

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

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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.

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	Olmесartan
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.

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

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

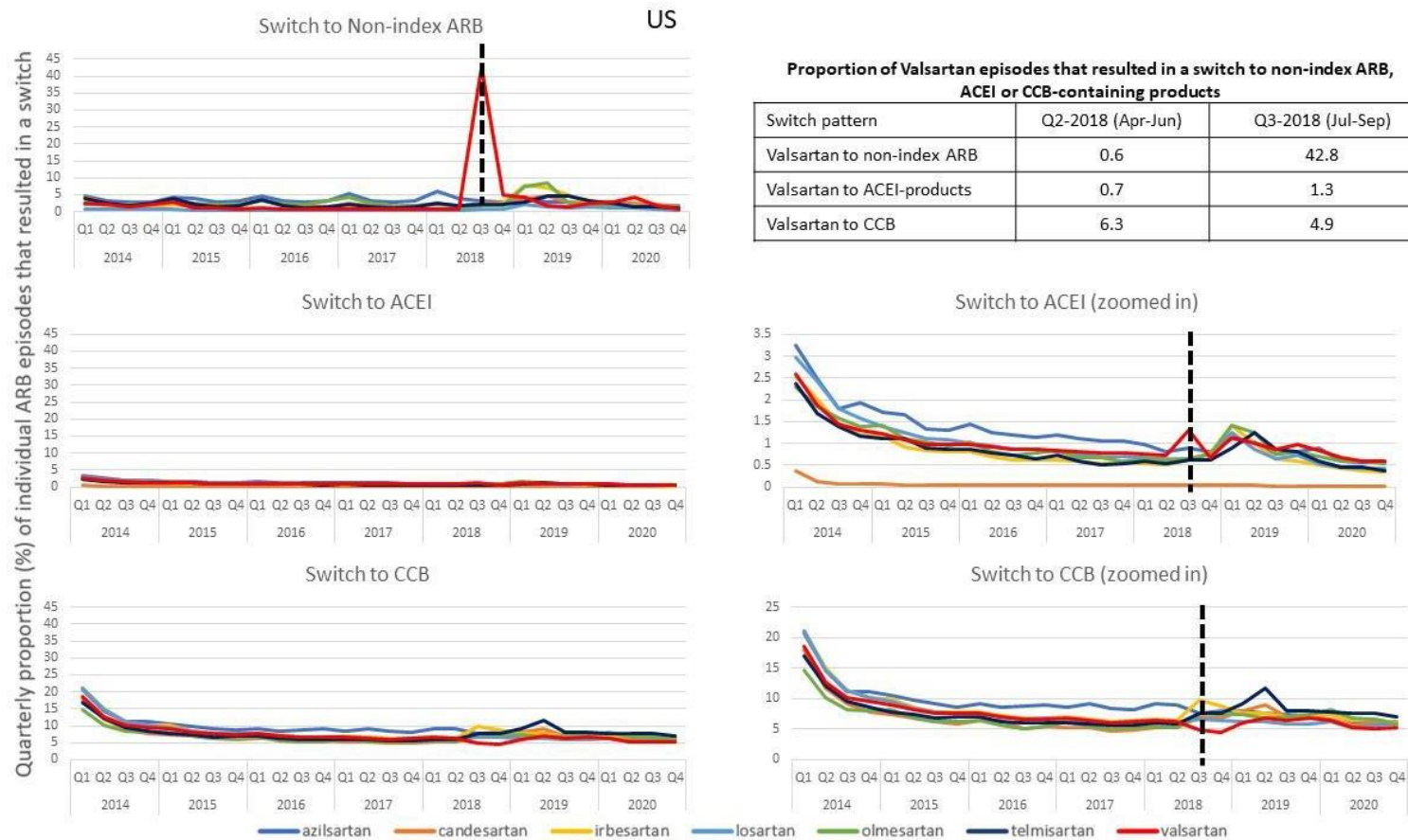
STable 3b. Interrupted Time Series Analysis using equal time points before and after the intervention date, including the transition period

