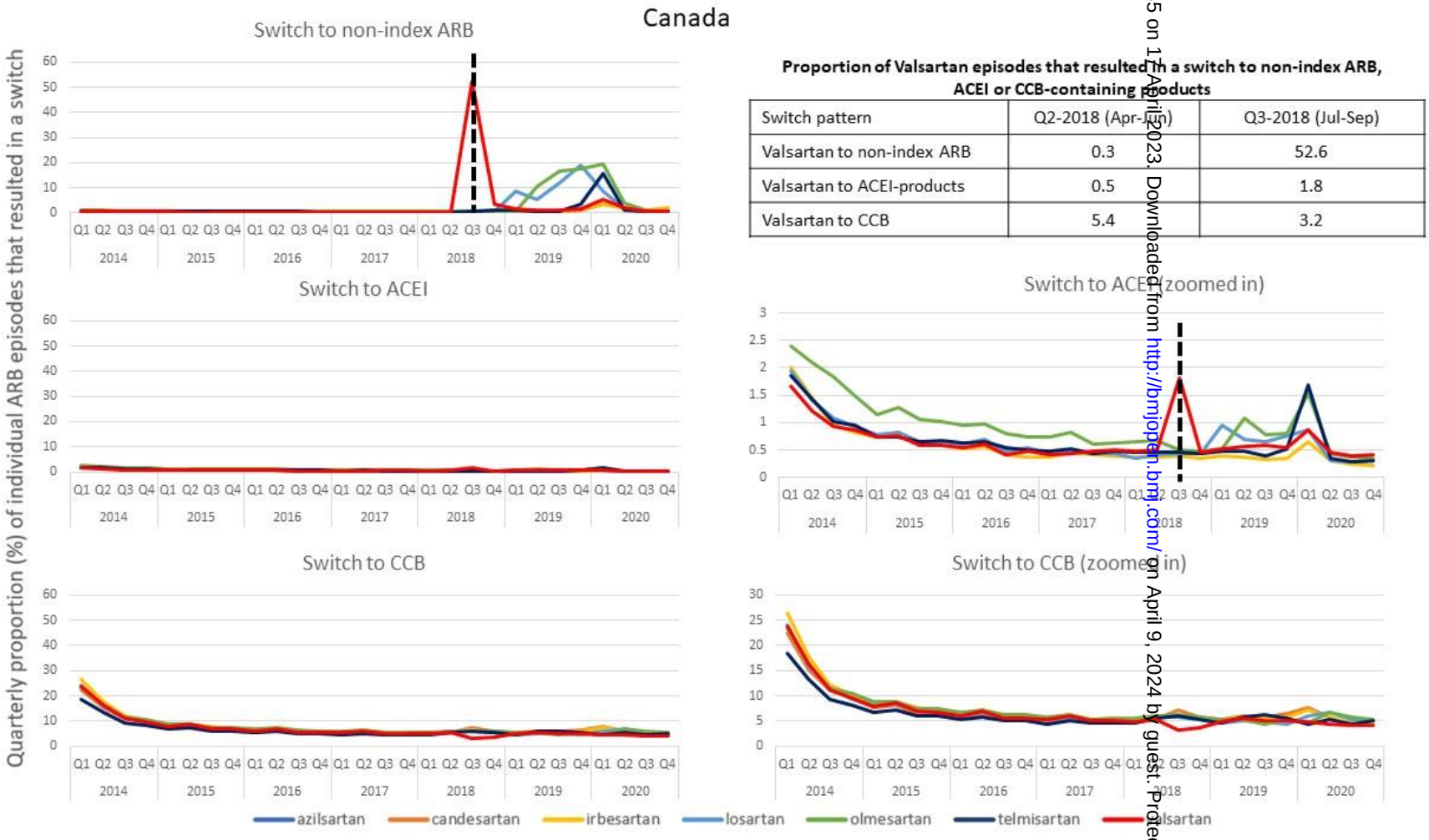
Proportion of Valsartan episodes that resulted in a switch to non-index ARB, ACEI or CCB-containing products

Switch pattern	Q2-2018 (Apr-Jun)	Q3-2018 (Jul-Sep)
Valsartan to non-index ARB	0.6	42.8
Valsartan to ACEI-products	0.7	1.3
Valsartan to CCB	6.3	4.9



10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

SFigure 2. Quarterly proportions (represented as percentages) for individual ARB episodes switching to non-index ARB, ACEI or CCB (individually) for Canada data.

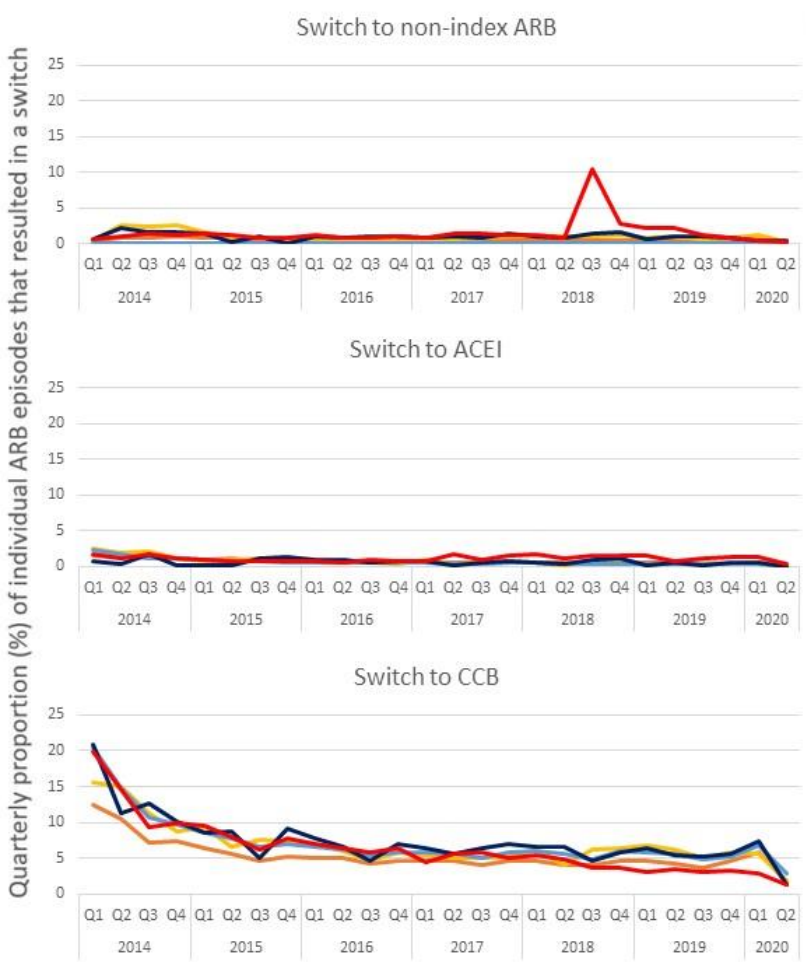


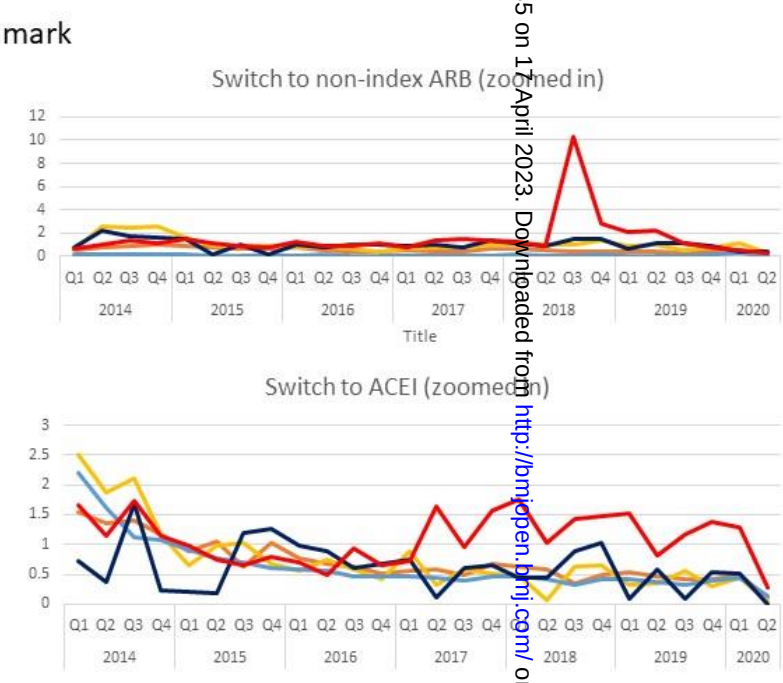
Proportion of Valsartan episodes that resulted in a switch to non-index ARB, ACEI or CCB-containing products

Switch pattern	Q2-2018 (Apr-Jun)	Q3-2018 (Jul-Sep)
Valsartan to non-index ARB	0.3	52.6
Valsartan to ACEI-products	0.5	1.8
Valsartan to CCB	5.4	3.2

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

SFigure 3. Quarterly proportions (represented as percentages) for individual ARB episodes switching to non-index ARB, ACEI or CCB (individually) for Denmark data.



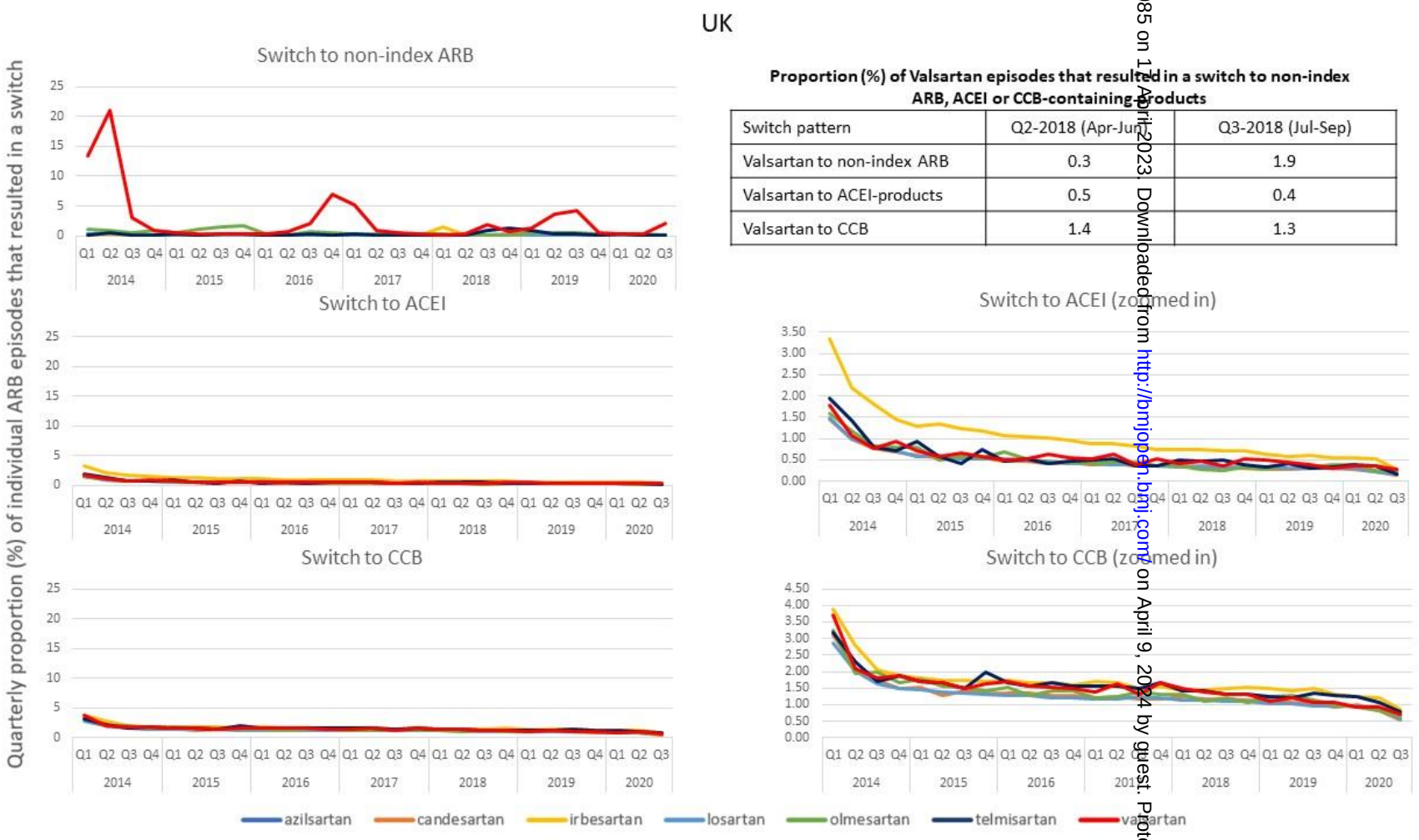


Proportion of Valsartan episodes that resulted in a switch to non-index ARB, ACEI or CCB-containing products

Switch pattern	Q2-2018 (Apr-Jun)	Q3-2018 (Jul-Sep)
Valsartan to non-index ARB	0.9	10.4
Valsartan to ACEI-products	1.1	1.4
Valsartan to CCB	4.8	3.6

10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 3, 2024 by guest. Protected by copyright.

SFigure 4. Quarterly proportions (represented as percentages) for individual ARB episodes switching to non-index ARB, ACEI or CCB (individually) for UK data.

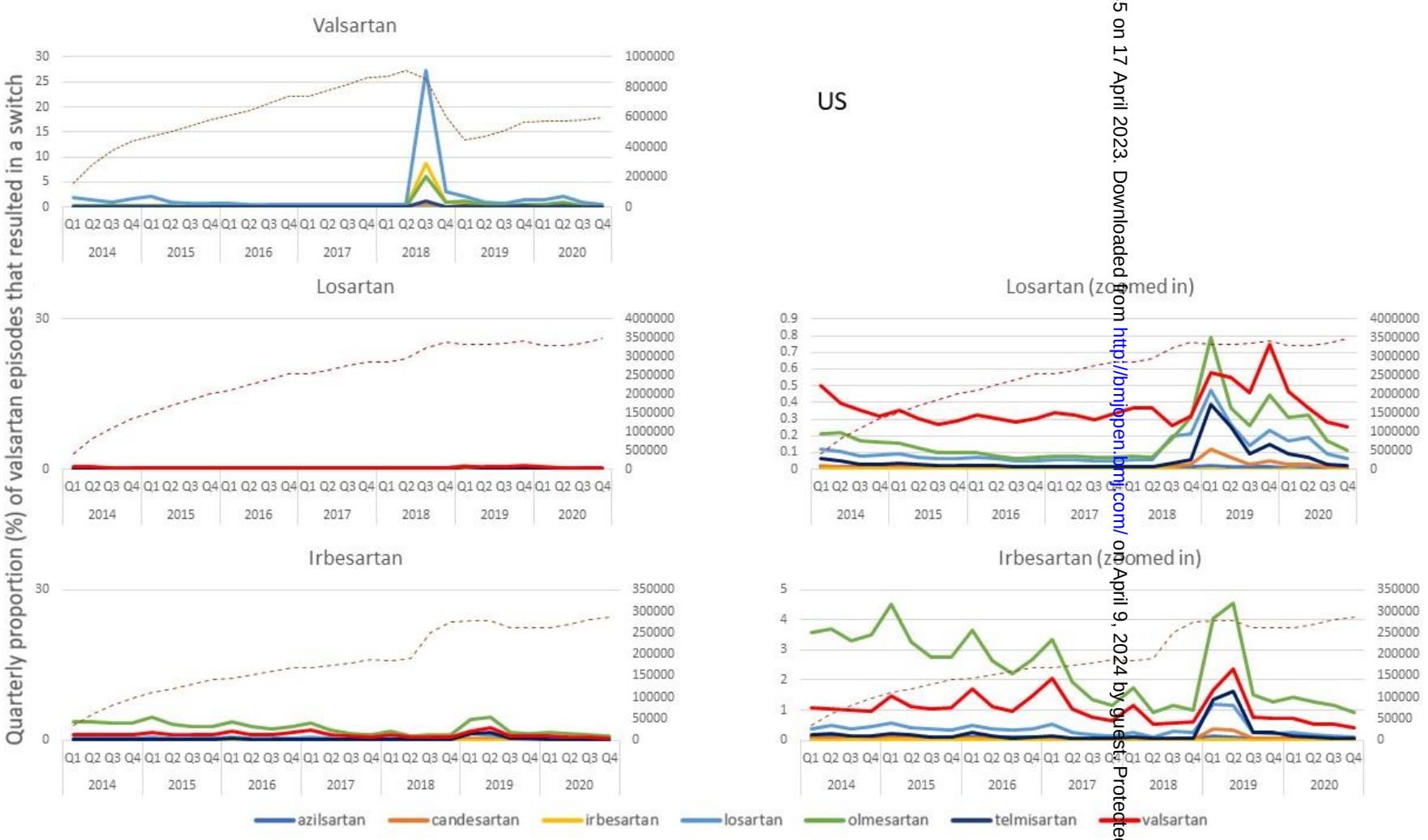


Proportion (%) of Valsartan episodes that resulted in a switch to non-index ARB, ACEI or CCB-containing products

Switch pattern	Q2-2018 (Apr-Jun)	Q3-2018 (Jul-Sep)
Valsartan to non-index ARB	0.3	1.9
Valsartan to ACEI-products	0.5	0.4
Valsartan to CCB	1.4	1.3

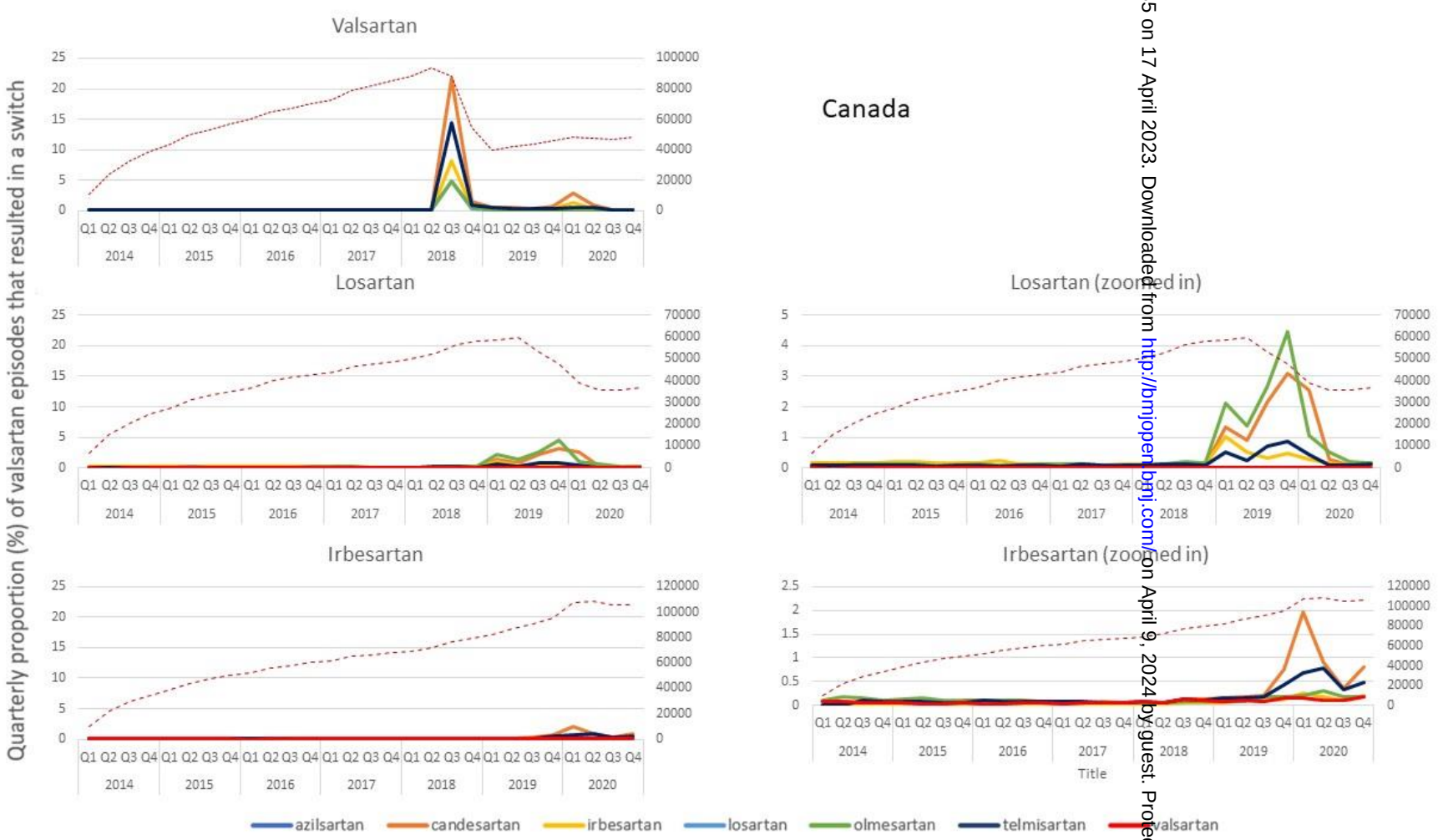
BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 14 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

SFigure 5. Quarterly proportions (represented as percentages) for Valsartan episodes switching to non-index ARB, ACEI or CCB (individually) for US data.



