

Angiotensin-Converting Enzyme Inhibitor Treatment and the Development of Urinary Tract Infections: A Prescription Sequence Symmetry Analysis

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Abstract

Background Angiotensin-converting enzyme inhibitors (ACEi) can reduce urine output, especially when treatment is first started. Since bacterial clearance from the urinary tract is dependent on urine output, it was hypothesized that ACEi may also increase the risk of urinary tract infections (UTIs).

Objective Our objective was to assess the risk of UTIs associated with ACEi therapy initiation in the general population.

Methods A prescription sequence symmetry analysis was performed with the Dutch ‘InterAction Database’ (IADB.nl) pharmacy prescription database. We selected all patients from the IADB who were incident users of both ACEi and nitrofurantoin (a proxy for UTIs). A relatively short maximum time-span of 4 weeks between both prescriptions was used to limit time-variant confounding. The sequence ratio was calculated by dividing the number of individuals starting ACEi first and nitrofurantoin second by the number of individuals starting nitrofurantoin treatment first and ACEi second. We adjusted for trends in prescribing and estimated 95 % confidence intervals using exact confidence intervals for binomial distributions. To evaluate whether the effect is specific to ACEi and to assess whether the possible mechanism behind an increased risk of UTIs is related to the renin–angiotensin–aldosterone system, we also estimated the risk for β -adrenoceptor antagonists (β -blockers).

Results In total, 22,959 incident users of ACEi therapy were eligible for analysis. Of these, 161 patients started ACEi therapy within 4 weeks prior to or after nitrofurantoin therapy initiation. A total of 101 (63 %) started ACEi therapy first followed by nitrofurantoin treatment, while 60 (37 %) patients started nitrofurantoin treatment first, which corresponds to a statistically significant adjusted sequence ratio (ASR) of 1.68 (95 % CI 1.21–2.36). No association was found between β -blockers and UTI treatment (ASR 1.01, 95 % CI 0.74–1.38).

Conclusions A significant excess of patients received UTI medication prescriptions following the first month after ACEi initiation. This prescription sequence asymmetry suggests that ACEi initiation increases the risk of developing UTIs.

1 Introduction

Angiotensin-converting enzyme inhibitors (ACEi) are one of the most frequently prescribed classes of antihypertensive drugs. ACEi are prescribed for the management of various cardiovascular and renal diseases, including diabetic and non-diabetic nephropathy. Although ACEi therapy has reno-protective effects in chronic kidney disease [1, 2], treatment with ACEi can occasionally lead to renal failure [3–5]. A possible mechanism behind this adverse event is that ACEi have a relatively greater dilating effect on the efferent than the afferent arterioles by reducing angiotensin-II levels. This hemodynamic effect can result in a decreased glomerular filtration rate (GFR) and urine output [6, 7]. An adverse hemodynamic effect is particularly relevant in patients with a reduced circulating volume, since the GFR is then more dependent on angiotensin-II levels [6]. However, treatment with ACEi can also result in

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decreased urine output in healthy elderly patients without known risk factors for adverse renal effects with ACEi therapy [7]. Such an adverse effect usually develops immediately after ACEi treatment has been started, but it has also occasionally been observed later in the treatment course, after months or even years [6]. Although this adverse effect is almost always reversible [8, 9], it is not uncommon that ACEi therapy leads to a reduced GFR and urine output without such severe consequences as oliguria, anuria, or acute renal failure [6, 7]. We hypothesized that, since bacterial clearance from the urinary tract is dependent on urine output [10], ACEi may also be associated with an increased risk of the development of urinary tract infections (UTIs), especially early in the treatment course. In a recent post hoc analysis of a randomized controlled trial, we indeed observed an increased risk of developing UTIs after ACEi initiation in adults with micro-albuminuria [11]. We now present the results from a population-based prescription sequence symmetry analysis [12], to assess the risk of developing UTIs after ACEi therapy initiation.