	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)

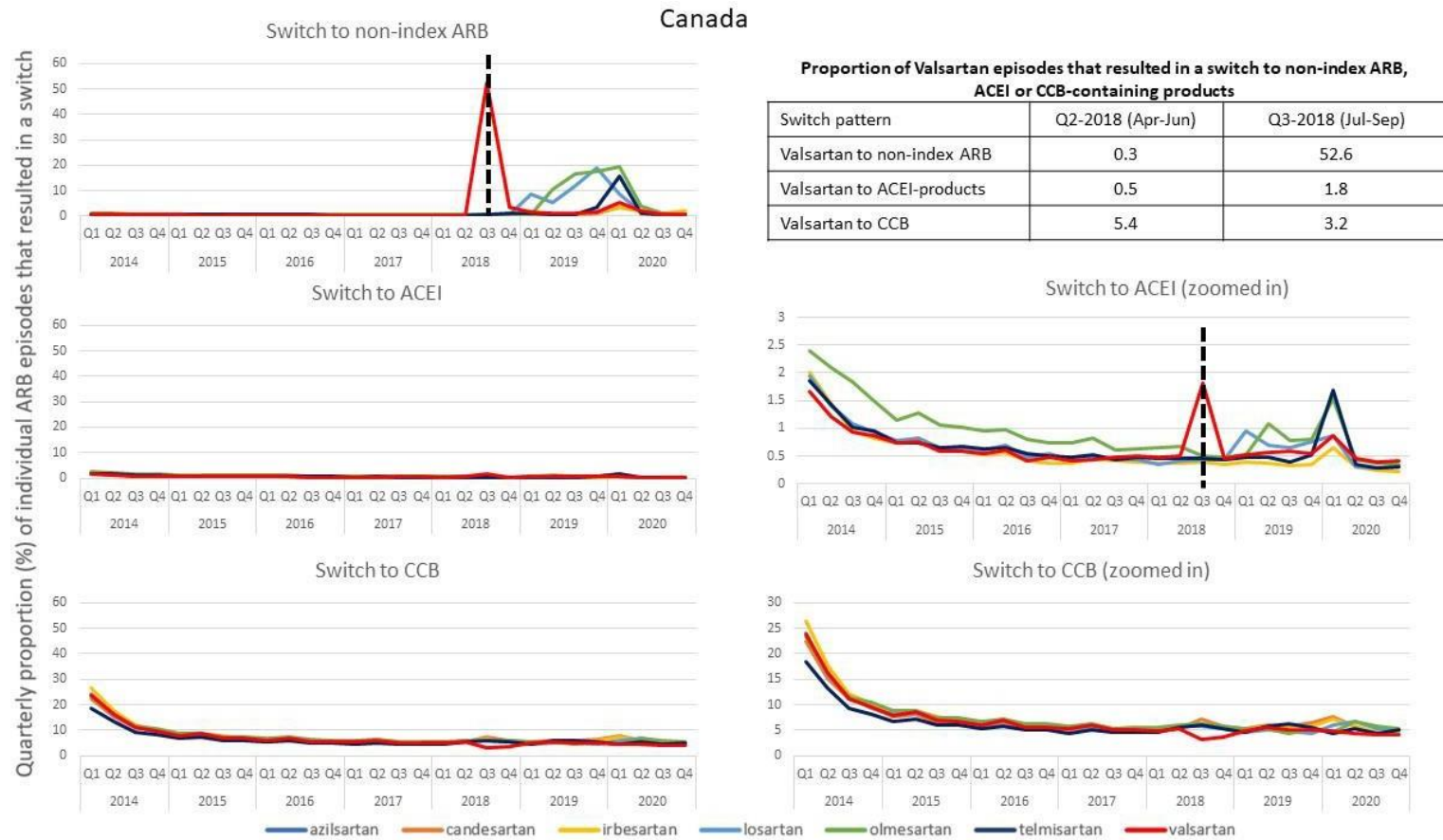
STable 4. Interrupted Time Series analysis using control time period (September 2014-May 2018) with intervention date, July 2016.