10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

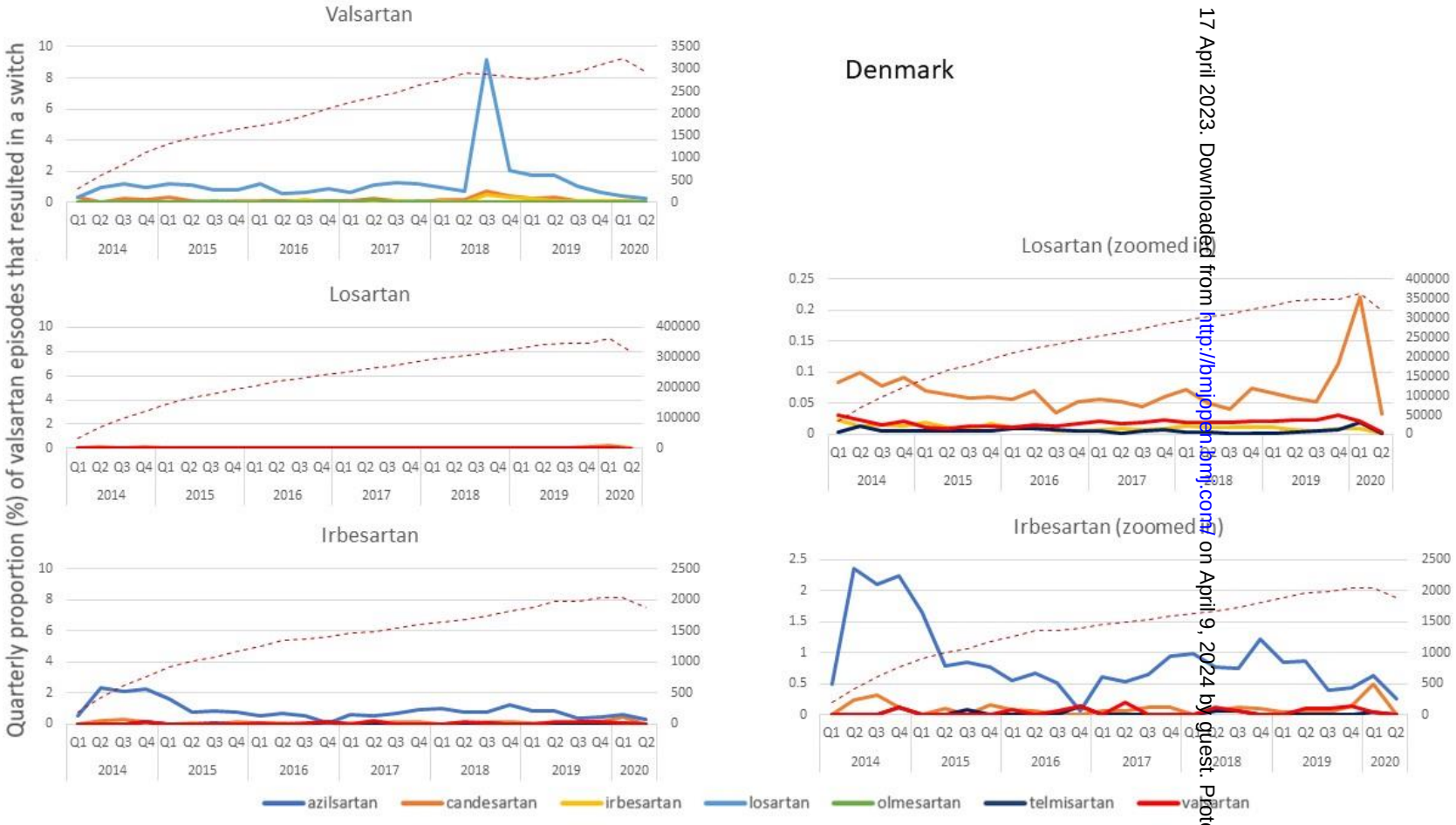
SFigure 6. Quarterly proportions (represented as percentages) for Valsartan episodes switching to non-index ARB, ACEI or CCB (individually) for Canada data.



http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

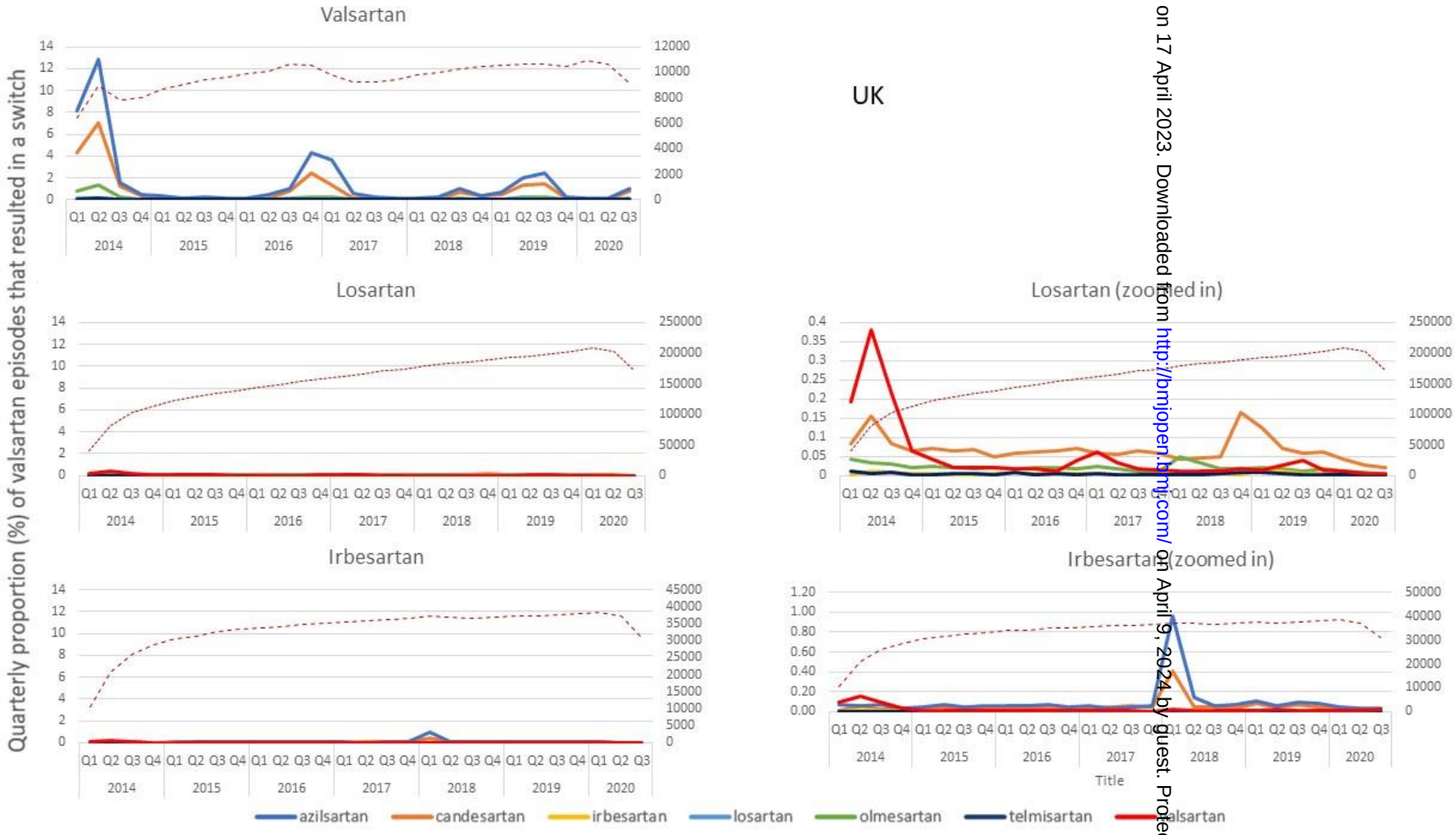
10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from

SFigure 7. Quarterly proportions (represented as percentages) for Valsartan episodes switching to non-index ARB, ACEI or CCB (individually) for Denmark data.



10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

SFigure 8. Quarterly proportions (represented as percentages) for Valsartan episodes switching to non-index ARB, ACEI or CCB (individually) for UK data.



http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4,5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4,5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	4,5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	NA
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	5
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	5
Outcome data	15*	Report numbers of outcome events or summary measures over time	5

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	5,6
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	5,6
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	5,6
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	7

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

For peer review only

BMJ Open

Utilization of Valsartan, Losartan and Irbesartan in US, UK, Canada, and Denmark after the nitrosamine recalls: a descriptive cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-070985.R1
Article Type:	Original research
Date Submitted by the Author:	07-Mar-2023
Complete List of Authors:	Eworuke, Efe; US Food and Drug Administration, Shinde, Mayura; Harvard Medical School and Harvard Pilgrim Health Care Institute, Department of Population Medicine Hou, Laura; Harvard Medical School and Harvard Pilgrim Health Care Institute, Department of Population Medicine Paterson, Michael; Canadian Network for Observational Drug Effect Studies (CNODES) Jensen, Peter Bjødstrup; University of Southern Denmark Maro, Judith; Harvard Medical School and Harvard Pilgrim Health Care Institute, Department of Population Medicine Rai, Ashish; Harvard Medical School and Harvard Pilgrim Health Care Institute, Department of Population Medicine Scarnecchia, Daniel; Harvard Medical School and Harvard Pilgrim Health Care Institute, Department of Population Medicine Pennap, Dinci; US Food and Drug Administration Woronow, Daniel; US Food and Drug Administration Ghosh, Rebecca; Clinical Practice Research Datalink, Medicines and Healthcare Products Regulatory Welburn, Stephen; Clinical Practice Research Datalink, Medicines and Healthcare Products Regulatory Pottegard, Anton; Odense Universitetshospital, Hospital Pharmacy; University of Southern Denmark, Department of Public Health, Clinical Pharmacology and Pharmacy Platt, Robert; Harvard Medical School and Harvard Pilgrim Health Care Institute, Department of Population Medicine Lee, Hana; US Food and Drug Administration Bradley, Marie; US Food and Drug Administration
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Health services research, Global health, Public health
Keywords:	Epidemiology < TROPICAL MEDICINE, Cardiac Epidemiology < CARDIOLOGY, Heart failure < CARDIOLOGY, Hypertension < CARDIOLOGY

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

SCHOLARONE™
Manuscripts

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

For peer review only

Utilization of Valsartan, Losartan and Irbesartan in US, UK, Canada, and Denmark after the nitrosamine recalls: a descriptive cohort study

Authors: Efe Eworuke,[1] Mayura Shinde,[2] Laura Hou,[2] J. Michael Paterson,[3] Peter Jensen,[4] Judith C. Maro,[2] Ashish Rai,[2] Daniel Scarnecchia,[2] Dinci Pennap,[1] Daniel Woronow,[1] Rebecca E. Ghosh[5], Stephen Welburn[5], Anton Pottegård,[4] Robert W Platt[3], Hana Lee,[1] Marie C Bradley[1]

Author Affiliations:

1. Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD, USA
2. Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, USA
3. Canadian Network for Observational Drug Effect Studies (CNODES), Montréal, QC, CA
4. University of Southern Denmark, Odense, DK
5. Clinical Practice Research Datalink, Medicines and Healthcare Products Regulatory Agency, UK

Corresponding author: Efe Eworuke

Division of Epidemiology II, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993

Telephone: 240-402-3972

Fax: 301-796-9850

Email: efeeworuke@gmail.com

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

For peer review only

Manuscript word count: 3022 (max: 3000)

Abstract word count: 297 (max: 300)

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Abstract

Objectives: To examine valsartan, losartan and irbesartan utilization and switching patterns in the US, UK, Canada, and Denmark before and after July 2018, when the first ARB (valsartan) was recalled.

Design: Retrospective cohort study

Setting: US, 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, angiotensin-converting-enzyme inhibitors (ACEI) or calcium channel blockers (CCB)-containing products.

Results: We identified 10.8, 3.2, 1.8; and 1.2 million ARB users in the US, UK, Canada, and Denmark respectively. Overall proportions of valsartan, losartan and irbesartan use were 18.4%, 67.9% and 5.2% in US; 3.1%, 48.3% and 10.2% in 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 US 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 US, 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

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

and irbesartan, to other ARBs throughout 2019, in the US and Canada, although the utilization trends in the US remained unchanged.

Conclusion: The first recall notice for valsartan resulted in substantial decline in utilization 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 utilization trends remained unchanged.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Strengths and limitations of this study

- This first international study to examine changes in the use of nitrosamine-affected angiotensin receptor blockers (ARB) (valsartan, losartan and irbesartan) in four different countries after the issuance of a global-wide ARB recall due to nitrosamine impurities.
- The study allowed for a comprehensive examination and comparison of switching patterns among 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.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

Introduction

In July 2018, several regulatory agencies around the world notified the public about the presence of a potential carcinogenic impurity, N-nitrosodimethylamine (NMDA) in valsartan-containing products, due to changes in the manufacturing process at Zhejiang Huahai Pharmaceuticals (ZHP) 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. 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. 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 US, more valsartan products (n=624) were recalled compared to 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 nanograms NDMA per day is considered reasonably safe.[7] Since cancer risk depends on both dose and years of exposure, it was determined that if 8,000 patients took the

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

maximum recommended daily dose of valsartan (320mg daily) for four 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 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 utilization 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 utilization, from 2014 through 2020 in four countries. Healthcare data from the US, four Canadian provinces, the UK and Denmark were converted to Sentinel's standardized common data model, allowing for the deployment of the same analysis in the four databases.

Methods

Data Sources

We analyzed 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 the appendix.

Study Cohorts

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

This retrospective descriptive cohort study was conducted using data from January 1, 2014, through December 31, 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.

Patient and Public Involvement

No patients were directly involved in the conduct of 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) i.e., switch to a different drug within the ARB class, ACEI, CCB or ACEI/CCB combination drugs. 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 disenrollment, death, the end of the data provided by each data partner or product discontinuation.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

Statistical Analysis

ARB utilization trends

We calculated the monthly percentage of individual ARB utilization 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 utilization. We examined (1) the change in the monthly proportions (level change) of individual ARB utilization immediately after the recall notice (July 2018) and (2) the change in trend in the monthly proportions (trend change) of individual ARB utilization 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 utilized ARBs for each country. Additionally, we considered three sensitivity analyses: First, we treated July 2018-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

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

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). Lastly, 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 Inc., Cary, NC, USA. This Sentinel activity is a public health surveillance activity conducted under the authority of the Food and Drug Administration 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 US, UK, Canada and Denmark respectively. The overall proportions of valsartan, losartan and irbesartan use were 18.4%, 67.9% and 5.2% in US; 3.1%, 48.3% and 10.2% in 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-year-old users compared to 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 US, Canada, and UK.

ARB Utilization Trends

The monthly trends for the percentage of individual ARB utilization differed by country (**Figure 2**).

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

US

For the US, 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% to 72%), olmesartan (5% to 6%), and olmesartan (4% to 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 (**STable 1**).

Canada

For Canada, over time, candesartan and valsartan accounted for the largest share of ARB episodes, followed by telmisartan and irbesartan. Like the US, 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% to 23%), telmisartan (18% to 20%) and irbesartan (16% to 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 (i.e., larger decrease in use) than those for candesartan, telmisartan, and irbesartan (**STable 1**).

Denmark

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

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 (i.e., larger decrease in use) compared to candesartan, telmisartan, and irbesartan (**STable 1**).

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 (**STable 1**).

Sensitivity ITS Analyses

Excluding the transition period (**STable 2**) strengthened the valsartan decline in US (from -6.4% to 10%), Canada (-8% to -12.2%) and in Denmark (-0.04% to -0.1%). Using equal time points prior to and after the intervention date (**STable 3a and b**) 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 (**STable 4**).

Trends for Incident ARB users

In the US, 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

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

For peer review only

accompanying increase in new users of losartan (71.4% to 73.2%); olmesartan (3.0% to 4.6%) and irbesartan (0.8% to 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 users increased (20.5% to 23.2% and 18.3% to 19.6%, respectively) during the same period. No changes to the rate of any incident ARB users were observed in Denmark and UK (**Figure 3**).

Switching

In the US and Canada, there was an immediate increase, from Q2-2018 (April-June) to Q3-2018 (July-August), in the proportions of valsartan episodes that switched to a non-index ARB, ACEI or CCB (US: 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 US, 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 (**SFigure 1-4**). In the US, from Q2 to Q3 2018, there was increased switching from valsartan to a non-index ARB (0.6% to 42.8%), but only a small increase for ACEI (0.7% to 1.3%) and a decrease in switching to CCB (6.3% to 4.9%) (**SFigure 1**). In Canada and Denmark (**SFigure 2-3**), similar trends were observed for valsartan; increased switching to a non-index ARB (Canada: 0.3% to 52.6%; Denmark: 0.9% to 10.4%); or to ACEI (Canada: 0.5% to 1.8%; Denmark:1.1%

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

to 1.4%) but decreased switching to CCB (Canada: 5.4% to 3.2%; Denmark: 4.8% to 3.6%). Switching trends in the UK were negligible (**SFigure 4**). Generally, patients on valsartan were switched to the most frequently used ARB in the respective country, following the recall notice. In the US, the majority of valsartan episodes were switched to losartan, followed by irbesartan and olmesartan (**SFigure 5**). In Canada, most valsartan episodes were switched to candesartan, followed by telmisartan, irbesartan and olmesartan (**SFigure 6**); in Denmark, majority of valsartan episodes were switched to losartan (**SFigure 7**) and in UK there was negligible switching in Q3-2018 (**SFigure 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, 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

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

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 US and Canada compared to Denmark and the UK, and a slight increase in switching to ACEI was also observed in the US and Canada. This is likely because the US and Canada had a higher proportion of valsartan users compared to 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 to 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 health care 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 to 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 US, Denmark and UK, there were only negligible changes to the overall utilization trends for losartan after the recall notice issued in November 2018. Some switching from losartan to other ARBs was observed in the US and UK, but there was no change to the losartan utilization trends. In Canada, increased switching from losartan to olmesartan, candesartan and telmisartan resulted in a decline in losartan utilization. The gradual increase in candesartan and irbesartan utilization between April 2019 and January 2020 is likely the result of the increased switching

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

from losartan to these products. Irbesartan utilization 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 utilization 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 utilizing data from the FDA Sentinel System, CNODES, the U.K CPRD and the Danish prescription registry. All data were converted to Sentinel's standardized common data model, allowing for the deployment of an identical analytic program 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 utilization 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 utilization waned over time.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

Table 1: Selected Demographic and Clinical Characteristics for all ARB users displayed by Country

Characteristics	US (%)	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
Hyperlipidemia	57.2	4.7	NR	0.9
Hypertension	86.1	46.1	NR	25.3
Myocardial infarction	2.2	1.1	NR	0.7

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

Renal disorders	20.7	5.4	NR	2.8
Stroke	4.7	1.8	NR	1.6

NR: Not reported; *Clinical History collected 183 days before the index date

§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.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

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

ARB	US		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	0.01 (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	-0.02 (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

*p<0.0001

For peer review only

http://dx.doi.org/10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

Figure 1. Timeline of nitrosamine recalls issued in US, Canada, Denmark and UK

For peer review only

10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Figure 2: Monthly ARB utilization trends between January 2014 and end of available data or December 2022 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.