2 Methods

2.1 Setting

This prescription sequence symmetry study was performed with the University of Groningen 'InterAction Database' (IADB.nl) pharmacy prescription database, which contains prescription data from 1994 through 2011 from approximately 55 community pharmacies, and covers an estimated population of 500,000 patients [13]. Registration in the database is irrespective of healthcare insurance, age, and gender. Prescription rates among the database population have been found to be representative for The Netherlands as a whole, and the database is widely used in research [14]. Each prescription record contains information on the date of dispensing, the quantity dispensed, the dose regimen, the number of days the prescription is valid, the prescribing physician, and the Anatomical Therapeutic Chemical (ATC) code. Each patient has a unique anonymous identifier; date of birth and gender are known. Due to a high patient pharmacy commitment in The Netherlands and sophisticated pharmacy software, the medication records for each patient are virtually complete, except for over-the-counter drugs and medication dispensed during hospitalization [15].

2.2 Study Population and Outcome Definition

The study population comprised all patients from the IADB who were incident users of both ACEi (ATC code C09A or C09B) and antibiotic UTI therapy with nitrofurantoin

(J01XE). Incidence was defined as not having been prescribed the drug in question for at least 12 months, while being captured in the database for at least 12 months prior to the first prescription.

Because patient diagnoses were not available from the IADB, UTIs were defined on the basis of the first start of a nitrofurantoin course. In The Netherlands, guidelines regarding the primary care treatment of UTIs changed in 2005, due to increased bacterial resistance to trimethoprim [16]. Nitrofurantoin became the first-choice drug for uncomplicated UTIs. Indeed, the IADB recorded an increase in nitrofurantoin prescriptions and a decrease in trimethoprim after 2005 [13].

Nitrofurantoin is almost exclusively used to treat uncomplicated UTIs; trimethoprim is more frequently used for other indications such as respiratory tract infections [17]. We defined a UTI as a nitrofurantoin prescription and used data between January 2006 and December 2011 in order to obtain a proxy with both high specificity and high sensitivity.

In 2001, when nitrofurantoin was prescribed, 96 % of the cases were for a UTI [17]. At that time, nitrofurantoin was used in approximately 33 % of cystitis cases [18]. However, due to the guideline change in 2005, the specificity, and especially the sensitivity, of nitrofurantoin is higher in our study. The use of nitrofurantoin in our database was, on average, approximately two times higher during 2006–2011 than in 2001, while the age and gender distribution remained similar. Simultaneously, the use of sulphonamides and trimethoprim in our database halved between these periods. Since the age-specific annual incidence of UTIs was similar in both periods in The Netherlands (Statistics Netherlands [<http://www.cbs.nl>]), we estimated the sensitivity of our proxy at 66 %.

2.3 Statistical Analysis

Incident use of ACEi or nitrofurantoin therapy was defined as absence of a prescription of the particular medical drug in the 12 months prior to the dispensing date. A prescription sequence symmetry analysis was performed to evaluate whether nitrofurantoin was prescribed more often following the start of ACEi therapy than the reverse in the period between first dispensing dates [12]. Such an analysis is a subtype of a case-crossover study, in which the sequence order is largely independent of time-invariant patient confounders as, similar to traditional case-crossover studies, patients serve as their own control group. However, this design is still vulnerable to confounding by indication, especially when using longer time intervals. When using short maximum time-spans between both prescriptions, confounding by indication due to diseases that slowly progress is largely eliminated, although

confounding by sudden-onset diseases or sudden increases in disease severity might still be present. To reduce time-variant confounding, we examined a relatively short time-span of 4 weeks in the primary analysis. Moreover, a reduced urine output and GFR after ACEi initiation have been reported in relatively short-term studies ranging from 7 days to 8 weeks [7, 19].

The sequence ratio (SR) was calculated by dividing the number of individuals starting ACEi first and nitrofurantoin second by the number of individuals starting nitrofurantoin treatment first and ACEi second. If no association exists between the drugs, patients should have an equal probability of receiving the drugs in either order. If there is an association, such that ACEi increase the risk of a UTI, ACEi should be prescribed more often prior to the start of nitrofurantoin, and the SR would be above one. Case-crossover studies and prescription sequence symmetry analyses are vulnerable to time trends. We therefore adjusted the crude SR for time trends in use of the study drugs. The adjusted sequence ratio (ASR) was obtained by dividing the crude SR by a null ratio, i.e. the crude SR obtained assuming no association between both drugs based on overall prescribing of both drugs in the total IADB population [12, 20].

For example, if nitrofurantoin were to be prescribed with increasing incidence while the prescribing of ACEi was stable over time, there would be a non-specific excess of nitrofurantoin prescribed last. Assuming no associations between both drugs, one would obtain a null ratio above one based on overall prescribing of both drugs in the total population. The ASR would then consequently be lower than the crude SR.