	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)
Olmесartan	-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

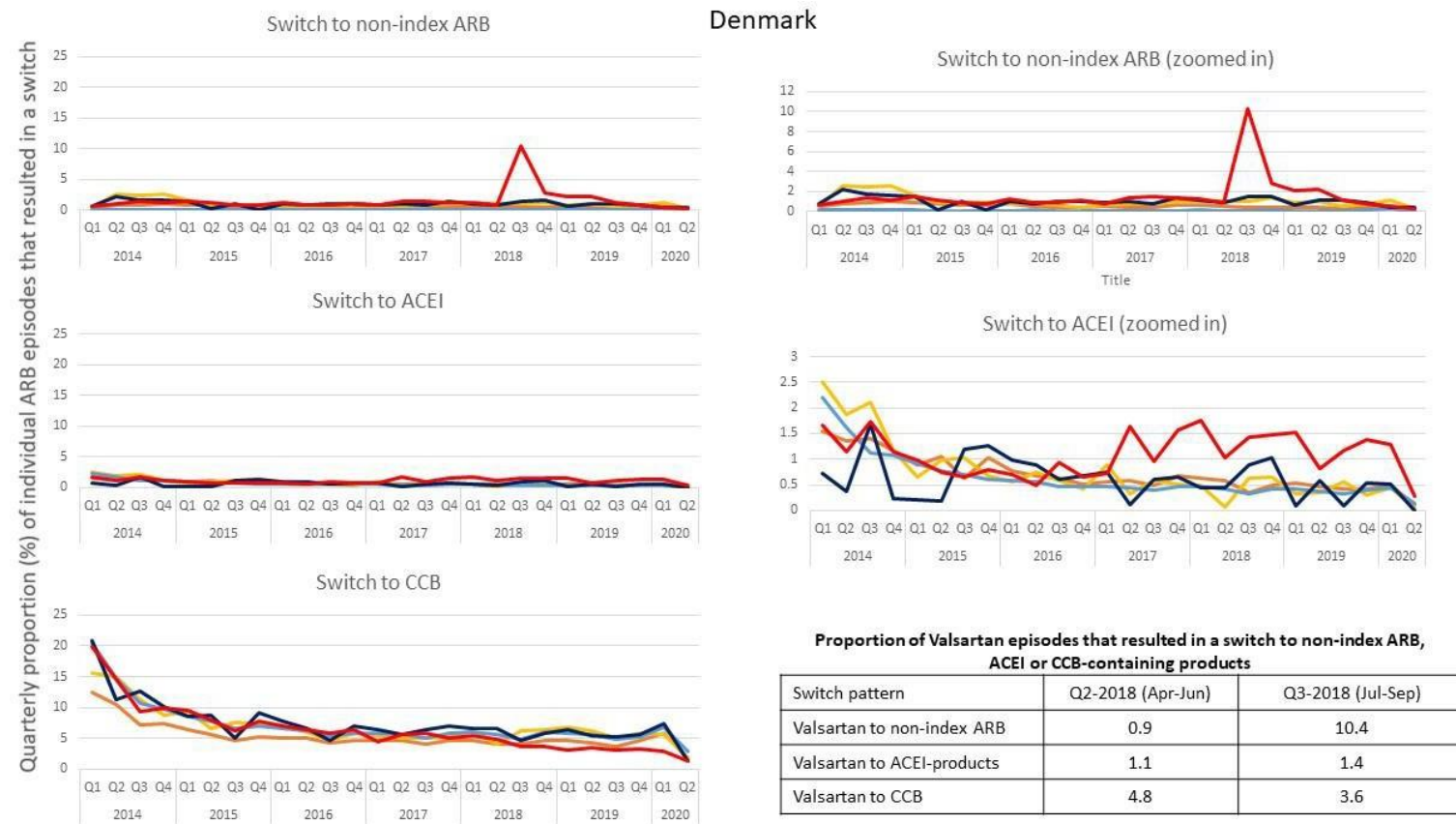
SFigure 1. Quarterly proportions (represented as percentages) for individual ARB episodes switching to non-index ARB, ACEI or CCB (individually) for US data.



