ACE-Inhibitors and the Risk of Urinary Tract Infections: Comparison of a Prescription Sequence Symmetry and a Case-Crossover Design (The Netherlands).

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INTRODUCTION: In a post-hoc analysis of a randomized controlled trial (RCT) (HR 1.82, 95% CI, 1.16–2.88) and a prescription sequence symmetry analysis (PSSA) (SR 1.56, 95% CI 1.11–2.20), we observed that angiotensin-converting enzyme inhibitor (ACEi) use was associated with an increased risk of urinary tract infections (UTIs). We evaluated the same association using a case-crossover design and compared the results obtained with the different designs.

METHODS: A case-crossover design was performed with a pharmacy prescription database (IADB.nl). The date of incident use of nitrofurantoin (a proxy for UTIs) was defined as the index date. The risk period was defined as 30 days before the index date and the control period as 60–90 days before that date. A person was considered exposed to ACEi if there was at least three days’ supply within the window. The following drugs were considered as time-varying confounders: β-blockers, calcium channel blockers, angiotensin-receptor blockers, diuretics, lipid-modifying agents, non-steroidal anti-inflammatory drugs and glucose-lowering drugs. In secondary analysis the definitions were set similar to the PSSA. Conditional logistic regression was used for all analyses.

RESULTS: There were 51,249 patients that received a first nitrofurantoin prescription and met eligibility criteria. Of these, 276 patients were only exposed to ACEi during the risk window and 150 patients only during the control window (crude OR 1.84, 95% CI 1.51–2.25; adjusted OR 1.74, 95% CI 1.42–2.13). Restricting the analysis to individuals within the same age-category as the previous RCT, the adjusted OR increased to 1.90 (95% CI 1.44–2.50). When using similar definitions and criteria as in the PSSA, the case-crossover estimates were slightly higher (adjusted OR 2.09, 95% CI 1.68–2.61).

CONCLUSIONS: These findings suggest that ACEi increase the risk of developing first UTIs. Despite the similarities between the case-crossover design and the PSSA, the PSSA led to slightly lower effect estimates than the case-crossover design and the RCT.