The ASR is an estimate of the incidence ratio of nitrofurantoin prescribing in ACEi-exposed versus non-exposed person time [12, 20].

For the primary analysis, the ASR was calculated for ACEi and UTI treatment within 4 weeks. We estimated 95 % confidence intervals using exact confidence intervals for binomial distributions [12, 21]. Statistical analyses were performed using STATA 12 software.

2.4 Secondary Analysis

It is possible that patients started ACEi treatment because they recently experienced a stroke. As the rates of infections are increased after a stroke [22], we conducted a secondary analysis to see whether excluding patients who recently experienced a stroke would change the ASR.

Most patients who experience a stroke are subsequently treated with a platelet aggregation inhibitor or a vitamin K antagonist. Therefore, we identified patients with stroke as those patients starting treatment with one of these drugs within 1 month before or on the same day as ACEi

treatment initiation. Additionally, we evaluated whether a possible association would be influenced by time-variant prescribing of diuretics. We also evaluated whether our findings would change if we excluded patients receiving second- or third-choice (during the study period of 2006–2011) UTI antibiotic treatment (trimethoprim and fosfomycin; ATC codes J01EE, J01EA, and J01XX01) in the year before their first nitrofurantoin prescription.

As adults with diabetes are at increased risk of UTIs [23], subgroup analyses with patients with and without diabetes were performed. Patients with diabetes were defined as individuals having received at least one prescription with glucose-lowering drugs (ATC codes A10A or A10B) in the year prior to and including the date of ACEi therapy initiation. For ACEi therapy, a Chi square test was used to assess whether there was a difference in the ASR among patients with and without diabetes. To evaluate whether the development of diabetes occurring concurrently with ACEi therapy initiation might explain the association, we assessed whether the SR was lower in more chronic patients with at least three prescriptions of oral glucose-lowering drugs and/or insulin during the year before starting ACEi treatment.

To evaluate whether the effect is specific to ACEi and to assess whether the possible mechanism behind an increased risk of UTI is related to the renin–angiotensin–aldosterone system, we estimated the ASR for β -adrenoceptor antagonists (β -blockers). These anti-hypertensive drugs are also known to affect the renin–angiotensin–aldosterone system. The same inclusion criteria were used as for the analysis with ACEi.

We did not estimate the ASR for angiotensin-receptor blockers, as most patients who developed a UTI within 28 days of starting angiotensin-receptor blockers were first treated with ACEi and/or experienced more UTIs in the year prior to the treatment initiation. Calcium channel blockers were not used as a control because they might decrease the antibacterial function of uroepithelial cells [24].

Furthermore, we calculated the SRs for receiving UTI treatment within different time-spans since ACEi or β -blocker therapy initiation, ranging from 1 to 8 weeks. For this analysis, each week was treated separately to show the epidemic curve. To reduce random fluctuation, we used a 3-week moving average for calculation of the SRs.

In line with the literature, we hypothesized that the strongest effect, if present, should be within the smaller time spans allowing for some time to develop a UTI (2–4 weeks). Additionally, we plotted the number of individuals with nitrofurantoin prescriptions within 6 months of ACEi therapy initiation to visually explore whether an increase in nitrofurantoin prescriptions is seen after starting ACEi treatment.

3 Results

In total, 27,101 incident users of ACEi therapy were identified between January 2006 and December 2011. After excluding all patients who were not present in the database 12 months prior to their nitrofurantoin prescription, who received a first nitrofurantoin prescription more than 1 year prior to ACEi therapy initiation, or who received a nitrofurantoin course prior to January 2006, a total of 22,959 patients were eligible for analysis.

The mean age of these patients at the start of ACEi therapy was 61.8 (SD 13.9), 42.7 % were female, 16.5 % had recorded use of glucose-lowering drugs and/or insulin, 39.6 % recorded use of diuretics and 22.8 % recorded use of nonsteroidal anti-inflammatory drugs.