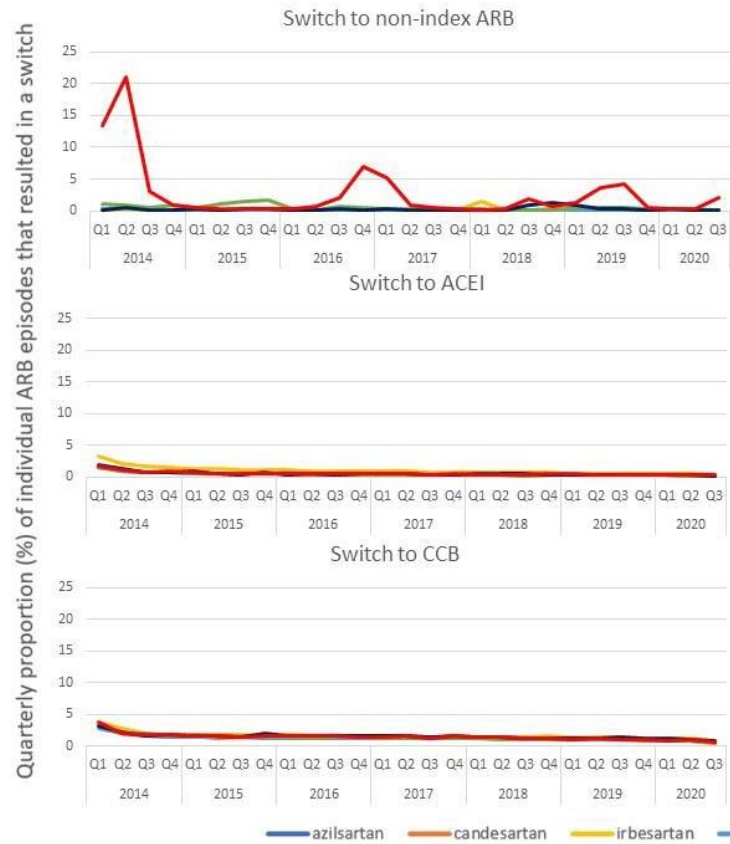
SFigure 2. Quarterly proportions (represented as percentages) for individual ARB episodes switching to non-index ARB, ACEI or CCB (individually) for Canada data.



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



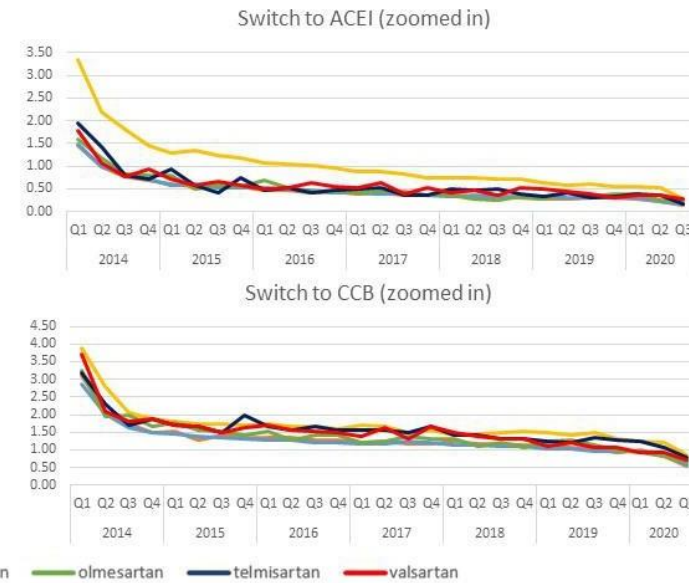
SFigure 4. Quarterly proportions (represented as percentages) for individual ARB episodes switching to non-index ARB, ACEI or CCB (individually) for UK data.



