Exposure to N-nitrosodimethylamine /N-nitrosodiethylamine-contaminated Angiotensin-II Receptor Blockers Products in the United States

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Background

- In 2018, N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA) were discovered in several valsartan (an angiotensin receptor blocker (ARB)-containing products. NDMA and NDEA are mutagenic carcinogens in several animal species
- NDMA and NDEA were generated as a by-product when the solvent used in the Zhejiang Huahai Pharmaceuticals' manufacturing process for valsartan was changed.[1]
- FDA coordinated a voluntary recall of these products (recalled products) and began retesting all valsartan products, including both recalled products and those currently marketed in the United States, for NDMA and NDEA.[2]
- Ongoing characterization of valsartan-containing products is crucial for future pharmacoepidemiologic safety assessments.
- We sought to examine the extent of exposure, duration of use and switching patterns from NDMA-/NDEA-contaminated valsartan products to other angiotensin-receptor blockers (non-valsartan ARBs) or other antihypertensives – angiotensin-converting-enzyme inhibitors (ACEIs) and calcium channel blockers (CCBs)) of these products

Methods

- Between January, 2010 to most recent available data (1/31/2019), we identified patients 18 years and older from 15 data partners in the Sentinel Distributed Database (SDD).
- Using NDCs, valsartan products were categorized as **probably contaminated** (NDMA/NDEA-positive, NDMA-positive, NDEA-positive based on FDA's testing of finished drug products (FDPs) and manufactured recalled products lots) **possibly contaminated** (recalled products but not tested), and **non-contaminated** (non-recalled and NDMA/NDEA-negative) products.
- Exposure episode lengths were defined using days supplied, allowing a gap of 15 days or less between dispensings to create continuous treatment.
- Follow-up began on the dispensing date of the respective valsartan category until the first occurrence of: disenrollment, end of data, end of the exposure episode or death.
- Annual trends of prevalence of each valsartan product category and duration to discontinuation or switch from probably-contaminated valsartan products to another valsartan product or antihypertensive were calculated.

Results

Descriptive Data

- We identified 1.6, 11.7, 7.3 and 5.3 million users of valsartan, ACEI, CCB and non-valsartan ARB users during the study period respectively.
- Non-recalled valsartan dispensings made up 58.1% of all valsartan dispensings, while lisinopril (61.2%), amlodipine (75.5%) and losartan (74.5%) were most frequently dispensed for ACEI, CCB and non-valsartan ARBs, respectively.
- Similar demographic and clinical characteristics for valsartan, CCB and non-valsartan ARBs were observed (Table 1).
- ACEI users were likely male with a lower proportion of users having a hypertension diagnosis at baseline (Table 1).

Table 1. Baseline Characteristics for Exposure Cohorts (Treatment Episodes)

Characteristics	Valsartan	ACEI	CCB	Non-valsartan ARBs
	n=4,125,459	n=30,804,602	n=17,602,062	n=13,311,608
Age: 18-44, %	11.4	16.4	13.1	12.3
Age: 45-64, %	55.8	54.1	47.2	53.7
Age: 65+, %	32.8	29.5	39.7	33.9
Female, %	50.3	44.1	51.1	51.3
Male, %	49.7	55.9	48.9	48.6
Recorded History among New Users Only (365-day washout period)				
Heart failure, %	11.5	7.2	8.7	7.9
Diabetes, %	30.7	28.7	26.5	31.5
Hypertension, %	92.3	83.6	87.1	91.3
Renal disorders, %	17.1	12.9	21.6	17.4