For peer review only

10.1136/bmjopen-2023-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Figure 3. Trends for incident ARB users 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.

For peer review only

10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Figure 4. Quarterly proportions (represented as percentages) for individual ARB episodes switching to non-index ARB, ACEI or CCB, stratified by country.

Data callouts represent the quarter-year, monthly percentage (%) for valsartan only.

For peer review only

10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Contributorship

EE and MCB planned the study. EE, MS, LH, MJP, PJ, JCM, AR DS, DP, DW, REG, SW, AP, RWP, HL, MCB were involved in the development of the protocol. EE, MS, LH, AR, HL, MCB were involved in the conduct of the study. EE drafted the first report and EE, MS, LH, MJP, PJ, JCM, AR, DS, DP, DW, REG, SW, AP, RWP, HL, MCB edited and approved the final manuscript.

Funding Statement

This project was supported by Task Order 75F40119F1900 under Master Agreement 75F40119D10037 from the US Food and Drug Administration. The Canadian Network for Observational Drug Effect Studies (CNODES), a collaborating center of the Drug Safety and Effectiveness Network (DSEN), is funded by the Canadian Institutes of Health Research (CIHR; Grant # DSE-146021). This study was made possible through data-sharing agreements between the CNODES member research centers and the respective provincial governments of Manitoba, Nova Scotia, Ontario, and Saskatchewan.

Competing Interests

All authors have no conflicts of interest to disclose.

Disclaimer

Disclaimer: The views expressed in this publication are those of the authors and do not necessarily reflect the official policy of the US Food and Drug Administration or Health Canada or the UK Medicines and Healthcare products Regulatory Agency.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Ethics Approval

This Sentinel activity is a public health surveillance activity conducted under the authority of the Food and Drug Administration and, accordingly, is not subject to Institutional Review Board oversight.

Data Sharing

Data sharing is not permissible due to confidentiality agreements with the data providers.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

References

1. FDA announces voluntary recall of several medicines containing valsartan following detection of an impurity. 2018. Accessed May 26, 2022. https://www.fda.gov/news-events/press-announcements/fda-announces-voluntary-recall-several-medicines-containing-valsartan-following-detection-impurity

2. EMA reviewing medicines containing valsartan from Zhejiang Huahai following detection of an impurity: some valsartan medicines being recalled across the EU. 2018. Accessed May 26, 2022. https://www.ema.europa.eu/en/news/ema-reviewing-medicines-containing-valsartan-zhejiang-huahai-following-detection-impurity-some

3. Several drugs containing valsartan being recalled due to contamination with a potential carcinogen. 2018. Accessed May 26, 2022. https://recalls-rappels.canada.ca/en/alert-recall/several-drugs-containing-valsartan-being-recalled-due-contamination-potential

4. Blood pressure and heart medication recalled from Pharmacie. 2018. Accessed May 26, 2022. https://www.gov.uk/government/news/blood-pressure-and-heart-medication-recalled-from-pharmacies

5. International Agency for Research on Cancer. *IARC monographs on the evaluation of carcinogenic risks to humans. Overall evaluations of carcinogenicity: an updating of IARC Monographs*. Vol. 1-42. 1987.

6. US Food and Drug Administration. Information about Nitrosamine Impurities in Medications. Accessed June 18, 2022, 2022. https://www.fda.gov/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications

7. Update - Analysis of N-nitrosodimethylamine (NDMA) Levels in Recalled Valsartan in the US. 2018. Accessed June 1 2022. https://www.fda.gov/drugs/drug-safety-and-

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan#6297781d0e2e7

8. Basic HHS Policy for Protection of Human Research Subjects, Title 45 82 FR 7259, 7273 1-23 (2017). https://www.fda.gov/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications

9. Federal Policy for the Protection of Human Subjects. In: Office for Human Research Protections (OHRP) DoHaHS, editor. 82 FR 71492017. p. 126.

10. Rosati K JN, Soliz M, Evans BJ. . Sentinel Initiative Principles and Policies: HIPAA and Common Rule Compliance in the Sentinel Initiative. 2018.

11. Peto R, Gray R, Brantom P, Grasso P. Effects on 4080 Rats of Chronic Ingestion of N-Nitrosodiethylamine or N-Nitrosodimethylamine: A Detailed Dose-Response Study1. *Cancer Research*. 1991;51(23_Part_2):6415-6451.

12. Peto R, Gray R, Brantom P, Grasso P. Dose and time relationships for tumor induction in the liver and esophagus of 4080 inbred rats by chronic ingestion of N-nitrosodiethylamine or N-nitrosodimethylamine. *Cancer Res*. Dec 1 1991;51(23 Pt 2):6452-69.

13. Desai RJ, Sarpatwari A, Gautam N, Lii J, Fischer MA, Gagne JJ. Changes in Utilization of Generic Angiotensin Receptor Blockers Following Product Recalls in the United States. *JAMA*. 2020;323(1):87. doi:10.1001/jama.2019.17521

14. Rudolph UM, Enners S, Kieble M, et al. Impact of angiotensin receptor blocker product recalls on antihypertensive prescribing in Germany. *Journal of Human Hypertension*. 2021;35(10):903-911. doi:10.1038/s41371-020-00425-z

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

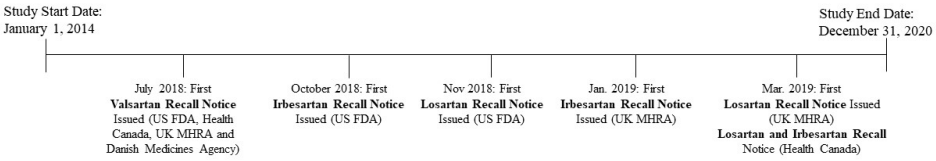


Figure 1. Timeline of nitrosamine recalls issued in US, Canada, Denmark and UK

338x190mm (96 x 96 DPI)

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

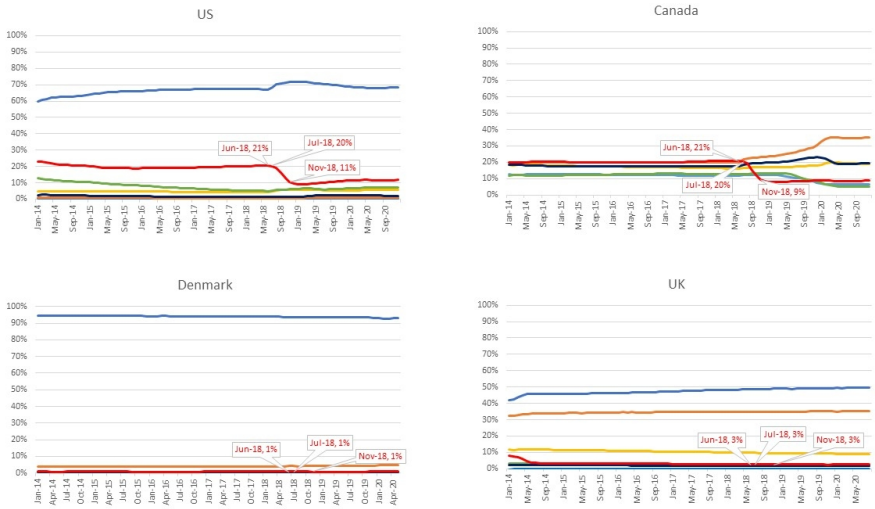


Figure 2: Monthly ARB utilization trends between January 2014 and end of available data or December 2020 by country

338x190mm (96 x 96 DPI)

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

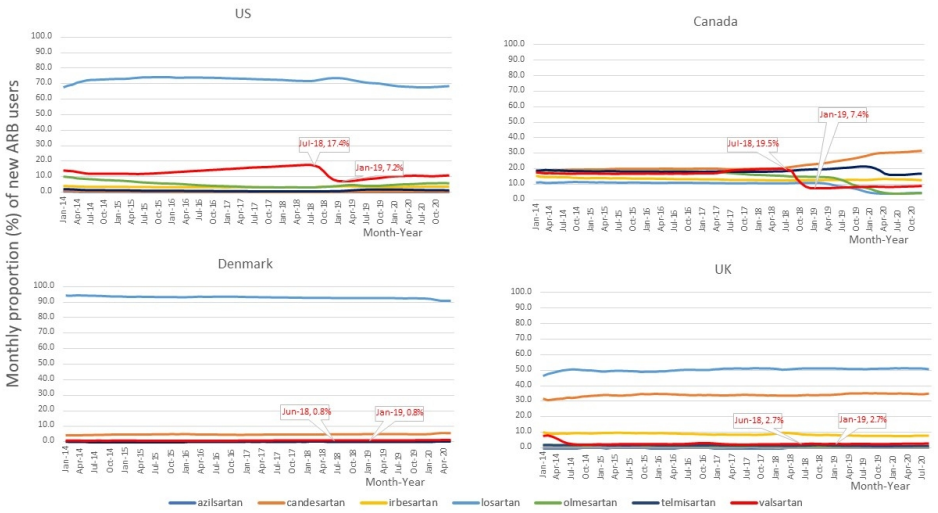


Figure 3. Trends for incident ARB users between January 2014 and end of available data or December 2020 by country

338x190mm (96 x 96 DPI)

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

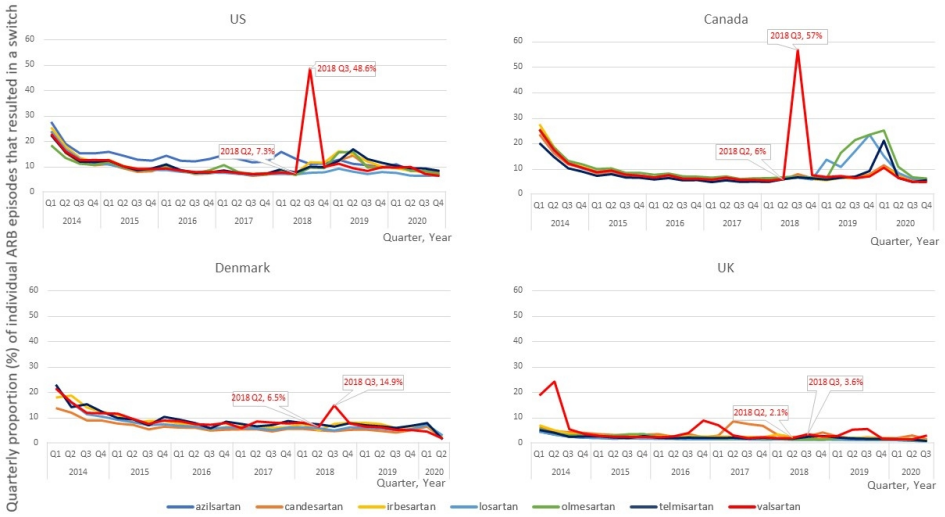


Figure 4. Quarterly proportions (represented as percentages) for individual ARB episodes switching to non-index ARB, ACEI or CCB, stratified by country.

338x190mm (96 x 96 DPI)

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

Utilization of Valsartan, Losartan and Irbesartan in US, UK, Canada, and Denmark after the nitrosamine recalls: a descriptive cohort study

Authors: Efe Eworuke,[1] Mayura Shinde,[2] Laura Hou,[2] J. Michael Paterson,[3] Peter Jensen,[4] Judy Maro,[2] Ashish Rai,[2] Daniel Scarnecchia,[2] Dinci Pennap,[1] Daniel Woronow,[1] Rebecca Ghosh[5], Stephen Welburn[5], Anton Pottegard,[4] Robert W Platt[3], Hana Lee,[1] Marie C Bradley[1]

Author Affiliations:

1. Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD, USA
2. Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, USA
3. Canadian Network for Observational Drug Effect Studies (CNODES), Montréal, QC, CA
4. University of Southern Denmark, Odense, DK
5. Medicines and Healthcare Products Regulatory Agency, UK

Disclaimer: The views expressed in this publication are those of the authors and do not necessarily reflect the official policy of the US Food and Drug Administration or Health Canada or the UK Medicines and Healthcare products Regulatory Agency.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

Appendix A. Description of Data Sources

Sentinel (US Data Source)

Sentinel comprises electronic health care data from a distributed network of 18 US based data partners including Medicare. These data partners, mostly commercial health insurers and integrated delivery care networks, convert their data into a common data model. The data domains include patient demographics, enrollment, inpatient, outpatient, and emergency room diagnoses and procedures and outpatient pharmacy dispensing based on National Drug Codes (NDCs).

CNODES (Canada Data Source)

CNODES is a collaborating center of the Canadian Drug Safety and Effectiveness Network. CNODES team members have access to linked healthcare and prescription drug records from seven provincial databases across Canada, including the four that contributed to this study; Saskatchewan, Manitoba, Ontario, and Nova Scotia; the first provinces to transform their data into the Sentinel Common Data Model. CNODES uses a distributed network like that in the Sentinel system and includes the same data domains. Outpatient prescription drug dispensings are identified using Health Canada Drug Identification Numbers (DINs).

Danish National Prescription Registry (Denmark Data Source)

The Danish National Prescription Registry (DNPR), one of the Danish national registries collects detailed information on prescriptions redeemed in Denmark since 1995. Prescription medicines are offered to Danish residents under a reimbursement scheme which allows for a patient co-payment until the out-of-pocket expenditure is reached. The DNPR receives data recorded in the electronic dispensing systems of community pharmacies and includes information on the patient, the drug dispensed (fill date, composition and amount of drug), the prescriber and dispensing pharmacy.

CPRD (UK Data Source)

The UK CPRD is a computerized database of anonymized longitudinal patient records from primary care linked to a range of other health related data. It collects data from around 674 general practices in the UK, covers about 8.5% of the population and is broadly representative in terms of age, sex and geography. Demographic information, lifestyle data, prescription details, clinical events and diagnoses, preventive care, specialist referrals, and hospital admissions and their major outcomes are all recorded in the database.

For peer review only

STable 1. Comparative Interrupted Time Series Analysis

Variable	Estimate (%)	P-value	Comparator ARB
US			
Level change	-13.2	<.0001	Losartan
Trend change	0.4	<.0001	
Level change	-11.7	<.0001	Olmesartan
Trend change	-0.06	0.0019	
Level change	-11.3	<.0001	Irbesartan
Trend change	0.1	<.0001	
Canada			
Level change	-14.1	<.0001	Candesartan
Trend change	-0.59	<.0001	
Level change	-16.0	<.0001	Telmisartan
Trend change	0.05	0.0	
Level change	-12.5	<.0001	Irbesartan
Trend change	-0.2	<.0001	
Denmark			
Level change	-0.16	<.0001	Candesartan
Trend change	-0.02	<.0001	
Level change	-0.07	<.0001	Telmisartan
Trend change	0.003	0.0052	
Level change	-0.09	<.0001	Irbesartan
Trend change	0.003	0.0454	
UK			
Level change	0.9	0.064	Candesartan
Trend change	0.1	0.120	
Level change	0.4	0.472	Losartan
Trend change	0.1	0.016	
Level change	0.8	0.055	Irbesartan
Trend change	0.0	0.189	

Negative values indicate a larger decrease in use compared to the comparator ARB.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

STable 2. Interrupted Time Series Analysis excluding the transition period

	US		Canada		Denmark		UK	
	Level Change	Trend Change	Level Change	Trend Change	Level Change	Trend Change	Level Change	Trend Change
Valsartan	-10.0*	0.14*	-12.2*	0.0	-0.1*	0.0	0.6 (0.1)	0.04 (0.09)
Azilsartan	0.03 (0.06)	0.0	NA		NA		0.0 (0.5)	0.0
Candesartan	0.2*	0.02*	0.2 (0.6)	0.6*	0.07 (0.1)	0.03*	-0.4 (0.006)	-0.01 (0.3)
Irbesartan	1.3*	0.0	0.4 (0.03)	0.2*	0.00 (0.6)	0.0	-0.2*	0.01 (0.0002)
Losartan	3.2*	-0.29*	1.1*	-0.3*	0.06 (0.3)	-0.04*	0.2 (0.5)	-0.05 (0.001)
Olmesartan	1.7*	0.2*	1.5*	-0.4*	NA		0.0 (0.2)	0.0
Telmisartan	0.8*	0.04*	3.8*	-0.04 (0.05)	-0.02 (0.1)	0.0	0.2*	0.02*

*p-value <0.0001

For peer review only

10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

STable 3a. Interrupted Time Series Analysis using equal time points before and after the intervention date and excluding the transition period

	US		Canada		Denmark		UK	
	Level Change	Trend Change	Level Change	Trend Change	Level Change	Trend Change	Level Change	Trend Change
Valsartan	-11.6*	0.09*	-12.8*	-0.04 (0.007)	-0.14*	0.0	0.2 (0.01)	0.02 (0.01)
Azilsartan	0.0	0.02*					0.0	0.0
Candesartan	0.1*	-0.03*	0.2 (0.7)	0.6*	-0.01 (0.8)	0.02*	-0.08 (0.05)	0.02*
Irbesartan	1.5*	-0.24*	0.0 (0.8)	0.2*	0.0	0.004*	-0.2*	0.0
Losartan	5.1*	0.06*	2.0*	-0.4*	0.1 (0.08)	-0.03*	0.2 (0.001)	-0.05*
Olmesartan	1.3*	0.0	2.6*	-0.5*			0.01 (0.4)	0.01*
Telmisartan	0.4 (0.0003)	0.1*	2.5*	0.1 (0.1)	-0.04*	0.0	-0.01 (0.2)	0.0

*p-value <0.0001

Stable 3b. Interrupted Time Series Analysis using equal time points before and after the intervention date, including the transition period

	US		Canada		Denmark		UK	
	Level Change	Trend Change	Level Change	Trend Change	Level Change	Trend Change	Level Change	Trend Change
Valsartan	-8.9*	0.2 (0.001)	-10.1*	0.1 (0.2)	-0.07*	0.01 (0.0004)	-0.11 (0.1)	0.0
Azilsartan	-0.02*	0.0					0.0	0.0
Candesartan	0.02 (0.4)	0.02*	1.1 (0.002)	0.8*	0.13 (0.006)	0.03*	0.03 (0.3)	0.02*
Irbesartan	1.3*	-0.04 (0.0001)	-0.5 (0.003)	0.2*	-0.02 (0.001)	0.003*	-0.7*	-0.02 (0.02)
Losartan	4.7*	-0.3*	1.3*	-0.4*	-0.17 (0.02)	-0.05	1.2*	0.0
Olmesartan	0.02 (0.9)	0.1 (0.008)	2.4*	0.1 (0.09)			-0.2*	0.0
Telmisartan	0.1 (0.05)	0.05*	1.8*	-0.5*	-0.03*	0.003*	-0.1*	-0.01 (0.002)

For peer review only

10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

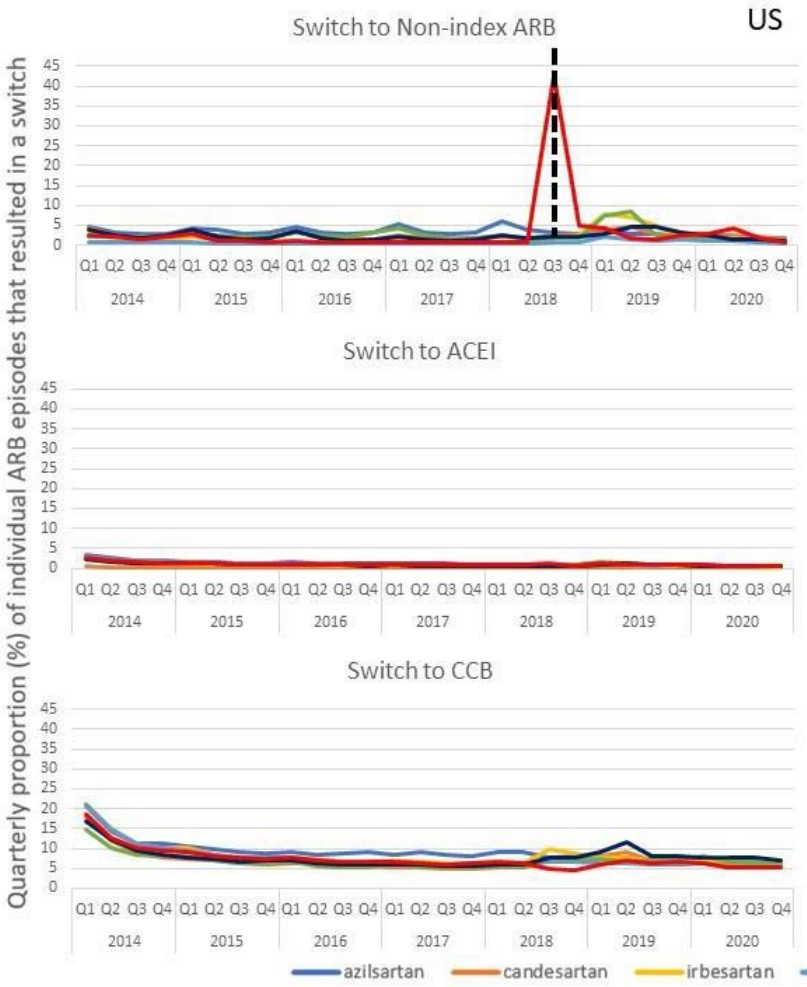
10.1136/bmjopen-2022-060985 on 19 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

STable 4. Interrupted Time Series analysis using control time period (September 2014-May 2018) with intervention date, July 2016.