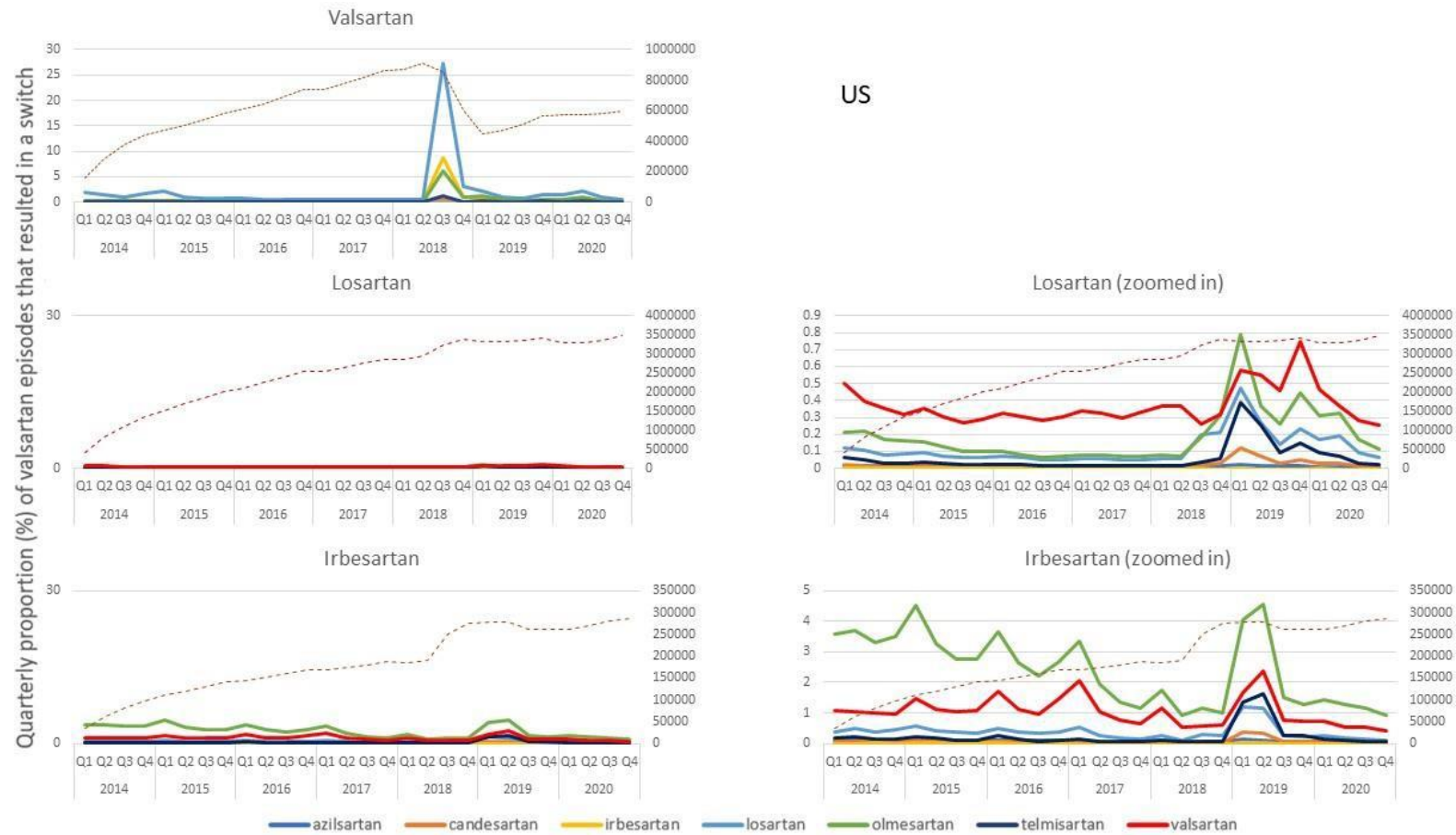
UK

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

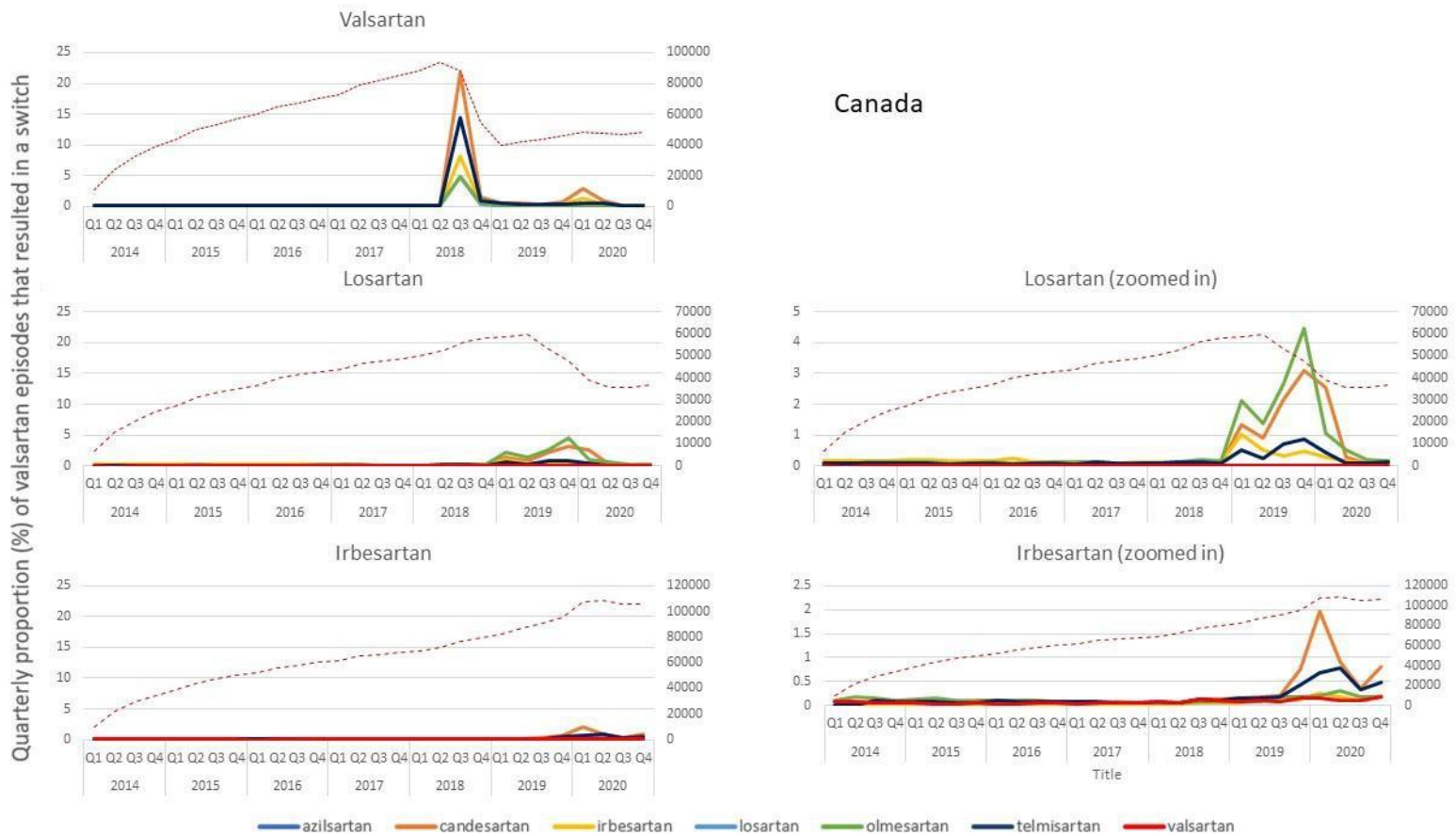


SFigure 5. Quarterly proportions (represented as percentages) for Valsartan episodes switching to non-index ARB, ACEI or CCB (individually) for US data.