Of these incident ACEi users, 582 patients received their first nitrofurantoin prescription in the year prior to starting ACEi therapy and 681 patients started their first nitrofurantoin course in the year after initiating ACEi therapy. Of these, 161 patients started ACEi therapy within 4 weeks prior to or after nitrofurantoin therapy initiation. The mean age of these patients at ACEi initiation was 69.3 years (SD 13.4); 78.9 % were female, 26.1 % had recorded use of glucose-lowering drugs and/or insulin, 54.0 % recorded use of diuretics and 24.2 % recorded use of nonsteroidal anti-inflammatory drugs.

Of all 161 study patients, 101 (63 %) started ACEi therapy first followed by nitrofurantoin treatment, while 60 (39 %) patients started nitrofurantoin treatment first with a corresponding statistically significant ASR of 1.68 (95 % CI 1.21–2.36) (Table 1). For all analyses, adjustment for trends in prescribing did not substantially change the SR, as the null ratios ranged from 0.999 to 1.002. This indicates that the prescribing of ACEi and β -blockers did not increase or decrease more than nitrofurantoin prescribing over time within the short time-spans used.

Excluding patients receiving other antibiotic treatment indicated for UTIs before receiving their nitrofurantoin prescription did not substantially change the ASR (1.56, 95 % CI 1.11–2.20).

Moreover, excluding patients who may have started with ACEi treatment because they recently experienced a stroke resulted in a slight increase of the ASR (1.86, 95 % CI 1.28–2.75).

Additionally, when patients starting treatment with diuretics within 1 month of ACEi treatment were excluded, the ASR (1.59, 95 % CI 1.05–2.44) was similar to our primary analysis.

No association was found between β -blocker therapy initiation and UTI treatment (Table 1). Subgroup analysis for diabetes patients on anti-diabetic therapy ($n = 42$) showed a higher ASR ($p < 0.05$) for diabetes patients than for non-diabetes patients (Table 2).

Table 1 Symmetry analysis with selected antihypertensive drugs

Drug	Nitrofurantoin prescribed second/first (n)	Sequence ratio (95 % CI) ^a
ACEi	101/60	1.68 (1.21–2.36)
β -blocker	87/86	1.01 (0.74–1.38)

Analyses are performed with all persons starting angiotensin-converting enzyme inhibitor or β -blocker therapy within 4 weeks of nitrofurantoin therapy initiation

ACEi angiotensin-converting enzyme inhibitors

^a Adjusted for trends in prescribing

Table 2 Symmetry analysis with angiotensin-converting enzyme inhibitors among patients with and without diabetes

Patients	Nitrofurantoin prescribed second/first (n)	Sequence ratio (95 % CI) ^a
Diabetes	32/10	3.20 (1.53–7.29)
No diabetes	69/50	1.38 (0.94–2.03)

Analyses are performed with all patients starting angiotensin-converting enzyme inhibitor therapy within 4 weeks of nitrofurantoin therapy initiation

^a Adjusted for trends in prescribing

The ASR was not lower when restricting the analysis to more chronic patients with diabetes instead of including all patients with diabetes (ASR 4.0 vs. ASR 3.2).

A histogram of the prescription asymmetry of first nitrofurantoin prescriptions within 6 months of ACEi therapy initiation is shown in Fig. 1. Nitrofurantoin prescriptions increased sharply within 1 month after ACEi therapy started. From this figure, it appears that nitrofurantoin prescription numbers were not random prior to the initiation of ACEi treatment, but instead show a steady increase. However, when looking at the 4 weeks prior to ACEi treatment, such a pattern is not apparent (Fig. 2). A steady increase in the number of nitrofurantoin prescriptions was also observed prior to the initiation of β -blockers (Fig. 3). Both findings indicate that confounding by disease severity would be present if time-spans longer than 4 weeks were used to evaluate the associations between ACEi or β -blockers and UTIs. However, this bias is likely largely eliminated by using a short time-span of 4 weeks, as the number of nitrofurantoin prescriptions does not clearly increase during the 4 weeks prior to ACEi initiation. In addition, we did not find an association between β -blockers and UTI treatment, despite a steady increase in the number of nitrofurantoin prescriptions during the months prior to initiation with this antihypertensive drug.