	US		Canada		Denmark		UK	
	Level Change	Trend Change	Level Change	Trend Change	Level Change	Trend Change	Level Change	Trend Change
Valsartan	3.5 (0.0001)	-0.09 (0.07)	3.2 (0.04)	-0.3*	0.05 (0.007)	0.0	0.6 (0.04)	0.1*
Azilsartan	0.0	0.01*					0.0	0.0
Candesartan	-0.1*	0.02*	-4.6*	0.3*	-0.17*	0.02*	-0.2 (0.004)	-0.04*
Irbesartan	-0.3 (0.02)	0.04*	-1.3*	0.1*	-0.03 (0.0002)	0.0	-0.1 (0.003)	0.0
Losartan	-0.3 (0.6)	-0.2*	1.5 (0.002)	-0.1*	0.13 (0.02)	-0.01*	0.1 (0.6)	-0.04 (0.0009)
Olmesartan	-1.6*	0.2*	2.7 (0.0001)	-0.2*			-0.1*	-0.03*
Telmisartan	-0.3 (0.002)	0.06*	-0.3 (0.5)	0.1*	0.05*	0.003*	0.0 (0.7)	0.0

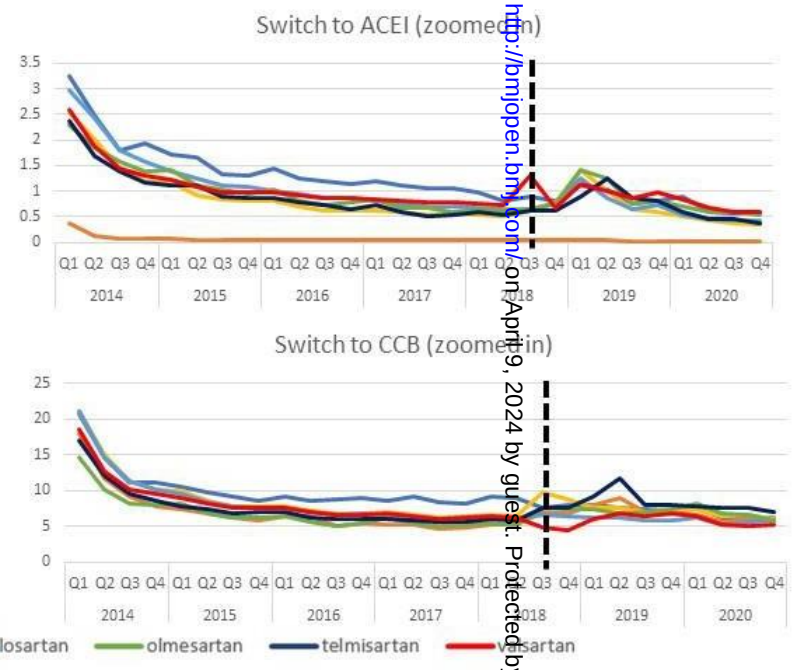
For peer review only

SFigure 1. Quarterly proportions (represented as percentages) for individual ARB episodes switching to non-index ARB, ACEI or CCB (individually) for US data.



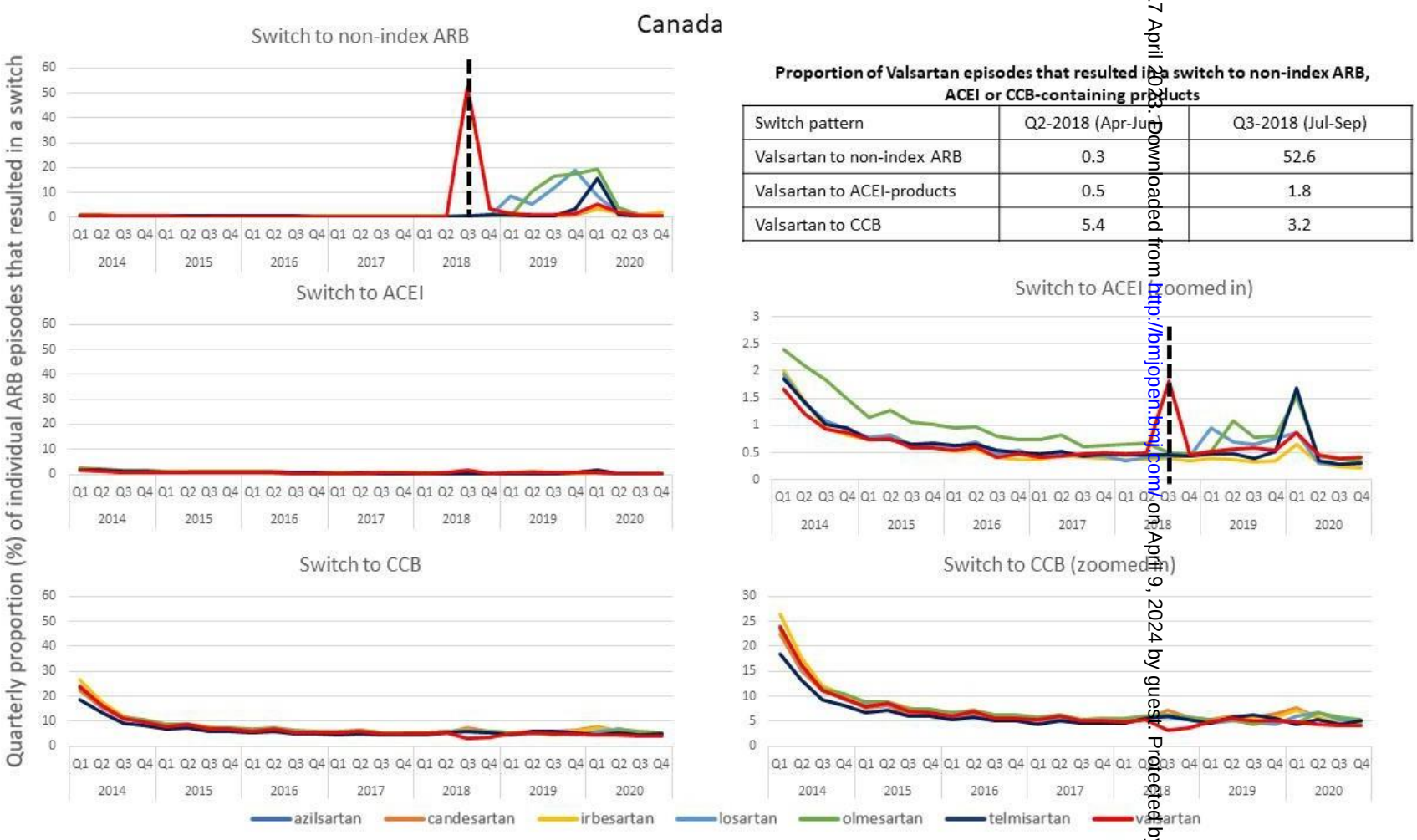
Proportion of Valsartan episodes that resulted in a switch to non-index ARB, ACEI or CCB-containing products

Switch pattern	Q2-2018 (Apr-Jun)	Q3-2018 (Jul-Sep)
Valsartan to non-index ARB	0.6	42.8
Valsartan to ACEI-products	0.7	1.3
Valsartan to CCB	6.3	4.9



10.1136/bmjopen-2022-070935 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.

SFigure 2. Quarterly proportions (represented as percentages) for individual ARB episodes switching to non-index ARB, ACEI or CCB (individually) for Canada data.

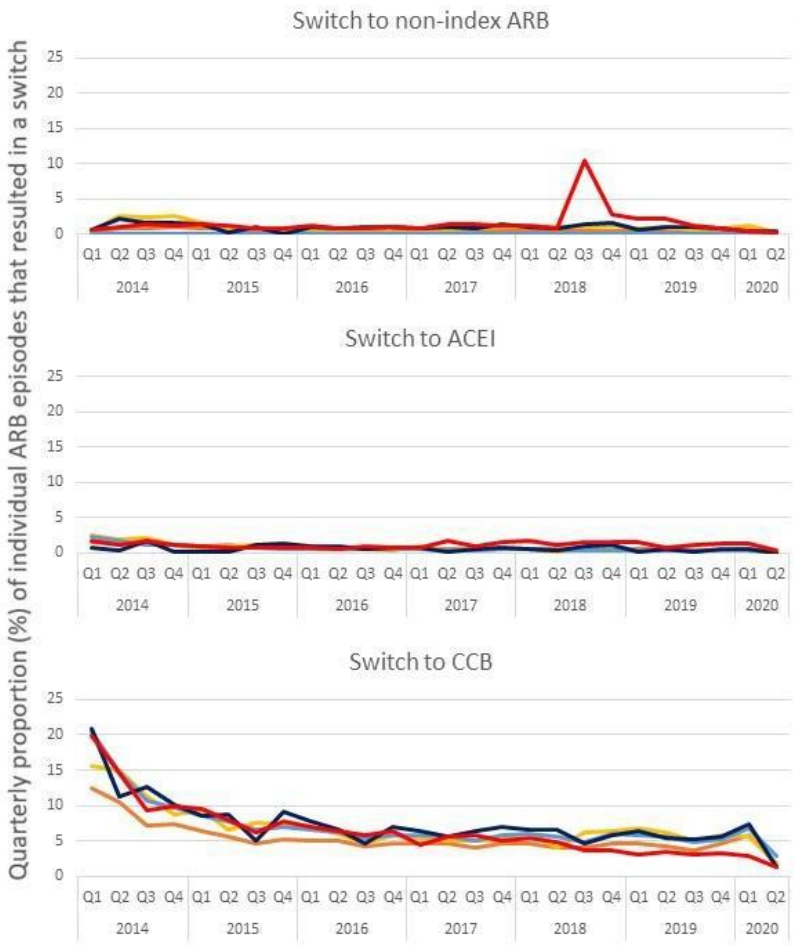


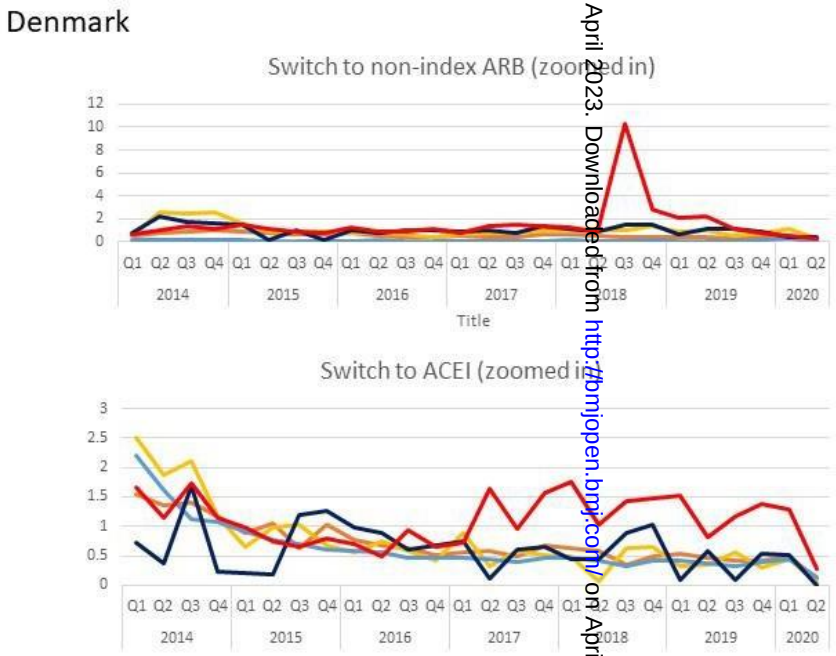
Proportion of Valsartan episodes that resulted in a switch to non-index ARB, ACEI or CCB-containing products

Switch pattern	Q2-2018 (Apr-Jun)	Q3-2018 (Jul-Sep)
Valsartan to non-index ARB	0.3	52.6
Valsartan to ACEI-products	0.5	1.8
Valsartan to CCB	5.4	3.2

BMJ Open: first published as 10.1136/bmjopen-2022-070935 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

SFigure 3. Quarterly proportions (represented as percentages) for individual ARB episodes switching to non-index ARB, ACEI or CCB (individually) for Denmark data.



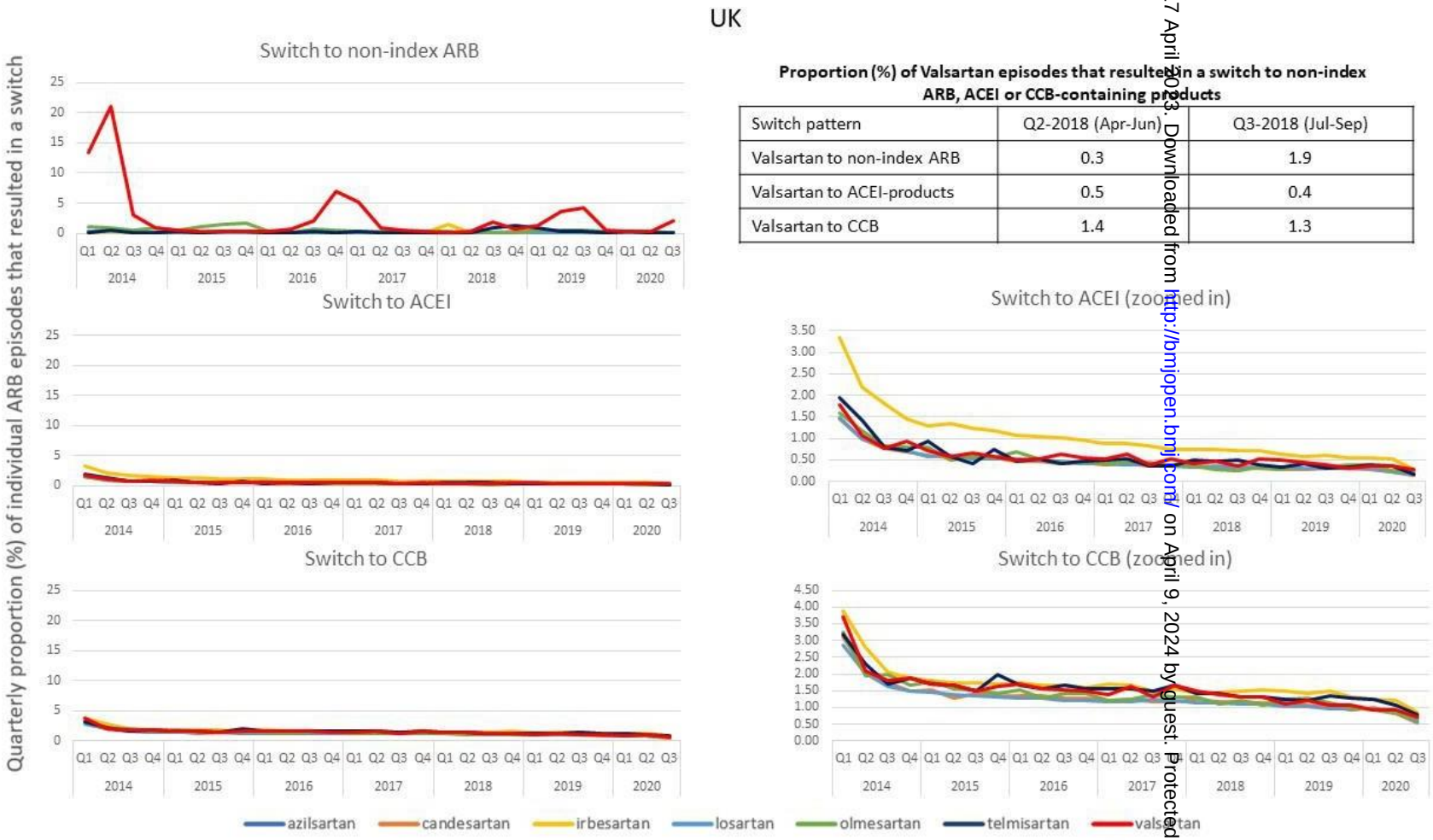


Proportion of Valsartan episodes that resulted in a switch to non-index ARB, ACEI or CCB-containing products

Switch pattern	Q2-2018 (Apr-Jun)	Q3-2018 (Jul-Sep)
Valsartan to non-index ARB	0.9	10.4
Valsartan to ACEI-products	1.1	1.4
Valsartan to CCB	4.8	3.6

10.1136/bmjopen-2022-070935 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

SFigure 4. Quarterly proportions (represented as percentages) for individual ARB episodes switching to non-index ARB, ACEI or CCB (individually) for UK data.

