Changes in Utilization of Antihypertensive Drugs Following Angiotensin Receptor Blocker Product Recalls in Germany

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Background and Objective

Discovery of unacceptable amounts of probable carcinogenic nitrosamines resulted in more than 30 recalls of generic angiotensin receptor blockers (ARBs), primarily valsartan (including combinations with hydrochlorothiazide), between July 4 and December 20, 2018 [1], and in subsequent drug shortages. We explored the potential impact of this huge recall on the utilization of valsartan, all ARBs, and other antihypertensive drugs (AHTs).

Methods

- Drug utilization study of AHTs using the DAPI database containing dispensings at the expense of the Statutory Health Insurance (SHI) Funds from >80% of German community pharmacies.
- Use was estimated as defined daily doses per 1,000 SHI-insured persons per day (DID), time trends analyzed using moving averages per month.
- All oral mono and fixed-dose combination products of ARBs, ACE inhibitors (ACEi), calcium channel blockers (CCB), and beta-blockers (BB) were included.
- To determine differences in the dispensings compared to the previous year, a ratio was calculated by dividing the DID of the weekdays in June and July 2018, the month of first recalls, by the weekdays in June and July 2017.
- The inability to fulfill rebate contracts of the SHI in the pharmacy due to unavailability of rebated drugs and the subsequent dispensing of a product not rebated was documented by printing the specific code on the prescription. The number of prescriptions with this code was determined as an indicator for drug shortages.

Results

Individual ARB dispensings (Figures 1 and 2)

- **Valsartan** → decreased substantially and continuously (-59%) after first recalls in July 2018:
  2Q18: 41.1 DID 4Q19: 16.9 DID
- **Other ARBs** → simultaneously increased (+57%):
  2Q18: 77.7 DID 4Q19: 121.9 DID
  → candesartan showed highest increase (+73%):
  2Q18: 57.7 DID 4Q19: 99.8 DID

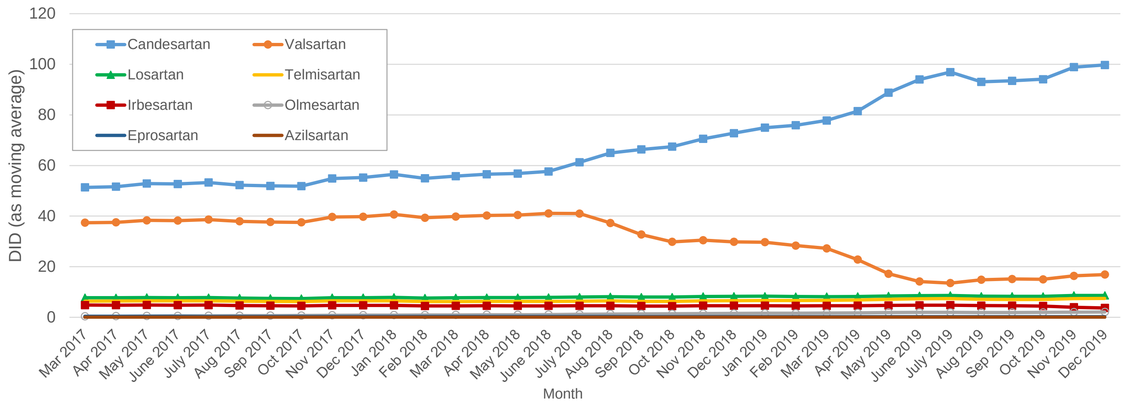

Fig. 1: Dispensings of ARBs

- **Ratio** of the matched daily dispensings for valsartan and candesartan
  → initially increased from 1 to 1.43 for valsartan and 1.30 for candesartan
  → then decreased substantially to 0.65 for valsartan
  → values for candesartan reached 1.56 to 1.27

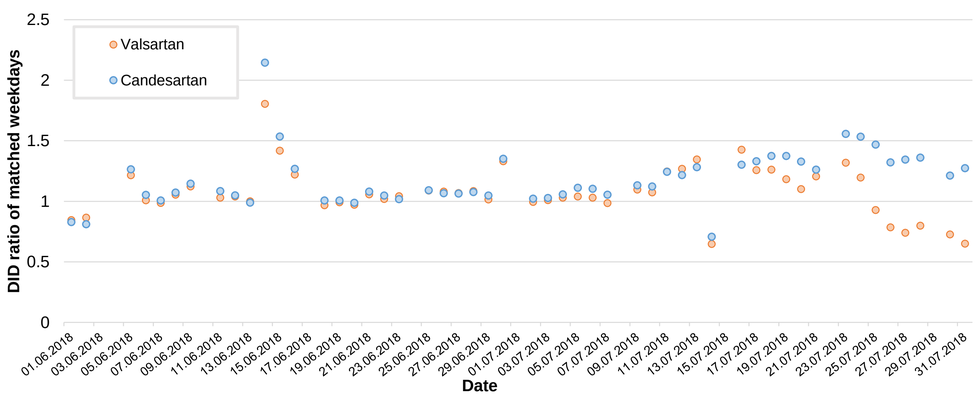

Fig. 2: DID ratios of matched June/July 2018 weekdays for valsartan and candesartan