Figure 4 shows that the risk of developing UTIs is especially high shortly after ACEi therapy initiation, but is elevated during all evaluated weeks (see also Table 3). In

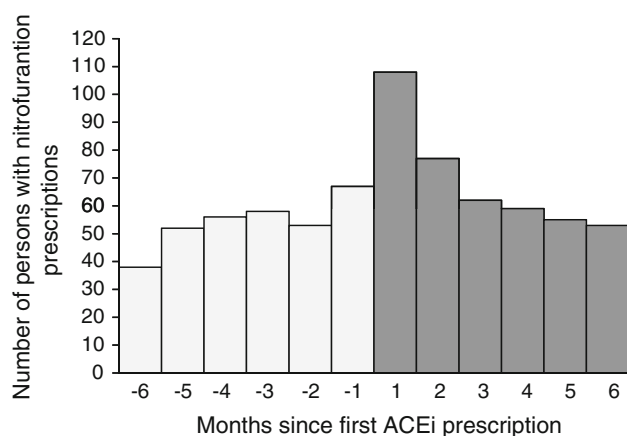


Fig. 1 Prescription asymmetry of first nitrofurantoin prescriptions within 6 months of angiotensin-converting enzyme inhibitor therapy initiation ($n = 738$). *ACEi* angiotensin-converting enzyme inhibitors

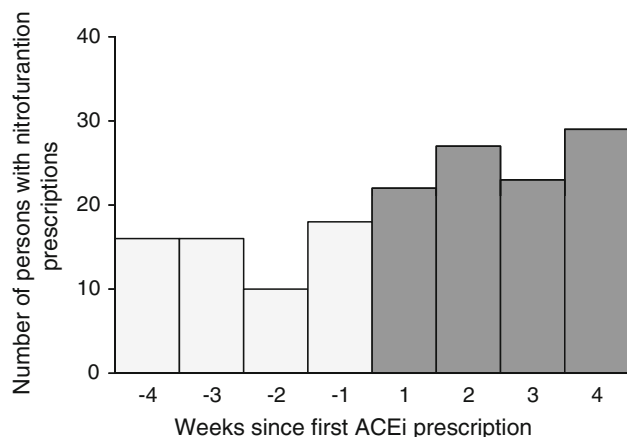


Fig. 2 Prescription asymmetry of first nitrofurantoin prescriptions within 4 weeks of angiotensin-converting enzyme inhibitor therapy initiation. *ACEi* angiotensin-converting enzyme inhibitors

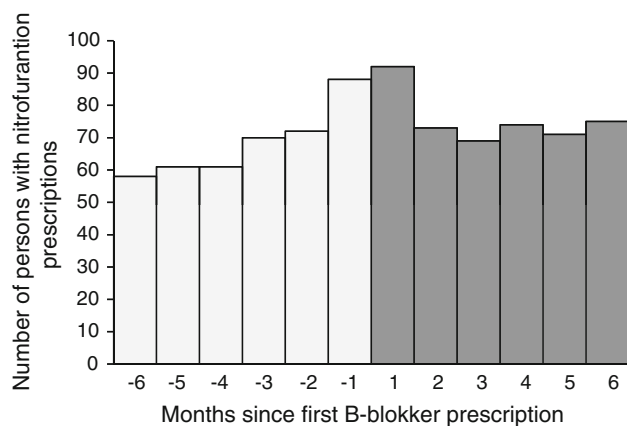


Fig. 3 Prescription asymmetry of first nitrofurantoin prescriptions within 6 months of β -blocker therapy initiation ($n = 864$). *ACEi* angiotensin-converting enzyme inhibitors

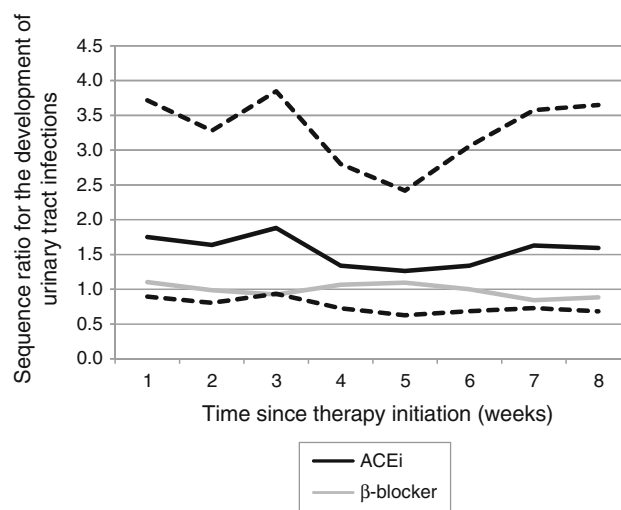


Fig. 4 Sequence ratios for the development of urinary tract infections using different time-spans since angiotensin-converting enzyme inhibitor/ β -blocker therapy initiation. The *dashed lines* represent the lower and upper confidence intervals of the sequence ratio for angiotensin-converting enzyme inhibitors. *ACEi* angiotensin-converting enzyme inhibitors