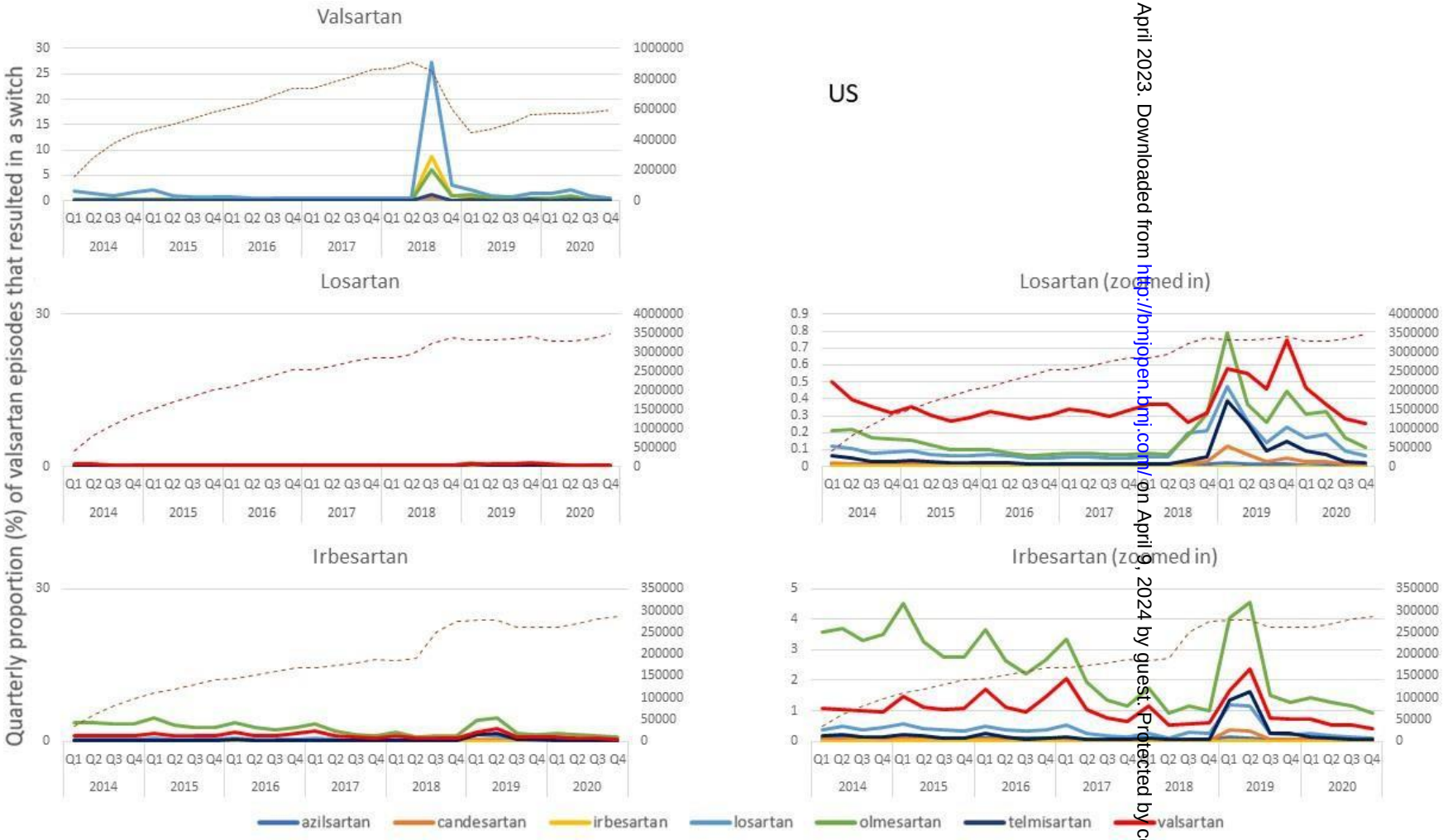


Proportion (%) of Valsartan episodes that resulted in a switch to non-index ARB, ACEI or CCB-containing products

Switch pattern	Q2-2018 (Apr-Jun)	Q3-2018 (Jul-Sep)
Valsartan to non-index ARB	0.3	1.9
Valsartan to ACEI-products	0.5	0.4
Valsartan to CCB	1.4	1.3

10.1136/bmjopen-2022-070935 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

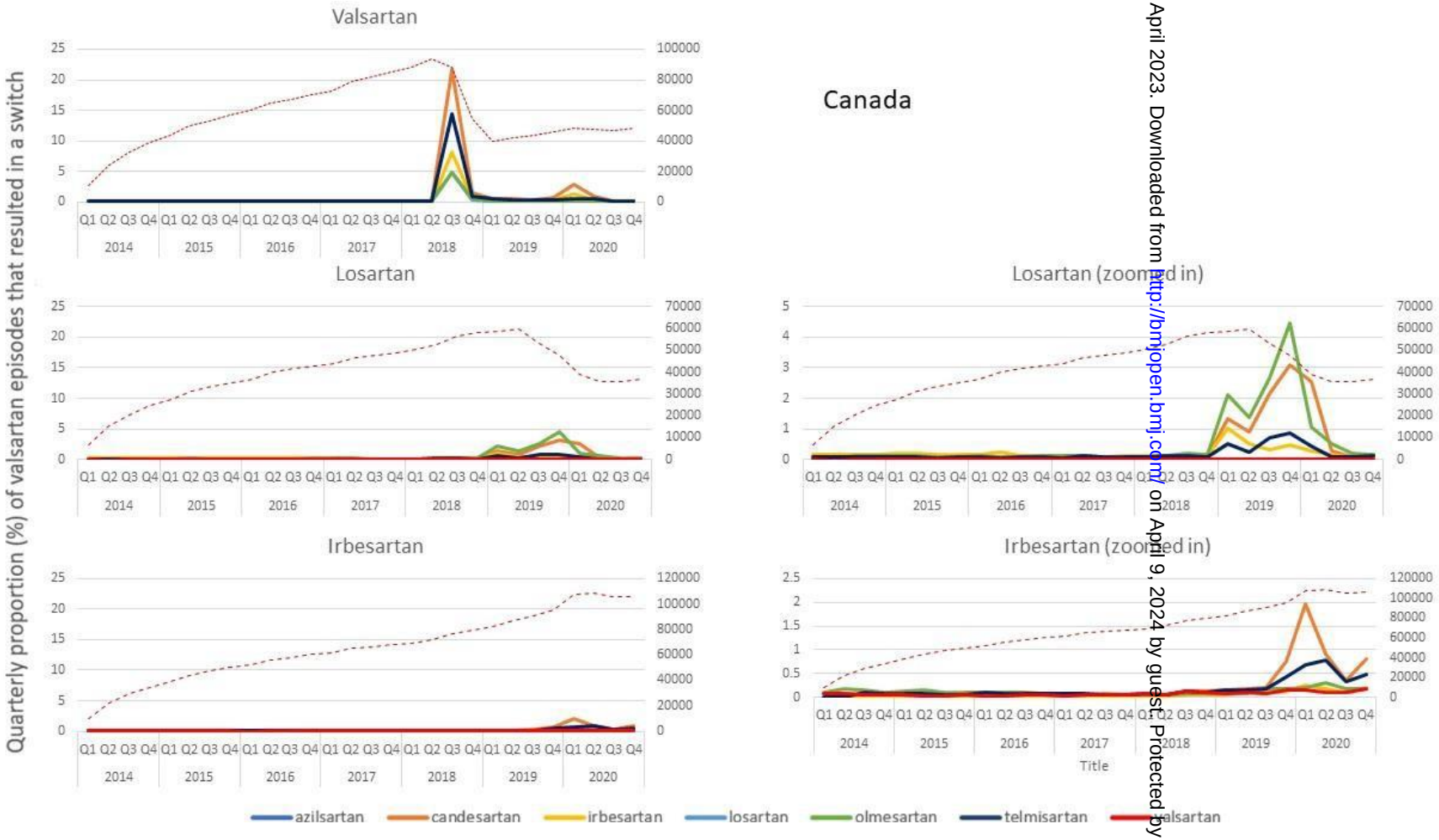
SFigure 5. Quarterly proportions (represented as percentages) for Valsartan episodes switching to non-index ARB/ACEI or CCB (individually) for US data.



The dotted lines denote the total number of valsartan episodes in each quarter, year

10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

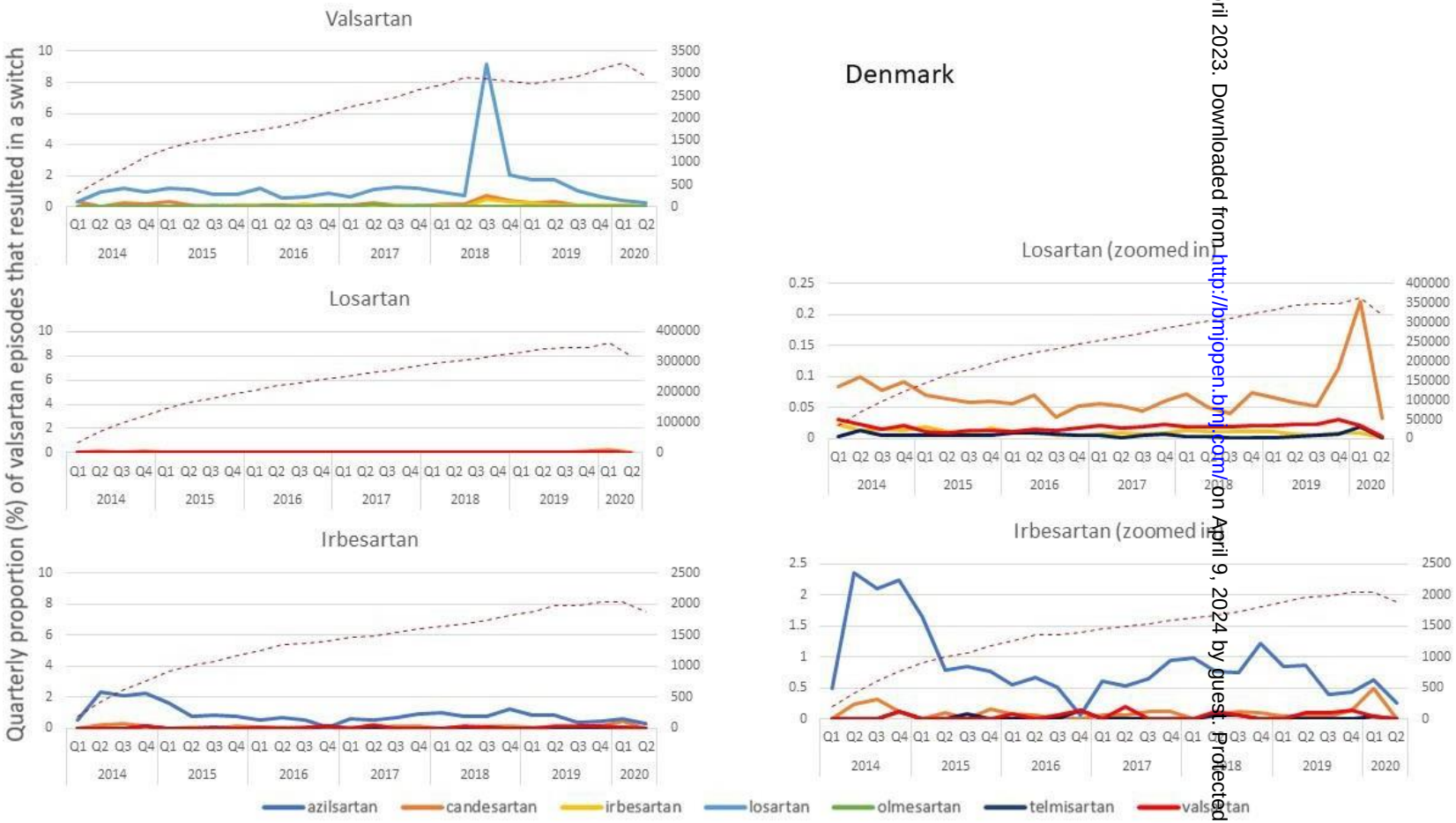
SFigure 6. Quarterly proportions (represented as percentages) for Valsartan episodes switching to non-index ARB, ACEI or CCB (individually) for Canada data.



The dotted lines denote the total number of valsartan episodes in each quarter, year

10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

SFigure 7. Quarterly proportions (represented as percentages) for Valsartan episodes switching to non-index ARB, ACEI or CCB (individually) for Denmark data.

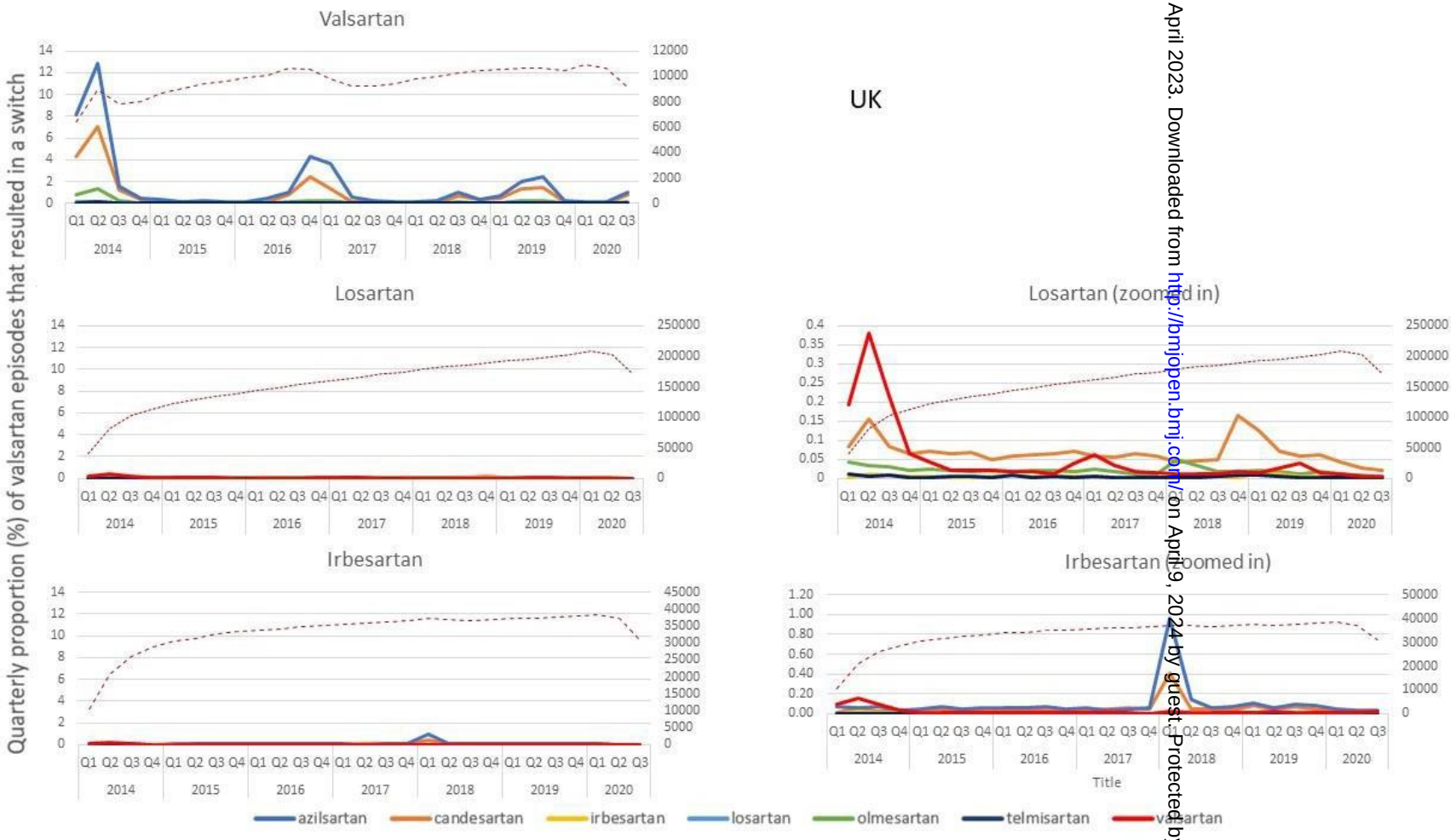


The dotted lines denote the total number of valsartan episodes in each quarter, year

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.

SFigure 8. Quarterly proportions (represented as percentages) for Valsartan episodes switching to non-index ARB, ACEI or CCB (individually) for UK data.



The dotted lines denote the total number of valsartan episodes in each quarter, year

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4,5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4,5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	4,5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	NA
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	5
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	5
Outcome data	15*	Report numbers of outcome events or summary measures over time	5

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	5,6
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	5,6
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	5,6
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	7

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open

Utilization of Valsartan, Losartan and Irbesartan in US, UK, Canada, and Denmark after the nitrosamine recalls: a descriptive cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-070985.R2
Article Type:	Original research
Date Submitted by the Author:	30-Mar-2023
Complete List of Authors:	Eworuke, Efe; US Food and Drug Administration, Shinde, Mayura; Harvard Medical School and Harvard Pilgrim Health Care Institute, Department of Population Medicine Hou, Laura; Harvard Medical School and Harvard Pilgrim Health Care Institute, Department of Population Medicine Paterson, Michael; Canadian Network for Observational Drug Effect Studies (CNODES) Jensen, Peter Bjødstrup; University of Southern Denmark Maro, Judith; Harvard Medical School and Harvard Pilgrim Health Care Institute, Department of Population Medicine Rai, Ashish; Harvard Medical School and Harvard Pilgrim Health Care Institute, Department of Population Medicine Scarnecchia, Daniel; Harvard Medical School and Harvard Pilgrim Health Care Institute, Department of Population Medicine Pennap, Dinci; US Food and Drug Administration Woronow, Daniel; US Food and Drug Administration Ghosh, Rebecca; Clinical Practice Research Datalink, Medicines and Healthcare Products Regulatory Welburn, Stephen; Clinical Practice Research Datalink, Medicines and Healthcare Products Regulatory Pottegard, Anton; Odense Universitetshospital, Hospital Pharmacy; University of Southern Denmark, Department of Public Health, Clinical Pharmacology and Pharmacy Platt, Robert; Harvard Medical School and Harvard Pilgrim Health Care Institute, Department of Population Medicine Lee, Hana; US Food and Drug Administration Bradley, Marie; US Food and Drug Administration
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Health services research, Global health, Public health
Keywords:	Epidemiology < TROPICAL MEDICINE, Cardiac Epidemiology < CARDIOLOGY, Heart failure < CARDIOLOGY, Hypertension < CARDIOLOGY

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

SCHOLARONE™
Manuscripts

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

For peer review only

Utilization of Valsartan, Losartan and Irbesartan in US, UK, Canada, and Denmark after the nitrosamine recalls: a descriptive cohort study

Authors: Efe Eworuke,[1] Mayura Shinde,[2] Laura Hou,[2] J. Michael Paterson,[3] Peter Jensen,[4] Judith C. Maro,[2] Ashish Rai,[2] Daniel Scarnecchia,[2] Dinci Pennap,[1] Daniel Woronow,[1] Rebecca E. Ghosh[5], Stephen Welburn[5], Anton Pottegård,[4] Robert W Platt[3], Hana Lee,[1] Marie C Bradley[1]

Author Affiliations:

1. Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD, USA
2. Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, USA
3. Canadian Network for Observational Drug Effect Studies (CNODES), Montréal, QC, CA
4. University of Southern Denmark, Odense, DK
5. Clinical Practice Research Datalink, Medicines and Healthcare Products Regulatory Agency, UK

Corresponding author: Efe Eworuke

Division of Epidemiology II, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993

Telephone: 240-402-3972

Fax: 301-796-9850

Email: efeeworuke@gmail.com

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

For peer review only

Manuscript word count: 3022 (max: 3000)

Abstract word count: 297 (max: 300)

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Abstract

Objectives: To examine valsartan, losartan and irbesartan utilization and switching patterns in the US, UK, Canada, and Denmark before and after July 2018, when the first ARB (valsartan) was recalled.

Design: Retrospective cohort study

Setting: US, 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, angiotensin-converting-enzyme inhibitors (ACEI) or calcium channel blockers (CCB)-containing products.

Results: We identified 10.8, 3.2, 1.8; and 1.2 million ARB users in the US, UK, Canada, and Denmark respectively. Overall proportions of valsartan, losartan and irbesartan use were 18.4%, 67.9% and 5.2% in US; 3.1%, 48.3% and 10.2% in 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 US 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 US, 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

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

and irbesartan, to other ARBs throughout 2019, in the US and Canada, although the utilization trends in the US remained unchanged.

Conclusion: The first recall notice for valsartan resulted in substantial decline in utilization 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 utilization trends remained unchanged.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Strengths and limitations of this study

- The study allowed for a comprehensive examination and comparison of switching patterns among 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.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

Introduction

In July 2018, several regulatory agencies around the world notified the public about the presence of a potential carcinogenic impurity, N-nitrosodimethylamine (NMDA) in valsartan-containing products, due to changes in the manufacturing process at Zhejiang Huahai Pharmaceuticals (ZHP) 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. 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. 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 US, more valsartan products (n=624) were recalled compared to 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 nanograms NDMA per day is considered reasonably safe.[7] Since cancer risk depends on both dose and years of exposure, it was determined that if 8,000 patients took the

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

maximum recommended daily dose of valsartan (320mg daily) for four 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 utilization 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 utilization, from 2014 through 2020 in four countries. Healthcare data from the US, four Canadian provinces, the UK and Denmark were converted to Sentinel's standardized common data model, allowing for the deployment of the same analysis in the four databases.

Methods

Data Sources

We analyzed 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 the appendix.

Study Cohorts

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

This retrospective descriptive cohort study was conducted using data from January 1, 2014, through December 31, 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- and 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) i.e., switch to a different drug within the ARB class, ACEI, 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

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

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 disenrollment, death, the end of the data provided by each data partner or product discontinuation.

