Title: Potential Thiazide induced prescribing cascades in Medicare Beneficiaries with and without Chronic Kidney Disease

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Background: Thiazide diuretics (TZD) are effective antihypertensives, but their adverse effects can prompt the use of additional therapy, i.e., a prescribing cascade (PC). Among individuals with chronic kidney disease (CKD), altered renal function affects drug clearance and response, potentially increasing risk of TZD adverse events and contributing to different prescribing patterns versus patients without CKD.

Objectives: To evaluate potential TZD-induced PCs, comparing patients with and without baseline CKD, utilizing high-throughput sequence symmetry analysis (HTSSA).

Methods: Using Medicare claims data (2011-2020), we identified new TZD users aged ≥66 years who had continuous enrollment for ≥360 days pre- and ≥180 days post-TZD initiation. Individuals were classified by presence of CKD diagnosis ≤360 days prior to TZD initiation. We screened for initiation of all other drug classes, based on WHO Anatomical Therapeutic Classification level 4 codes. We generated sequence ratios (SRs) representing the proportion of TZD initiators starting each class after, compared to before, TZD initiation. Adjusted SRs (aSRs), accounting for prescribing trends over time, were calculated, with 95% CIs >1 indicative of a potential PC.

Results:
We identified 210,954 new TZD users (66% women; 90% with hypertension, 33% with diabetes, and 72% with a Charlson Comorbidity Index ≥5). Of new TZD initiators, 54,056 (26%) had baseline CKD. Eight potential PC signals were observed in both CKD and non-CKD groups, top 3 signals by aSR were: ARBs and diuretics (aSR CKD: 1.81 [1.58-2.07], non-CKD: 2.23 [2.07-2.41]), Class Ib antiarrhythmics (aSR CKD: 1.67 [1.18-2.35], non-CKD: 1.49 [1.06-2.09], ARBs and other combinations (aSR CKD: 2.12 [1.45-3.11], non-CKD: 1.49 [1.09-2.03]. An additional 23 statistically significant signals were observed exclusively in the non-CKD group, top 3 signals by aSR were, other nervous system drugs (aSR CKD: 5.28 [1.12-24.90] non-CKD: 5.28 [1.12-24.9]), SGLT2 inhibitors (CKD: 2.97 [2.05-4.30] non-CKD: 2.97 [2.05-4.3]), and carbapenems (CKD: 2.63 [1.54-4.47] non-CKD: 2.63 [1.54-4.47]). Notably, no PC signals were unique to the CKD group. For most shared signals, aSRs were consistently lower in the CKD group compared to the non-CKD group, though the magnitude of difference varied by drug class.

Conclusions: Potential TZD induced PCs were more common and of greater magnitude in patients without CKD. This may reflect more conservative prescribing in CKD patients due to concerns about kidney function or reduced TZD effectiveness in advanced

CKD limiting the manifestation of adverse effects. Further investigation is necessary to evaluate the impact of these potential PCs on patient outcomes.