N represents the number of episodes not number of users

Figure 1. Proportion of SDD Patients Exposed to Each Antihypertensive Category

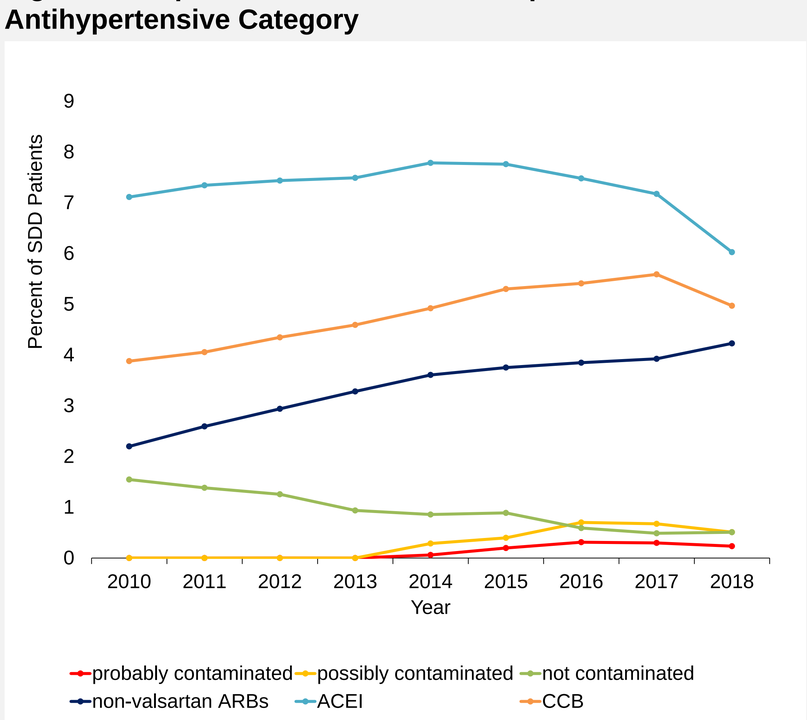


Figure 2. Proportion of Valsartan-Exposed Patients Stratified by Contamination Status

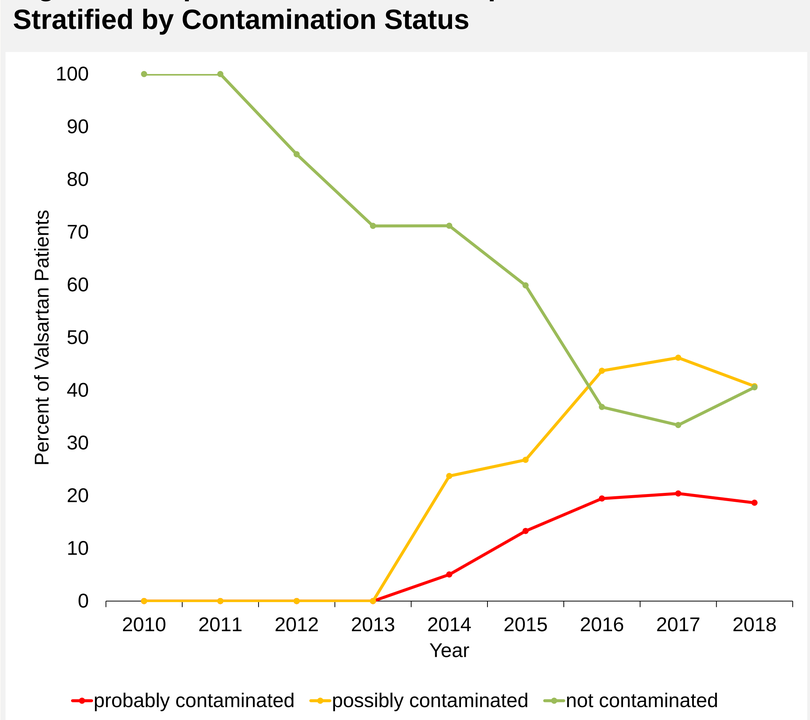


Figure 3. Proportion of Probably Contaminated Users Who Switch to non-valsartan ARBs, ACEI or CCB

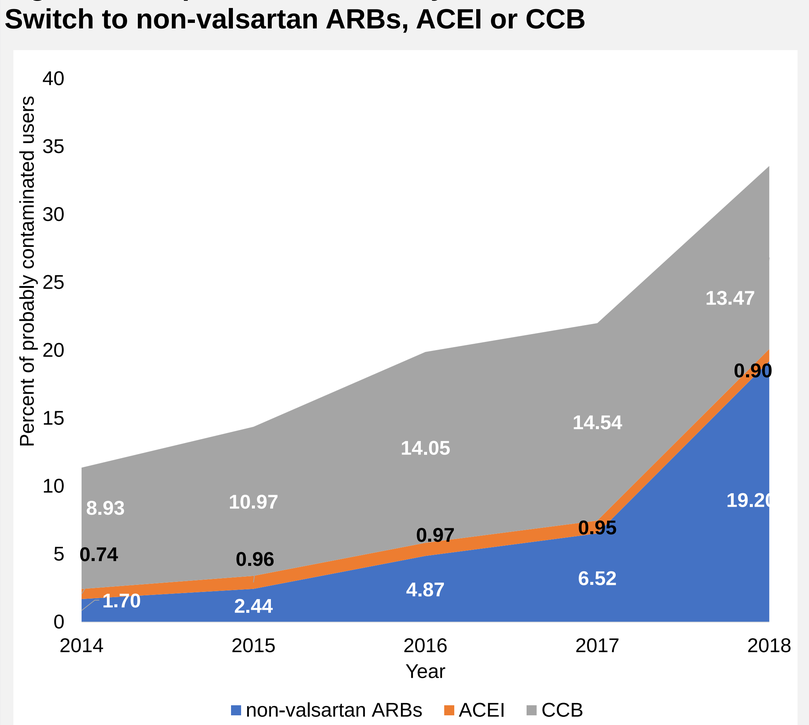
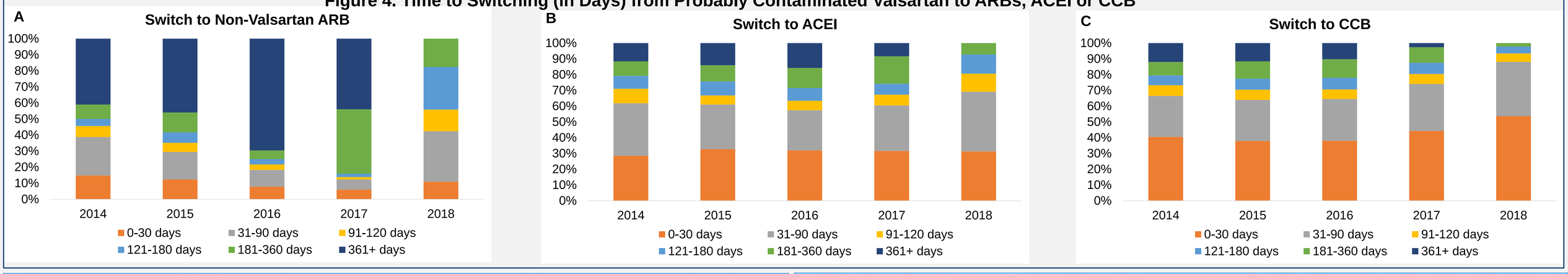


Figure 4. Time to Switching (in Days) from Probably Contaminated Valsartan to ARBs, ACEI or CCB



Discussion

- Probably-contaminated valsartan dispensings increased steadily and were the most frequently dispensed valsartan product in 2016 and 2017.
- In 2018, probably- and possibly-contaminated valsartan dispensings declined with most patients switched to non-valsartan ARBs. Switching trends to ACEI or CCB were consistent over time, suggesting that these were intended medical switches rather than in response to the recall.
- Shorter time to switching from probably-contaminated to non-valsartan ARBs in 2018 ensured patients their continued treatment after discontinuation of contaminated product.
- Exposure misclassification is possible since we rely on dispensed data to ascertain trends

Conclusion

- Though valsartan dispensings were already on the decline prior to contamination, we observed further decline in dispensings likely due to the recall notice.
- Patients were more likely to switch to another ARB rather than another antihypertensive medication within 1-3 months.
- Future analyses will be updated as data is accrued to examine whether the observed trends continue.
- Additional analyses will also examine time to discontinuation and switching to non-recalled valsartan products.

References

1.Snodin DJ, Elder DP. Short commentary on NDMA (N-nitrosodimethylamine) contamination of valsartan products. Regulatory toxicology and pharmacology : RTP. 2019;103:325-9.

2.FDA Press Release. FDA announces voluntary recall of several medicines containing valsartan following detection of an impurity 2018 [cited 7/18/2019].Available from: https://www.fda.gov/news-events/press-announcements/fda-announces-voluntary-recall-several-medicines-containing-valsartan-following-detection-impurity.

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