Statistical Analysis

ARB utilization trends

We calculated the monthly percentage of individual ARB utilization 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 utilization. We examined (1) the change in the monthly proportions (level change) of individual ARB utilization immediately after the recall notice (July 2018) and (2) the change in trend in the monthly proportions (trend change) of individual ARB utilization before and after the recall notice. We

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

also performed a controlled ITS (CITS) analysis looking at the difference in levels and trends between valsartan (reference) and the top three frequently utilized ARBs for each country. Additionally, we considered three sensitivity analyses: First, we treated July 2018-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). Lastly, 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 Inc., Cary, NC, USA. All data are deidentified and this study was conducted as a public health surveillance activity under the authority of the Food and Drug Administration 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 US, UK, Canada and Denmark respectively. The overall proportions of valsartan, losartan and irbesartan use were 18.4%, 67.9% and 5.2% in US; 3.1%, 48.3% and 10.2% in 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-year-old users compared to the other countries. Generally, there was a higher proportion of

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

female users than male users across all countries. Prominent co-morbid conditions among ARB users were hypertension and diabetes in the US, Canada, and UK.

ARB Utilization Trends

The monthly trends for the percentage of individual ARB utilization differed by country (**Figure 2**).

US

For the US, 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% to 72%), olmesartan (5% to 6%), and olmesartan (4% to 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 (**STable 1**).

Canada

For Canada, over time, candesartan and valsartan accounted for the largest share of ARB episodes, followed by telmisartan and irbesartan. Like the US, 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% to 23%), telmisartan (18% to 20%) and irbesartan (16% to 17%) was observed for the same period. ITS analyses (**Table 2**) confirmed significant level and trend

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

changes for valsartan (-8%). Significant level change was observed for telmisartan, olmesartan and losartan (**Table 2**). The level change for valsartan was significantly higher (i.e., larger decrease in use) than those for candesartan, telmisartan, and irbesartan (**STable 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 (i.e., larger decrease in use) compared to candesartan, telmisartan, and irbesartan (**STable 1**).

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 (**STable 1**).

Sensitivity ITS Analyses

Excluding the transition period (**STable 2**) strengthened the valsartan decline in US (from -6.4% to 10%), Canada (-8% to -12.2%) and in Denmark (-0.04% to -0.1%). Using equal time points prior to and after the intervention date (**STable 3a and b**) 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 (**STable 4**).

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

For peer review only

Trends for Incident ARB users

In the US, 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% to 73.2%); olmesartan (3.0% to 4.6%) and irbesartan (0.8% to 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 users increased (20.5% to 23.2% and 18.3% to 19.6%, respectively) during the same period. No changes to the rate of any incident ARB users were observed in Denmark and UK (**Figure 3**).

Switching

In the US and Canada, there was an immediate increase, from Q2-2018 (April-June) to Q3-2018 (July-August), in the proportions of valsartan episodes that switched to a non-index ARB, ACEI or CCB (US: 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 US, 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**).

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

Patients on valsartan were more likely switched to other ARBs than to ACEIs or CCBs (**SFigure 1-4**). In the US, from Q2 to Q3 2018, there was increased switching from valsartan to a non-index ARB (0.6% to 42.8%), but only a small increase for ACEI (0.7% to 1.3%) and a decrease in switching to CCB (6.3% to 4.9%) (**SFigure 1**). In Canada and Denmark (**SFigure 2-3**), similar trends were observed for valsartan; increased switching to a non-index ARB (Canada: 0.3% to 52.6%; Denmark: 0.9% to 10.4%); or to ACEI (Canada: 0.5% to 1.8%; Denmark:1.1% to 1.4%) but decreased switching to CCB (Canada: 5.4% to 3.2%; Denmark: 4.8% to 3.6%). Switching trends in the UK were negligible (**SFigure 4**). Generally, patients on valsartan were switched to the most frequently used ARB in the respective country, following the recall notice. In the US, the majority of valsartan episodes were switched to losartan, followed by irbesartan and olmesartan (**SFigure 5**). In Canada, most valsartan episodes were switched to candesartan, followed by telmisartan, irbesartan and olmesartan (**SFigure 6**); in Denmark, majority of valsartan episodes were switched to losartan (**SFigure 7**) and in UK there was negligible switching in Q3-2018 (**SFigure 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, 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

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

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 US and Canada compared to Denmark and the UK, and a slight increase in switching to ACEI was also observed in the US and Canada. This is likely because the US and Canada had a higher proportion of valsartan users compared to 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 to 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 health care 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 to 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 US, Denmark and UK, there were only negligible changes to the overall utilization trends for losartan after the recall notice issued in November 2018. Some switching from losartan to

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

other ARBs was observed in the US and UK, but there was no change to the losartan utilization trends. In Canada, increased switching from losartan to olmesartan, candesartan and telmisartan resulted in a decline in losartan utilization. The gradual increase in candesartan and irbesartan utilization between April 2019 and January 2020 is likely the result of the increased switching from losartan to these products. Irbesartan utilization 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 utilization 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 utilizing data from the FDA Sentinel System, CNODES, the U.K CPRD and the Danish prescription registry. All data were converted to Sentinel's standardized common data model, allowing for the deployment of an identical analytic program 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 utilization 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.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

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 utilization waned over time.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 1: Selected Demographic and Clinical Characteristics for all ARB users displayed by Country

Characteristics	US (%)	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
Hyperlipidemia	57.2	4.7	NR	0.9
Hypertension	86.1	46.1	NR	25.3
Myocardial infarction	2.2	1.1	NR	0.7

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

Renal disorders	20.7	5.4	NR	2.8
Stroke	4.7	1.8	NR	1.6

NR: Not reported; *Clinical History collected 183 days before the index date

§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.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

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

ARB	US		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	0.01 (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	-0.02 (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

*p<0.0001

For peer review only

http://dx.doi.org/10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

Figure 1. Timeline of nitrosamine recalls issued in US, Canada, Denmark and UK

For peer review only

10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Figure 2: Monthly ARB utilization trends between January 2014 and end of available data or December 2022 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.

For peer review only

10.1136/bmjopen-2023-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Figure 3. Trends for incident ARB users 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.

For peer review only

10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Figure 4. Quarterly proportions (represented as percentages) for individual ARB episodes switching to non-index ARB, ACEI or CCB, stratified by country.

Data callouts represent the quarter-year, monthly percentage (%) for valsartan only.

For peer review only

10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Contributorship

EE and MCB planned the study. EE, MS, LH, MJP, PJ, JCM, AR DS, DP, DW, REG, SW, AP, RWP, HL, MCB were involved in the development of the protocol. EE, MS, LH, AR, HL, MCB were involved in the conduct of the study. EE drafted the first report and EE, MS, LH, MJP, PJ, JCM, AR, DS, DP, DW, REG, SW, AP, RWP, HL, MCB edited and approved the final manuscript.

Funding Statement

This project was supported by Task Order 75F40119F1900 under Master Agreement 75F40119D10037 from the US Food and Drug Administration. The Canadian Network for Observational Drug Effect Studies (CNODES), a collaborating center of the Drug Safety and Effectiveness Network (DSEN), is funded by the Canadian Institutes of Health Research (CIHR; Grant # DSE-146021). This study was made possible through data-sharing agreements between the CNODES member research centers and the respective provincial governments of Manitoba, Nova Scotia, Ontario, and Saskatchewan.

Competing Interests

All authors have no conflicts of interest to disclose.

Disclaimer

Disclaimer: The views expressed in this publication are those of the authors and do not necessarily reflect the official policy of the US Food and Drug Administration or Health Canada or the UK Medicines and Healthcare products Regulatory Agency.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Ethics Approval

This Sentinel activity is a public health surveillance activity conducted under the authority of the Food and Drug Administration and, accordingly, is not subject to Institutional Review Board oversight.

Data Sharing

Data sharing is not permissible due to confidentiality agreements with the data providers.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

References

1. FDA announces voluntary recall of several medicines containing valsartan following detection of an impurity. 2018. Accessed May 26, 2022. https://www.fda.gov/news-events/press-announcements/fda-announces-voluntary-recall-several-medicines-containing-valsartan-following-detection-impurity

2. EMA reviewing medicines containing valsartan from Zhejiang Huahai following detection of an impurity: some valsartan medicines being recalled across the EU. 2018. Accessed May 26, 2022. https://www.ema.europa.eu/en/news/ema-reviewing-medicines-containing-valsartan-zhejiang-huahai-following-detection-impurity-some

3. Several drugs containing valsartan being recalled due to contamination with a potential carcinogen. 2018. Accessed May 26, 2022. https://recalls-rappels.canada.ca/en/alert-recall/several-drugs-containing-valsartan-being-recalled-due-contamination-potential

4. Blood pressure and heart medication recalled from Pharmacie. 2018. Accessed May 26, 2022. https://www.gov.uk/government/news/blood-pressure-and-heart-medication-recalled-from-pharmacies

5. International Agency for Research on Cancer. *IARC monographs on the evaluation of carcinogenic risks to humans. Overall evaluations of carcinogenicity: an updating of IARC Monographs*. Vol. 1-42. 1987.

6. US Food and Drug Administration. Information about Nitrosamine Impurities in Medications. Accessed June 18, 2022, 2022. https://www.fda.gov/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications

7. Update - Analysis of N-nitrosodimethylamine (NDMA) Levels in Recalled Valsartan in the US. 2018. Accessed June 1 2022. https://www.fda.gov/drugs/drug-safety-and-

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan#6297781d0e2e7

8. Basic HHS Policy for Protection of Human Research Subjects, Title 45 82 FR 7259, 7273 1-23 (2017). https://www.fda.gov/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications

9. Federal Policy for the Protection of Human Subjects. In: Office for Human Research Protections (OHRP) DoHaHS, editor. 82 FR 71492017. p. 126.

10. Rosati K JN, Soliz M, Evans BJ. . Sentinel Initiative Principles and Policies: HIPAA and Common Rule Compliance in the Sentinel Initiative. 2018.

11. Peto R, Gray R, Brantom P, Grasso P. Effects on 4080 Rats of Chronic Ingestion of N-Nitrosodiethylamine or N-Nitrosodimethylamine: A Detailed Dose-Response Study1. *Cancer Research*. 1991;51(23_Part_2):6415-6451.

12. Peto R, Gray R, Brantom P, Grasso P. Dose and time relationships for tumor induction in the liver and esophagus of 4080 inbred rats by chronic ingestion of N-nitrosodiethylamine or N-nitrosodimethylamine. *Cancer Res*. Dec 1 1991;51(23 Pt 2):6452-69.

13. Desai RJ, Sarpatwari A, Gautam N, Lii J, Fischer MA, Gagne JJ. Changes in Utilization of Generic Angiotensin Receptor Blockers Following Product Recalls in the United States. *JAMA*. 2020;323(1):87. doi:10.1001/jama.2019.17521

14. Rudolph UM, Enners S, Kieble M, et al. Impact of angiotensin receptor blocker product recalls on antihypertensive prescribing in Germany. *Journal of Human Hypertension*. 2021;35(10):903-911. doi:10.1038/s41371-020-00425-z

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

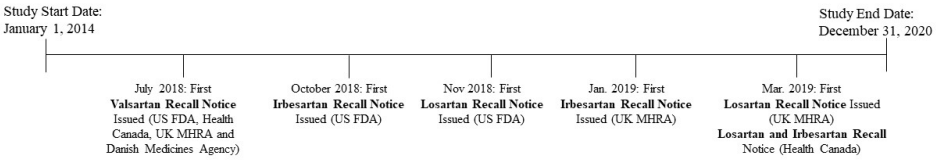


Figure 1. Timeline of nitrosamine recalls issued in US, Canada, Denmark and UK

338x190mm (96 x 96 DPI)

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

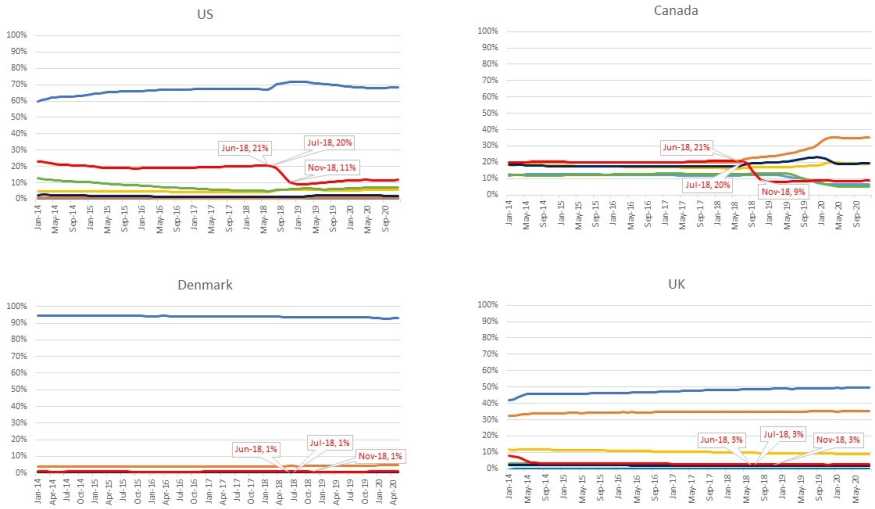


Figure 2: Monthly ARB utilization trends between January 2014 and end of available data or December 2020 by country

338x190mm (96 x 96 DPI)

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

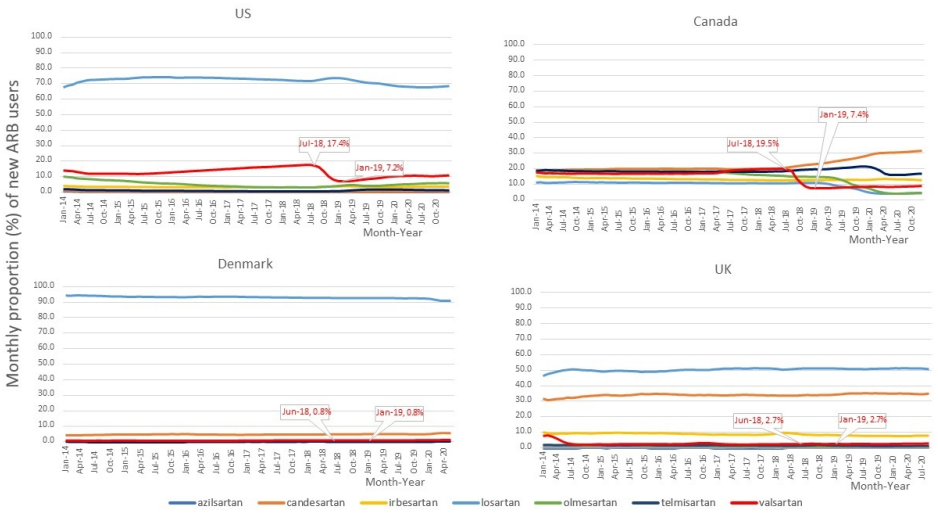


Figure 3. Trends for incident ARB users between January 2014 and end of available data or December 2020 by country

338x190mm (96 x 96 DPI)

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

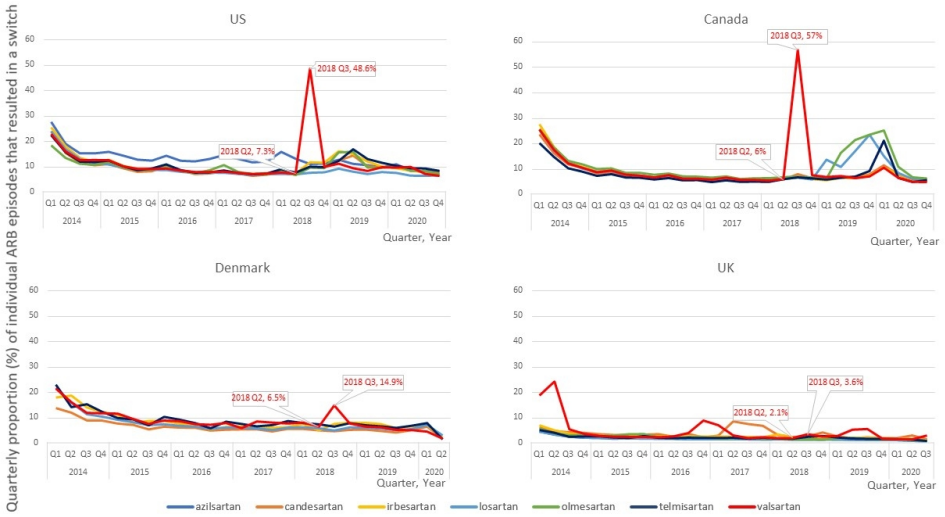


Figure 4. Quarterly proportions (represented as percentages) for individual ARB episodes switching to non-index ARB, ACEI or CCB, stratified by country.

338x190mm (96 x 96 DPI)

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

Utilization of Valsartan, Losartan and Irbesartan in US, UK, Canada, and Denmark after the nitrosamine recalls: a descriptive cohort study

Authors: Efe Eworuke,[1] Mayura Shinde,[2] Laura Hou,[2] J. Michael Paterson,[3] Peter Jensen,[4] Judy Maro,[2] Ashish Rai,[2] Daniel Scarnecchia,[2] Dinci Pennap,[1] Daniel Woronow,[1] Rebecca Ghosh[5], Stephen Welburn[5], Anton Pottegard,[4] Robert W Platt[3], Hana Lee,[1] Marie C Bradley[1]

Author Affiliations:

1. Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD, USA
2. Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, USA
3. Canadian Network for Observational Drug Effect Studies (CNODES), Montréal, QC, CA
4. University of Southern Denmark, Odense, DK
5. Medicines and Healthcare Products Regulatory Agency, UK

Disclaimer: The views expressed in this publication are those of the authors and do not necessarily reflect the official policy of the US Food and Drug Administration or Health Canada or the UK Medicines and Healthcare products Regulatory Agency.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

Appendix A. Description of Data Sources

Sentinel (US Data Source)

Sentinel comprises electronic health care data from a distributed network of 18 US based data partners including Medicare. These data partners, mostly commercial health insurers and integrated delivery care networks, convert their data into a common data model. The data domains include patient demographics, enrollment, inpatient, outpatient, and emergency room diagnoses and procedures and outpatient pharmacy dispensing based on National Drug Codes (NDCs).

CNODES (Canada Data Source)

CNODES is a collaborating center of the Canadian Drug Safety and Effectiveness Network. CNODES team members have access to linked healthcare and prescription drug records from seven provincial databases across Canada, including the four that contributed to this study; Saskatchewan, Manitoba, Ontario, and Nova Scotia; the first provinces to transform their data into the Sentinel Common Data Model. CNODES uses a distributed network like that in the Sentinel system and includes the same data domains. Outpatient prescription drug dispensings are identified using Health Canada Drug Identification Numbers (DINs).

Danish National Prescription Registry (Denmark Data Source)

The Danish National Prescription Registry (DNPR), one of the Danish national registries collects detailed information on prescriptions redeemed in Denmark since 1995. Prescription medicines are offered to Danish residents under a reimbursement scheme which allows for a patient co-payment until the out-of-pocket expenditure is reached. The DNPR receives data recorded in the electronic dispensing systems of community pharmacies and includes information on the patient, the drug dispensed (fill date, composition and amount of drug), the prescriber and dispensing pharmacy.

CPRD (UK Data Source)

The UK CPRD is a computerized database of anonymized longitudinal patient records from primary care linked to a range of other health related data. It collects data from around 674 general practices in the UK, covers about 8.5% of the population and is broadly representative in terms of age, sex and geography. Demographic information, lifestyle data, prescription details, clinical events and diagnoses, preventive care, specialist referrals, and hospital admissions and their major outcomes are all recorded in the database.