Table 3 Symmetry analysis with angiotensin-converting enzyme inhibitors and β -blockers using different time-spans since therapy initiation

Time since therapy initiation (weeks) ^a	Nitrofurantoin prescribed second/first (n)	Sequence ratio (95 % CI)
ACEi		
1	25/14	1.75 (0.9–3.7)
2	24/15	1.64 (0.8–3.3)
3	26/14	1.88 (0.9–3.8)
4	24/18	1.34 (0.7–2.8)
5	22/18	1.26 (0.6–2.4)
6	20/15	1.34 (0.7–3.1)
7	19/12	1.63 (0.7–3.6)
8	17/11	1.59 (0.7–3.7)
β-blockers		
1	22/20	1.10 (0.6–2.3)
2	22/22	0.99 (0.5–1.9)
3	21/22	0.93 (0.5–1.8)
4	22/20	1.07 (0.5–1.9)
5	19/18	1.09 (0.5–2.1)
6	16/16	1.00 (0.4–2.0)
7	14/17	0.84 (0.4–1.8)
8	15/17	0.88 (0.4–2.1)

ACEi angiotensin-converting enzyme inhibitors

^a Each week is treated separately to show the epidemic curve. To reduce random fluctuation, a 3-week moving average was used for calculation of the sequence ratios

contrast, the SR for β -blockers fluctuates around one during the same period.

4 Discussion

The results of this population-based prescription sequence symmetry analysis are compatible with the hypothesis that there is a statistically significant increased risk of starting UTI antibiotic therapy after the initiation of ACEi therapy, notably within the first month.

The study confirms a post hoc analysis of a randomized controlled trial in which we observed an increased risk of developing UTIs in patients aged 28 to 75 years on fosinopril treatment [11]. Given that the mechanism underlying this increased risk is likely reversible by either changing the dose or switching to another antihypertensive drug [6], it is not surprising that the increased risk for UTIs is mainly seen during the first month after initiation of ACEi treatment. Moreover, as with renal failure, reduced urine output resulting in UTIs will likely develop early in the course when ACEi treatment is started. Importantly, in the specific group of patients with chronic kidney disease, longer-term ACEi therapy may even reduce the risk of developing UTIs because of its reno-protective effects in these patients [8].

Secondary analysis showed that the association between ACEi therapy and UTI antibiotic prescriptions was stronger among patients with diabetes than patients without diabetes. This increased risk among patients with diabetes might be because diabetes is strongly associated with renal impairment [25, 26], which increases the risk of ACEi-induced renal failure [25, 26], and possibly the short-term risk of ACEi-associated reduced urine output. However, as our database contains no diagnoses and clinical information for individual patients, we could not establish whether these patients with diabetes indeed had more frequent renal impairment.

Alternatively, this increased risk might be due to confounding by the presence of diabetes itself, since patients who have diabetes are more likely to be prescribed ACEi and are more likely to have UTIs. However, the association is likely not confounded by the presence of diabetes, because an ASR of 4.0 was obtained when only patients with at least three prescriptions of glucose-lowering drugs and/or insulin during the year before starting ACEi treatment were included.

Inherent to observational studies, those who start ACEi treatment may have different risk factors than those who do not initiate this treatment [27], which may confound the association between ACEi therapy and UTI development. For example, as ACEi are considered to be more reno-protective than antihypertensive agents not affecting the

renin–angiotensin pathway [28–30], patients who start ACEi therapy are more likely to have risk factors for renal impairment.

Different design and analytical techniques exist to control for such confounding bias [31]. Though suited for a limited number of epidemiological questions, a powerful design technique is the case-crossover study, and the prescription sequence symmetry analysis is a variation on this design. By performing a prescription sequence symmetry analysis, we controlled for time-invariant (unmeasured) confounding, since patients act as their own controls. Furthermore, no trends in prescribing that vary within the short time-spans were present in this study.

However, the prescription sequence symmetry analysis is still vulnerable to confounding by disease severity or sudden-onset diseases. The increased risk of UTI after starting with ACEi treatment might be due to a change in disease severity unrelated to the effects of ACEi. Although Figs. 1 and 3 both suggest that confounding by disease severity or disease progression might bias analyses using longer time intervals between both prescriptions, Fig. 2 and the results of the prescription sequence symmetry analysis with β -blockers both suggest that confounding by disease severity is largely eliminated when using a short maximum time-span of 4 weeks.

An alternative explanation for our findings could be that some of the patients who developed a UTI after starting ACEi treatment started this therapy because they recently experienced a sudden-onset disease. It is possible that patients started ACEi treatment because they recently experienced a stroke, which is often a sudden-onset disease. Because rates of infections are increased after an acute stroke, more patients might get UTIs after than before ACEi therapy initiation [22]. Most patients who experience a stroke are subsequently treated with a platelet aggregation inhibitor or a vitamin K antagonist. When patients starting one of these drugs within 1 month before or on the same day as ACEi treatment initiation were excluded from our primary analysis, the ASR slightly increased (ASR 1.86, 95 % CI 1.28–2.75). This indicates that our results were not affected much by acute strokes among patients starting ACEi treatment. When patients starting treatment with diuretics within 1 month of ACEi treatment were also excluded, the ASR (1.59, 95 % CI 1.05–2.44) was similar to our primary analysis (ASR 1.68, 95 % CI 1.21–2.36), indicating that our results were not confounded by time-variant prescribing of diuretics.

We performed a secondary analysis with β -blockers to evaluate whether the mechanism behind an increased risk could be related to the renin–angiotensin–aldosterone system. The lack of an effect of β -blockers on the development of UTIs indicates that either the effect of β -blockers on renin and/or angiotensin-II is not strong enough to

increase the risk of UTIs, or that another unknown mechanism might be involved. Additionally, this finding indicates that there is a real class effect of ACEi, and that potential confounding by hypertension or bias due to an increase in physician contacts after starting antihypertensive treatment were eliminated.

This study has potential limitations. First, we used nitrofurantoin prescriptions obtained from a pharmacy prescription database as a proxy for UTIs. While the specificity of this proxy is very high [17], the sensitivity is estimated to be somewhat lower, at 66 % [13, 18]. Although we may have consequently missed some UTIs, it is unlikely that UTIs are systematically treated differently just before than just after ACEi therapy initiation. Moreover, excluding patients receiving other antibiotics that are used to treat UTIs did not substantially alter our findings.

Second, because we used a prescription sequence symmetry analysis, reverse causality might have influenced the results [32]. Although the sharp increase in the number of patients receiving nitrofurantoin prescriptions following ACEi therapy initiation supports the hypothesis that ACEi treatment initiation increases the risk of developing UTIs, this phenomenon would also have been observed if the probability of receiving ACEi therapy reduces after getting a nitrofurantoin prescription. However, both drugs are not used for the same indication and, to our knowledge, there is no reason why physicians should avoid using ACEi in patients who have recently experienced a UTI. The fact that UTIs are not a well documented side effect of ACEi therapy further reduces the probability that reverse causality biased the results. A prescription sequence symmetry analysis would be more prone to reverse causality bias with well documented side effects, as physicians may try to avoid prescribing a drug that further increases the risk of a recently experienced disease.

Finally, as with all prescription sequence symmetry analyses, only patients using both drugs were included in the analyses. Therefore, generalizability of our results might be limited, as only a small fraction of all incident ACEi users was included in the analyses. Patients included in the primary analysis were slightly older, more frequently female, and had more frequently recorded use of diuretics and glucose-lowering drugs and/or insulin compared with all incident ACEi users from our database. However, this might not be surprising as all these factors are risk factors or indicators of diseases that increase the risk for UTIs [23, 33]. On the other hand, we previously found, in a post hoc analysis of a randomized controlled trial, an increased risk of developing UTIs after fosinopril therapy initiation in a patient population without diabetes [11]. This suggests that, although the magnitude of the risk may vary, different patient populations are at increased risk of developing UTIs after starting ACEi therapy.

5 Conclusion

We found a significant excess of patients receiving UTI medication prescriptions following the first month after ACEi initiation. This prescription sequence asymmetry suggests that ACEi therapy initiation, at least during the first month, increases the risk of developing UTIs.

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