Overall dispensings (Figure 3)

- **All ARBs** → no impact on moderate, but continuous increase of total dispensings (+16%)
  2Q18: 129.4 DID 4Q19: 150.2 DID

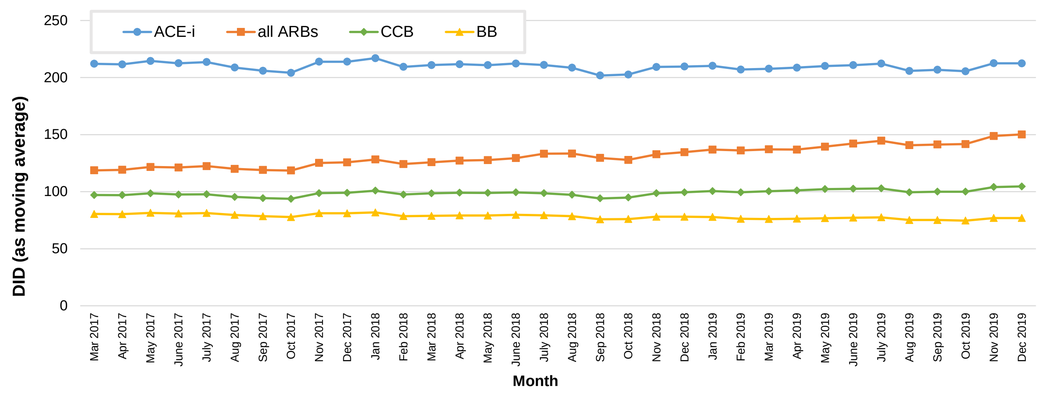

Fig. 3: Dispensings of antihypertensive drug classes

Prescriptions with documented unavailability (Figure 4)

- **Valsartan** → increased after first recalls until 01/2019
  06/18: 2,200 0.4% of prescriptions
  01/19: 242,400 51.3% of prescriptions
  → decreased again
  12/19: 4,900 2.0% of prescriptions
- **Candesartan** → increased after first recalls continuously
  06/18: 1,400 0.2% of prescriptions
  12/19: 378,000 28.7% of prescriptions

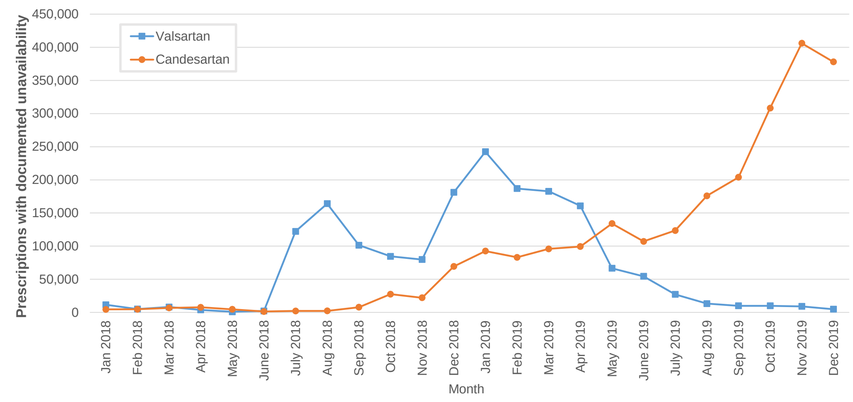

Fig. 4: # prescriptions with documented unavailability for valsartan and candesartan

Discussion and Conclusions

We noted a substantial decrease in utilization of valsartan but not losartan, irbesartan, olmesartan, or telmisartan after generic ARB product recalls. The total volume of ARB further increased and AHT utilization overall remained nearly unchanged suggesting shifts within the class of ARBs, mostly to candesartan. In contrast to previous safety warnings/recalls, our data do not suggest an under-treatment with AHTs during this period despite documented drug shortages.

Reference:

[1] ABDA. Online-Nachricht: AMK: Liste der (Chargen-)Rückrufe Sartan-haltiger Arzneimittel. https://www.abda.de/fuer-apotheker/arzneimittelkommission/amk-nachrichten/detail/online-nachricht-amk-liste-der-chargen-rueckrufe-sartan-haltiger-arzneimittel/. Updated March 4, 2019. Last accessed July 1, 2020.

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Conflicts of interest:

UR has received scientific support and speaker honoraria from Bayer, Berlin Chemie and Bristol Myers Squibb. FM is supported by Deutsche Gesellschaft für Kardiologie and has received scientific support and speaker honoraria from Bayer, Boehringer Ingelheim, Medtronic, and ReCor Medical. FM and MB are supported by the Deutsche Forschungsgemeinschaft. UL has received speaker honoraria from Bayer, Boehringer Ingelheim, Novartis and Servier. MS has received speaker honoraria from Novartis and Sanofi. All other authors declare no conflict of interest.