For peer review only

STable 1. Comparative Interrupted Time Series Analysis

Variable	Estimate (%)	P-value	Comparator ARB
US			
Level change	-13.2	<.0001	Losartan
Trend change	0.4	<.0001	
Level change	-11.7	<.0001	Olmesartan
Trend change	-0.06	0.0019	
Level change	-11.3	<.0001	Irbesartan
Trend change	0.1	<.0001	
Canada			
Level change	-14.1	<.0001	Candesartan
Trend change	-0.59	<.0001	
Level change	-16.0	<.0001	Telmisartan
Trend change	0.05	0.0	
Level change	-12.5	<.0001	Irbesartan
Trend change	-0.2	<.0001	
Denmark			
Level change	-0.16	<.0001	Candesartan
Trend change	-0.02	<.0001	
Level change	-0.07	<.0001	Telmisartan
Trend change	0.003	0.0052	
Level change	-0.09	<.0001	Irbesartan
Trend change	0.003	0.0454	
UK			
Level change	0.9	0.064	Candesartan
Trend change	0.1	0.120	
Level change	0.4	0.472	Losartan
Trend change	0.1	0.016	
Level change	0.8	0.055	Irbesartan
Trend change	0.0	0.189	

Negative values indicate a larger decrease in use compared to the comparator ARB.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

STable 2. Interrupted Time Series Analysis excluding the transition period

	US		Canada		Denmark		UK	
	Level Change	Trend Change	Level Change	Trend Change	Level Change	Trend Change	Level Change	Trend Change
Valsartan	-10.0*	0.14*	-12.2*	0.0	-0.1*	0.0	0.6 (0.1)	0.04 (0.09)
Azilsartan	0.03 (0.06)	0.0	NA		NA		0.0 (0.5)	0.0
Candesartan	0.2*	0.02*	0.2 (0.6)	0.6*	0.07 (0.1)	0.03*	-0.4 (0.006)	-0.01 (0.3)
Irbesartan	1.3*	0.0	0.4 (0.03)	0.2*	0.00 (0.6)	0.0	-0.2*	0.01 (0.0002)
Losartan	3.2*	-0.29*	1.1*	-0.3*	0.06 (0.3)	-0.04*	0.2 (0.5)	-0.05 (0.001)
Olmesartan	1.7*	0.2*	1.5*	-0.4*	NA		0.0 (0.2)	0.0
Telmisartan	0.8*	0.04*	3.8*	-0.04 (0.05)	-0.02 (0.1)	0.0	0.2*	0.02*

*p-value <0.0001

For peer review only

10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

STable 3a. Interrupted Time Series Analysis using equal time points before and after the intervention date and excluding the transition period

	US		Canada		Denmark		UK	
	Level Change	Trend Change	Level Change	Trend Change	Level Change	Trend Change	Level Change	Trend Change
Valsartan	-11.6*	0.09*	-12.8*	-0.04 (0.007)	-0.14*	0.0	0.2 (0.01)	0.02 (0.01)
Azilsartan	0.0	0.02*					0.0	0.0
Candesartan	0.1*	-0.03*	0.2 (0.7)	0.6*	-0.01 (0.8)	0.02*	-0.08 (0.05)	0.02*
Irbesartan	1.5*	-0.24*	0.0 (0.8)	0.2*	0.0	0.004*	-0.2*	0.0
Losartan	5.1*	0.06*	2.0*	-0.4*	0.1 (0.08)	-0.03*	0.2 (0.001)	-0.05*
Olmesartan	1.3*	0.0	2.6*	-0.5*			0.01 (0.4)	0.01*
Telmisartan	0.4 (0.0003)	0.1*	2.5*	0.1 (0.1)	-0.04*	0.0	-0.01 (0.2)	0.0

*p-value <0.0001

Stable 3b. Interrupted Time Series Analysis using equal time points before and after the intervention date, including the transition period

	US		Canada		Denmark		UK	
	Level Change	Trend Change	Level Change	Trend Change	Level Change	Trend Change	Level Change	Trend Change
Valsartan	-8.9*	0.2 (0.001)	-10.1*	0.1 (0.2)	-0.07*	0.01 (0.0004)	-0.11 (0.1)	0.0
Azilsartan	-0.02*	0.0					0.0	0.0
Candesartan	0.02 (0.4)	0.02*	1.1 (0.002)	0.8*	0.13 (0.006)	0.03*	0.03 (0.3)	0.02*
Irbesartan	1.3*	-0.04 (0.0001)	-0.5 (0.003)	0.2*	-0.02 (0.001)	0.003*	-0.7*	-0.02 (0.02)
Losartan	4.7*	-0.3*	1.3*	-0.4*	-0.17 (0.02)	-0.05	1.2*	0.0
Olmesartan	0.02 (0.9)	0.1 (0.008)	2.4*	0.1 (0.09)			-0.2*	0.0
Telmisartan	0.1 (0.05)	0.05*	1.8*	-0.5*	-0.03*	0.003*	-0.1*	-0.01 (0.002)

For peer review only

10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

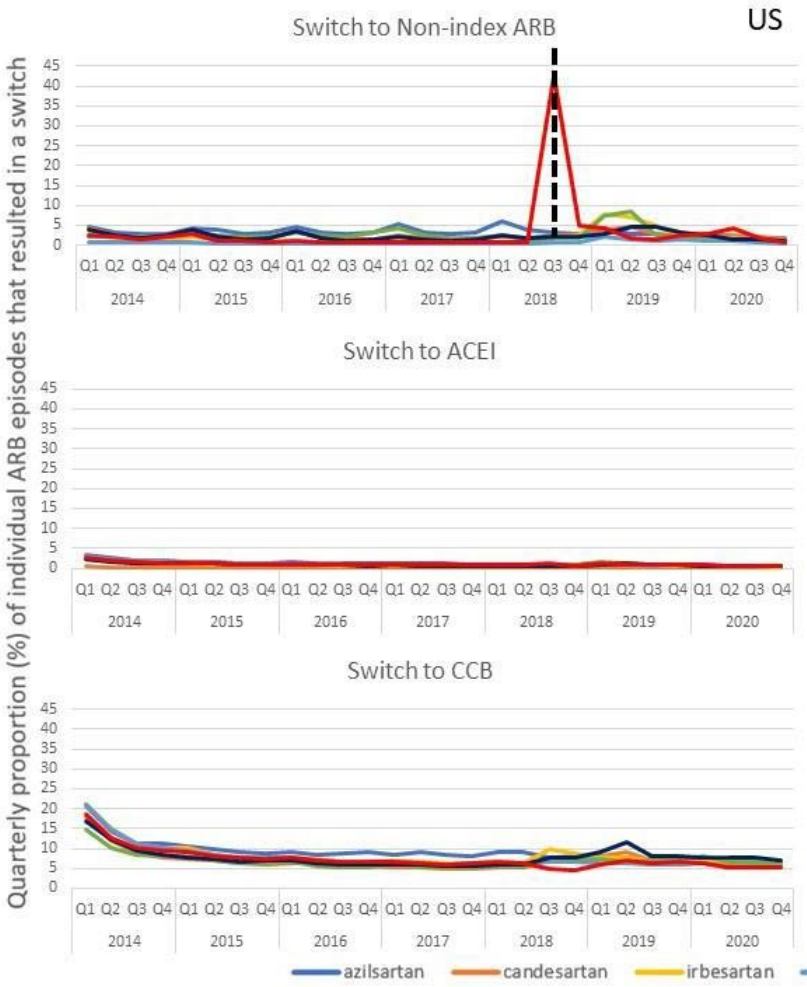
10.1136/bmjopen-2022-060985 on 19 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

STable 4. Interrupted Time Series analysis using control time period (September 2014-May 2018) with intervention date, July 2016.

	US		Canada		Denmark		UK	
	Level Change	Trend Change	Level Change	Trend Change	Level Change	Trend Change	Level Change	Trend Change
Valsartan	3.5 (0.0001)	-0.09 (0.07)	3.2 (0.04)	-0.3*	0.05 (0.007)	0.0	0.6 (0.04)	0.1*
Azilsartan	0.0	0.01*					0.0	0.0
Candesartan	-0.1*	0.02*	-4.6*	0.3*	-0.17*	0.02*	-0.2 (0.004)	-0.04*
Irbesartan	-0.3 (0.02)	0.04*	-1.3*	0.1*	-0.03 (0.0002)	0.0	-0.1 (0.003)	0.0
Losartan	-0.3 (0.6)	-0.2*	1.5 (0.002)	-0.1*	0.13 (0.02)	-0.01*	0.1 (0.6)	-0.04 (0.0009)
Olmesartan	-1.6*	0.2*	2.7 (0.0001)	-0.2*			-0.1*	-0.03*
Telmisartan	-0.3 (0.002)	0.06*	-0.3 (0.5)	0.1*	0.05*	0.003*	0.0 (0.7)	0.0

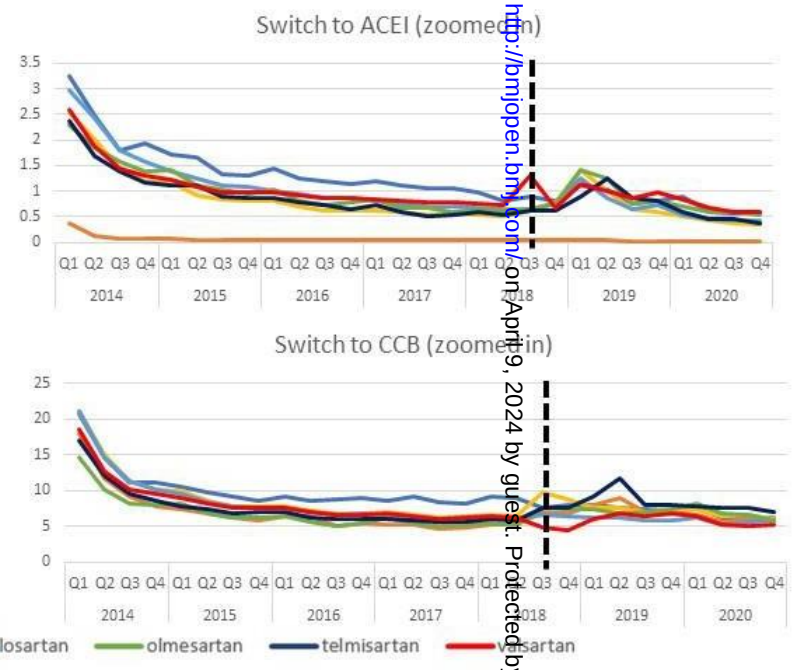
For peer review only

SFigure 1. Quarterly proportions (represented as percentages) for individual ARB episodes switching to non-index ARB, ACEI or CCB (individually) for US data.



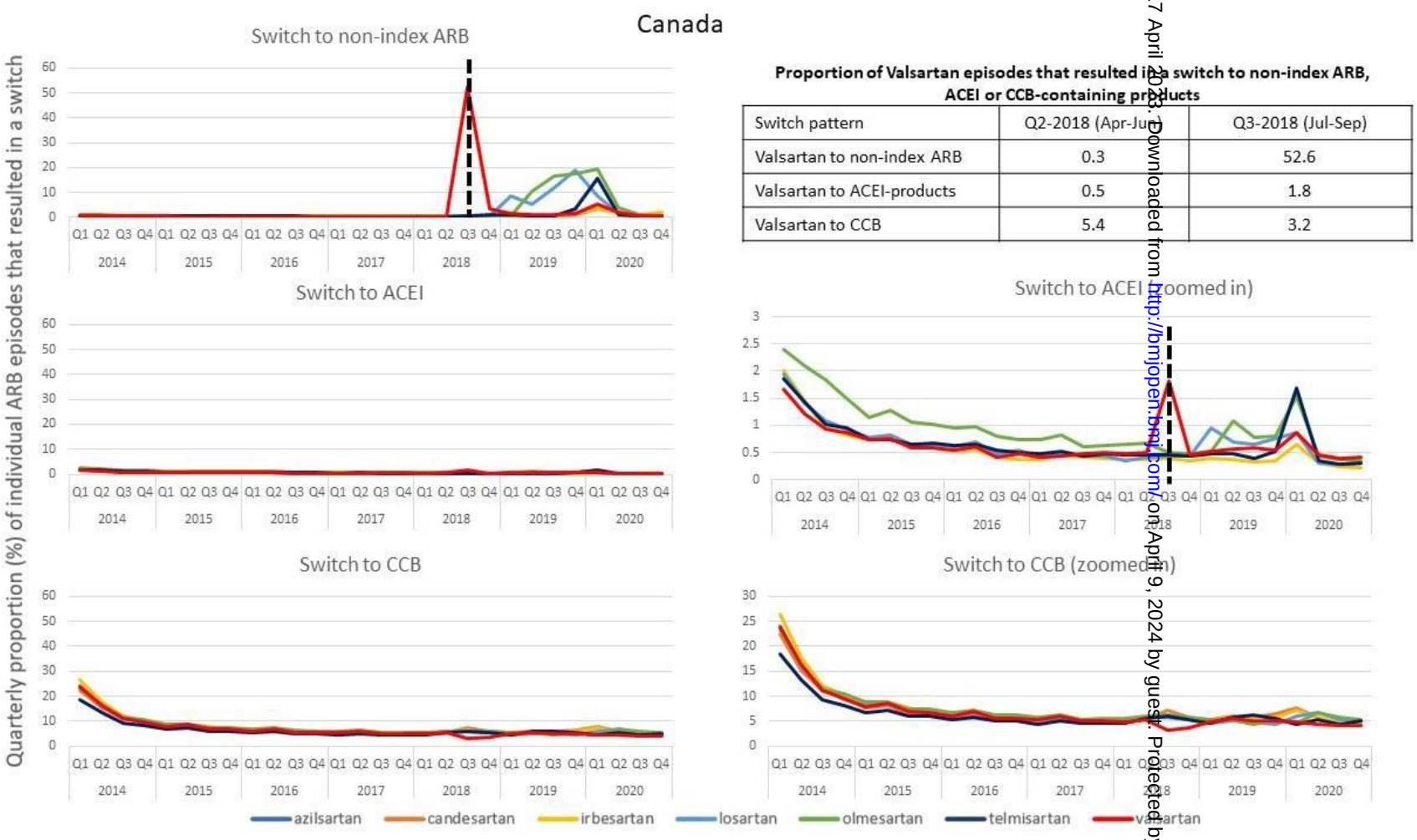
Proportion of Valsartan episodes that resulted in a switch to non-index ARB, ACEI or CCB-containing products

Switch pattern	Q2-2018 (Apr-Jun)	Q3-2018 (Jul-Sep)
Valsartan to non-index ARB	0.6	42.8
Valsartan to ACEI-products	0.7	1.3
Valsartan to CCB	6.3	4.9



10.1136/bmjopen-2022-070935 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.

SFigure 2. Quarterly proportions (represented as percentages) for individual ARB episodes switching to non-index ARB, ACEI or CCB (individually) for Canada data.

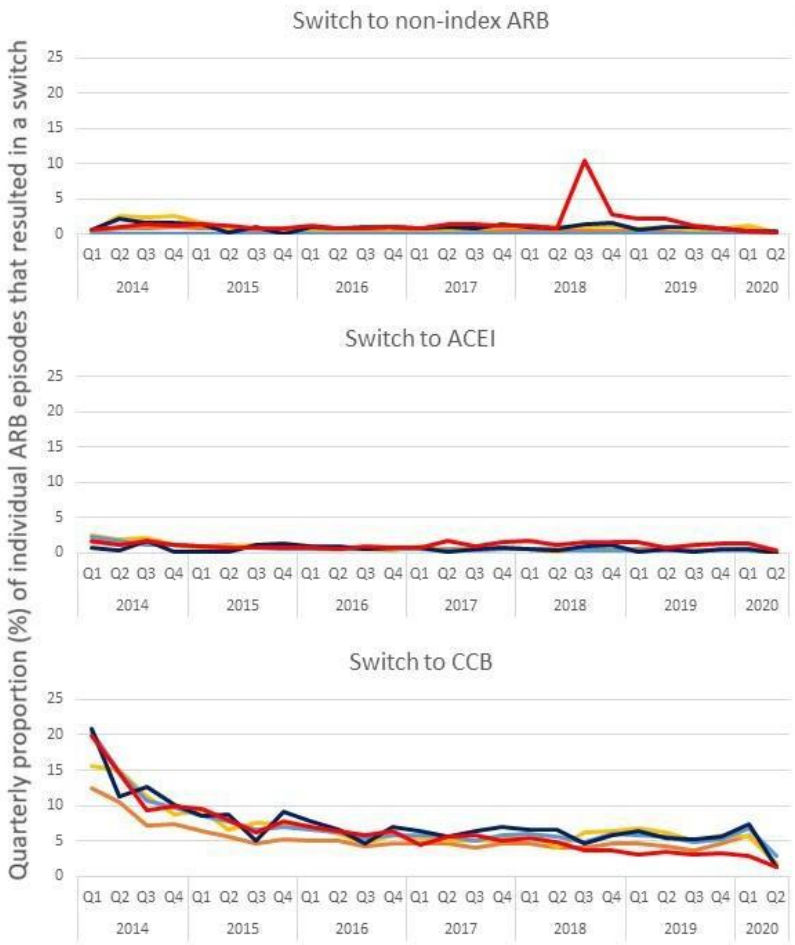


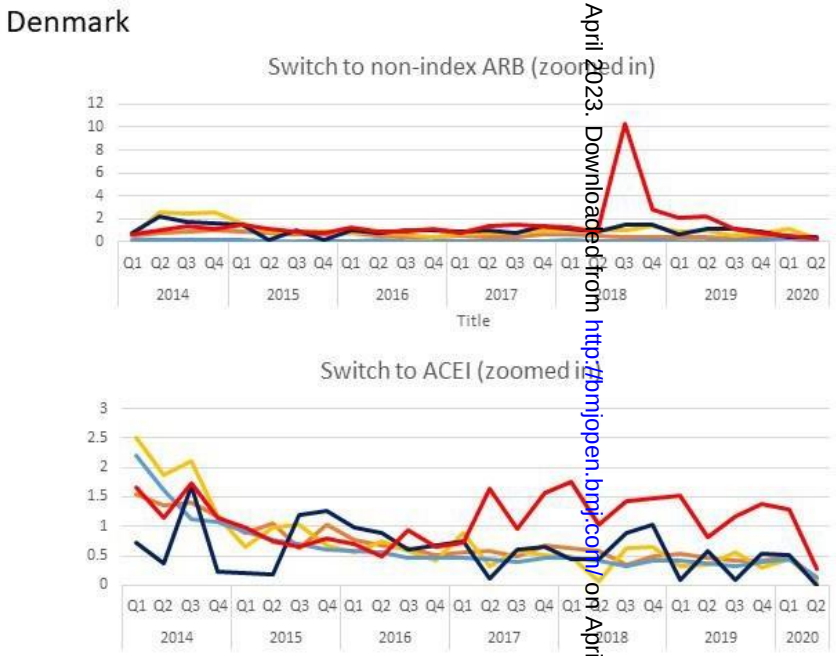
Proportion of Valsartan episodes that resulted in a switch to non-index ARB, ACEI or CCB-containing products

Switch pattern	Q2-2018 (Apr-Jun)	Q3-2018 (Jul-Sep)
Valsartan to non-index ARB	0.3	52.6
Valsartan to ACEI-products	0.5	1.8
Valsartan to CCB	5.4	3.2

BMJ Open: first published as 10.1136/bmjopen-2022-070935 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

SFigure 3. Quarterly proportions (represented as percentages) for individual ARB episodes switching to non-index ARB, ACEI or CCB (individually) for Denmark data.