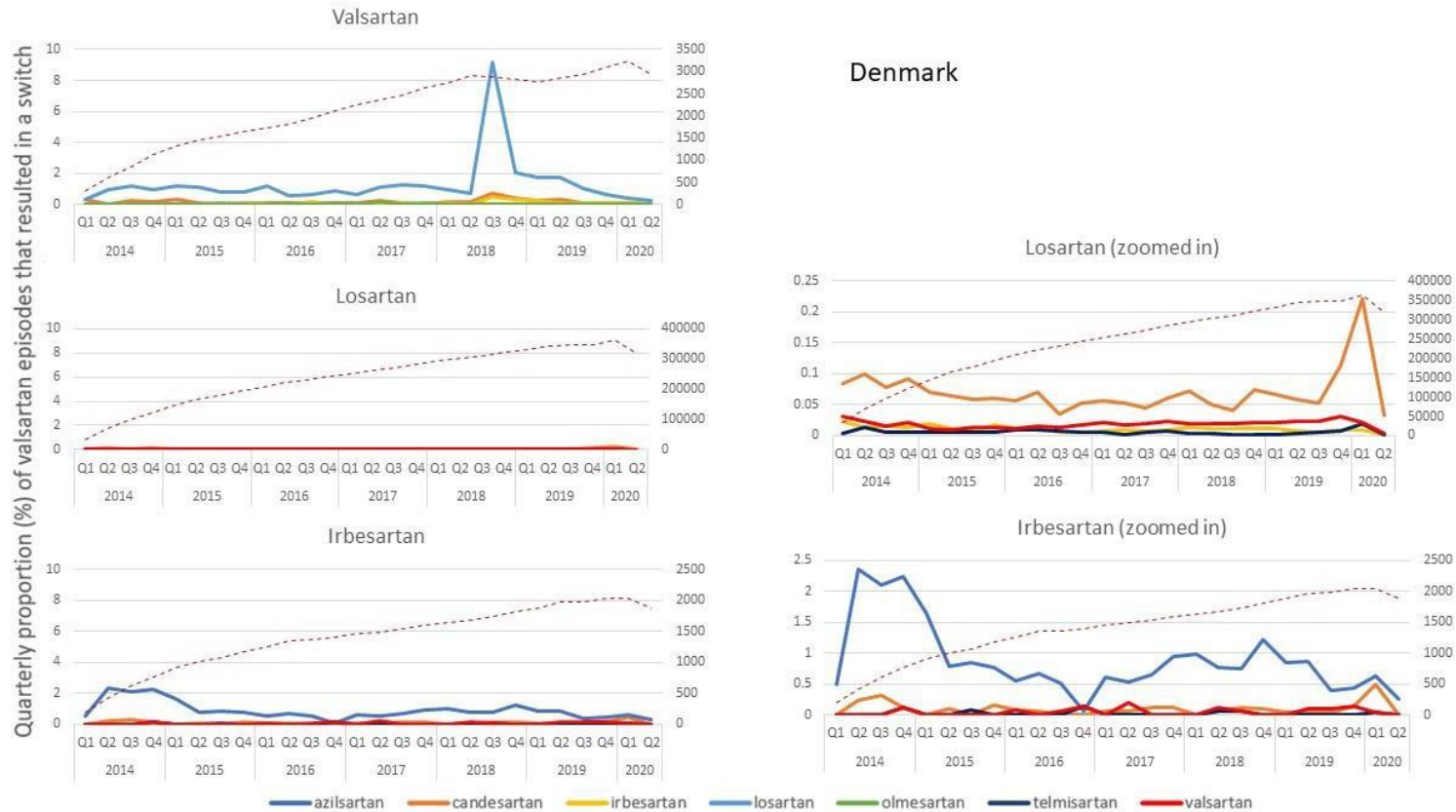
The dotted lines denote the total number of valsartan episodes in each quarter, year

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



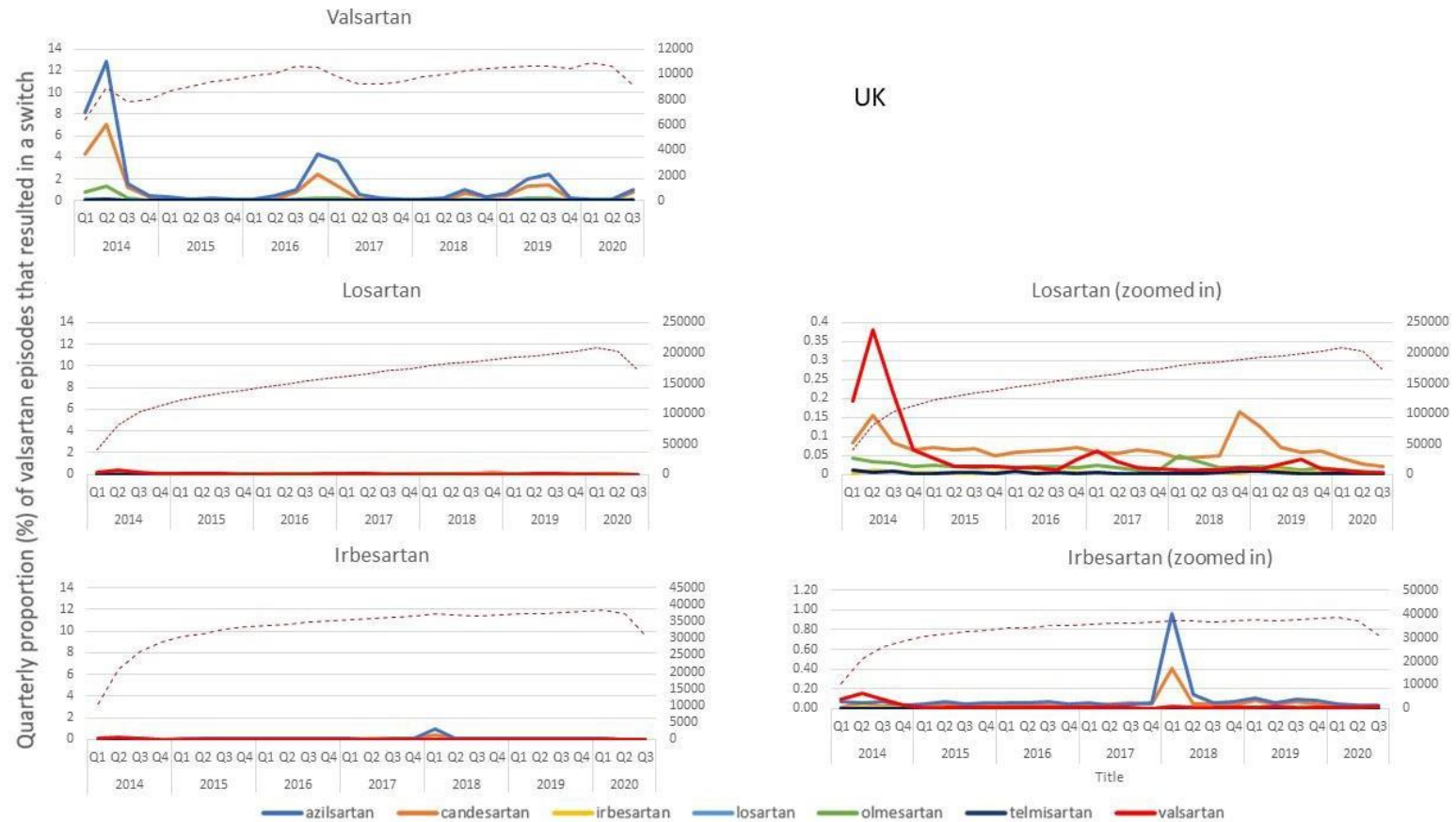
The dotted lines denote the total number of valsartan episodes in each quarter, year

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

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