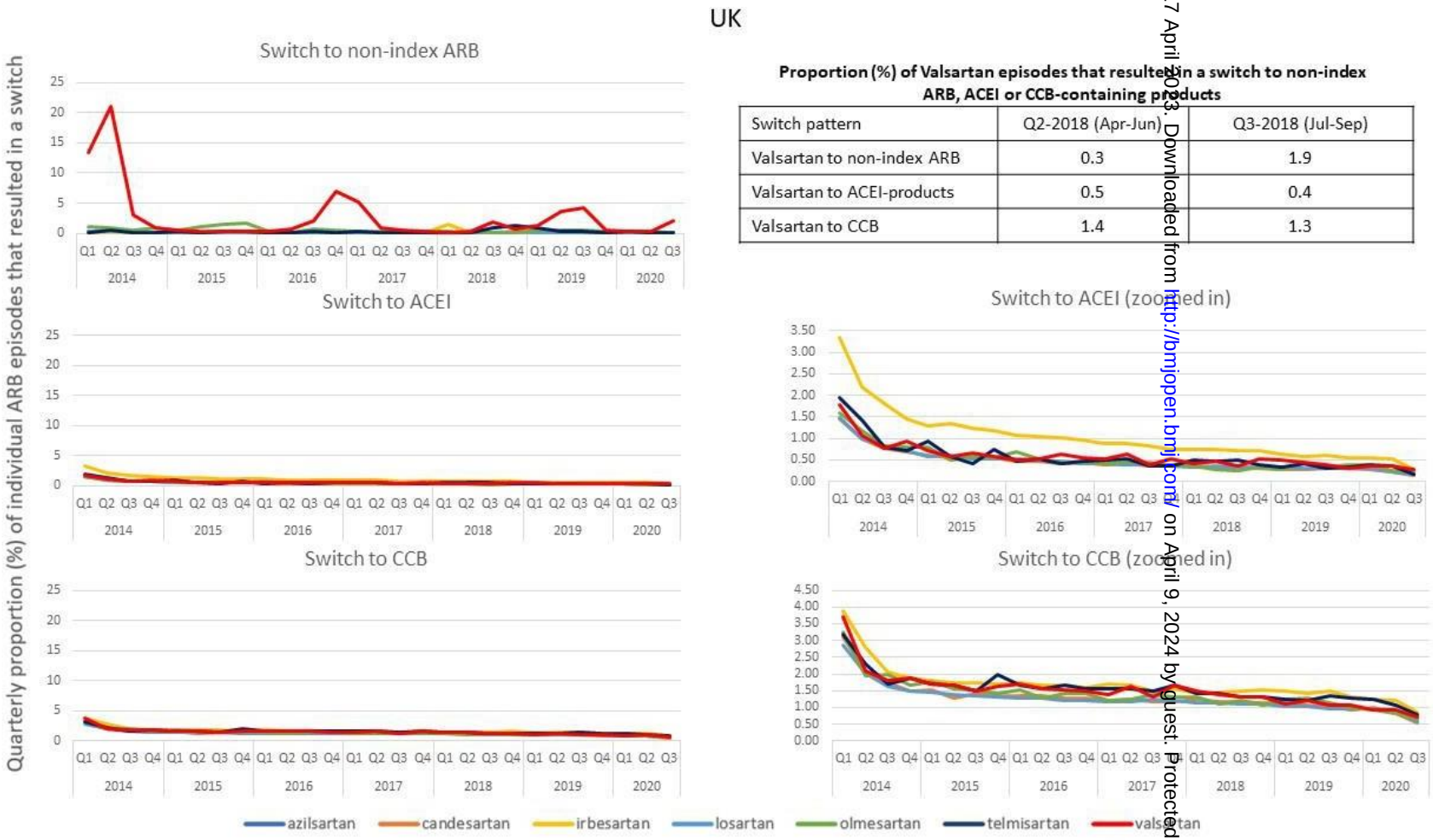


Proportion of Valsartan episodes that resulted in a switch to non-index ARB, ACEI or CCB-containing products

Switch pattern	Q2-2018 (Apr-Jun)	Q3-2018 (Jul-Sep)
Valsartan to non-index ARB	0.9	10.4
Valsartan to ACEI-products	1.1	1.4
Valsartan to CCB	4.8	3.6

10.1136/bmjopen-2022-070935 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

SFigure 4. Quarterly proportions (represented as percentages) for individual ARB episodes switching to non-index ARB, ACEI or CCB (individually) for UK data.

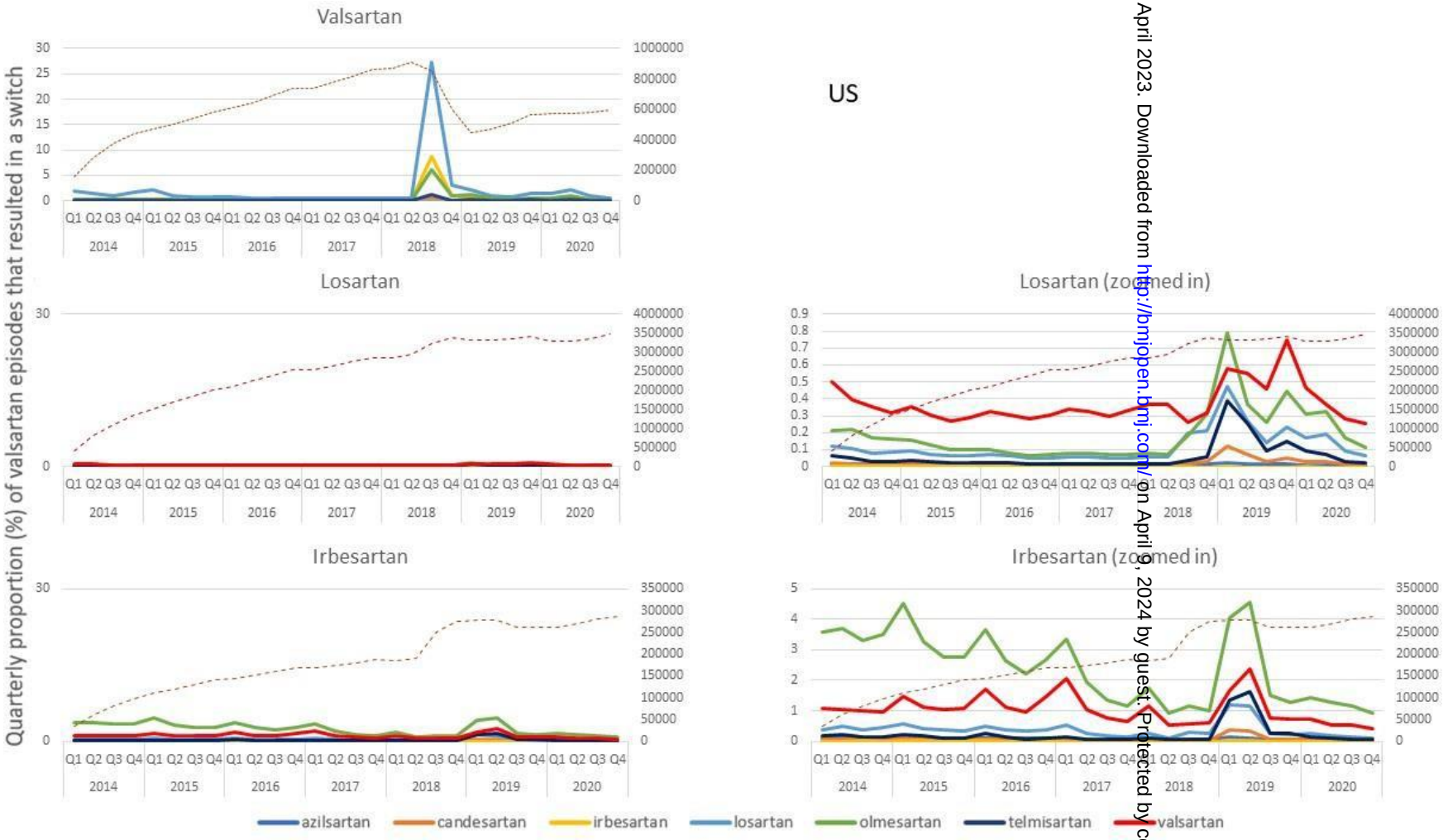


Proportion (%) of Valsartan episodes that resulted in a switch to non-index ARB, ACEI or CCB-containing products

Switch pattern	Q2-2018 (Apr-Jun)	Q3-2018 (Jul-Sep)
Valsartan to non-index ARB	0.3	1.9
Valsartan to ACEI-products	0.5	0.4
Valsartan to CCB	1.4	1.3

10.1136/bmjopen-2022-070935 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

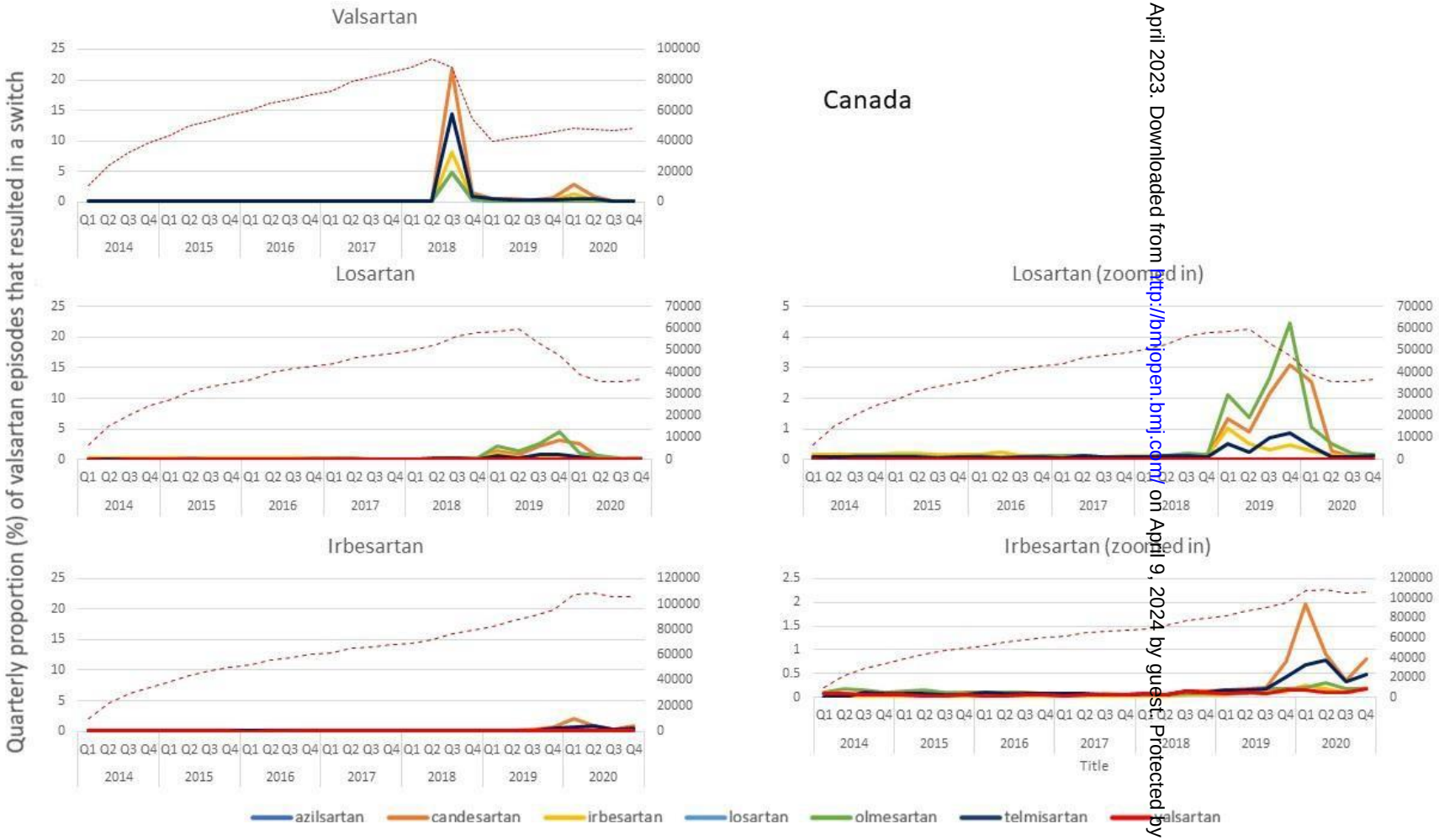
SFigure 5. Quarterly proportions (represented as percentages) for Valsartan episodes switching to non-index ARB/ACEI or CCB (individually) for US data.



The dotted lines denote the total number of valsartan episodes in each quarter, year

10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

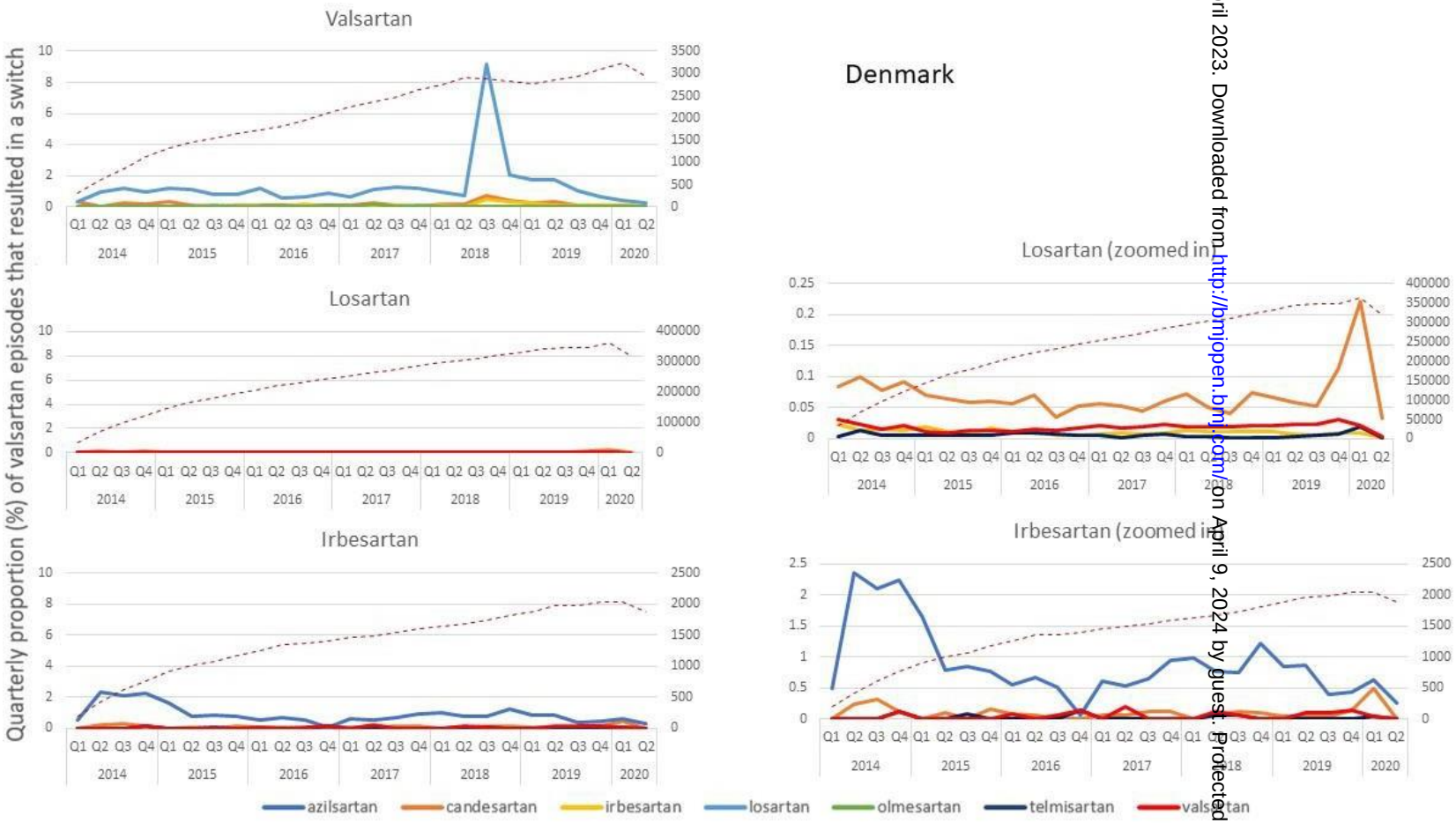
SFigure 6. Quarterly proportions (represented as percentages) for Valsartan episodes switching to non-index ARB, ACEI or CCB (individually) for Canada data.



The dotted lines denote the total number of valsartan episodes in each quarter, year

10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

SFigure 7. Quarterly proportions (represented as percentages) for Valsartan episodes switching to non-index ARB, ACEI or CCB (individually) for Denmark data.

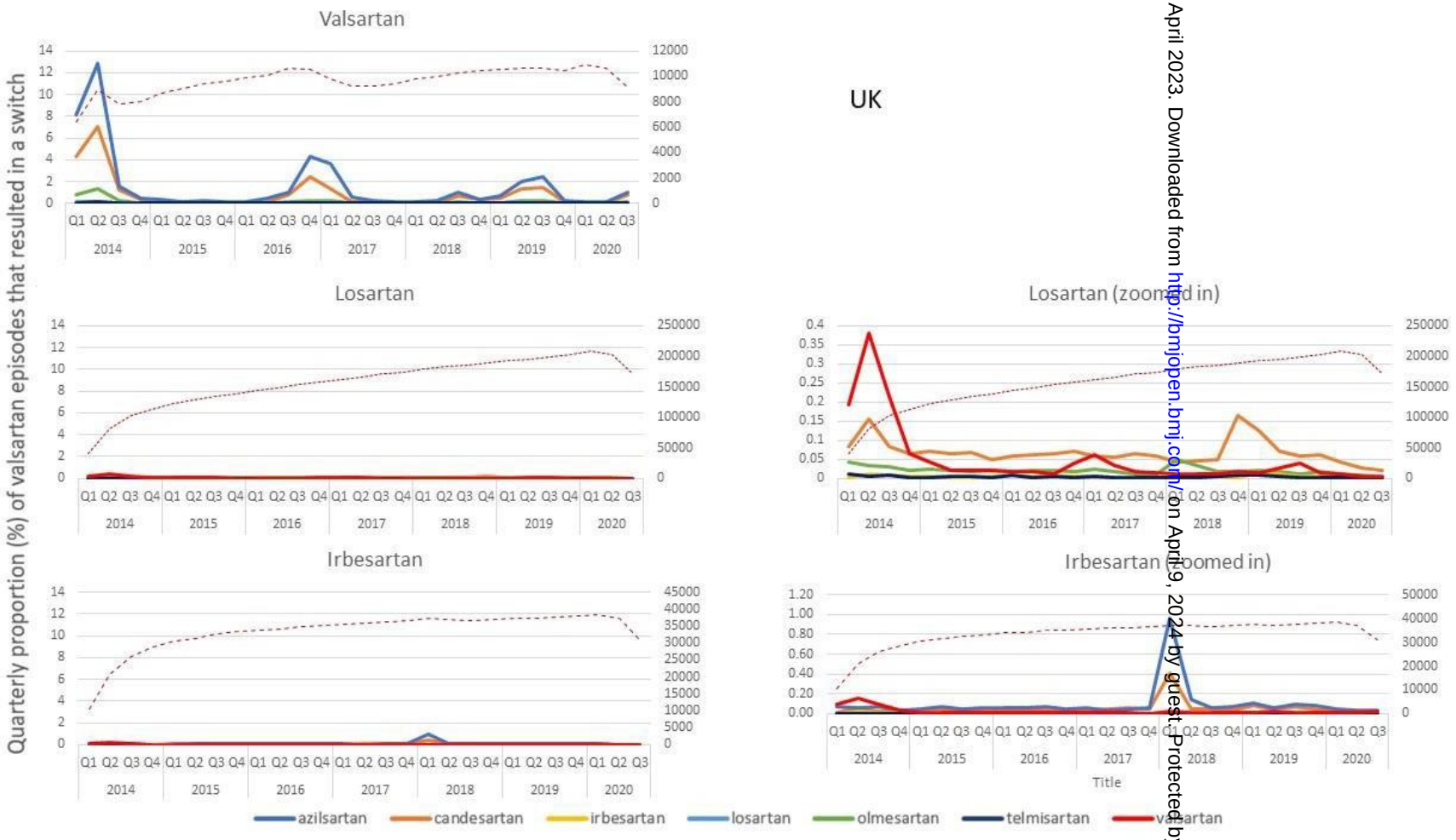


The dotted lines denote the total number of valsartan episodes in each quarter, year

BMJ Open: first published as 10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.

10.1136/bmjopen-2022-070985 on 17 April 2023. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.

SFigure 8. Quarterly proportions (represented as percentages) for Valsartan episodes switching to non-index ARB, ACEI or CCB (individually) for UK data.



The dotted lines denote the total number of valsartan episodes in each quarter, year

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4,5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4,5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	4,5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	NA
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	5
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	5
Outcome data	15*	Report numbers of outcome events or summary measures over time	5

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	5,6
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	5,6
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	5,6
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	7

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml