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Original article

Nitrofurantoin 100 mg versus 50 mg prophylaxis for urinary tract infections, a cohort study

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ABSTRACT

Objectives: Guidelines do not distinguish between 50 mg or 100 mg nitrofurantoin as daily prophylaxis for recurrent urinary tract infection (UTI), although 50 mg might have a better safety profile. Our objective was to compare the effectiveness and safety of both regimens.
Methods: Data were retrospectively collected from 84 Dutch GP practices between 2013 and 2020. Nitrofurantoin prescriptions of 100 mg and 50 mg every 24 hours in women were included. Cox proportional hazard regression analysis was used to calculate hazard ratios on first episode of UTI, pyelonephritis and (adverse) events. Patients were followed for the duration of consecutive repeated prescriptions, assuming non-informative right censoring, up to 1 year.
Results: Nitrofurantoin prophylaxis was prescribed in 1893 patients. Median lengths of follow up were 90 days (interquartile range (IQR) 37–179 days) for 100 mg ($n = 551$) and 90 days (IQR 30–146 days) for 50 mg ($n = 1342$) with few differences in baseline characteristics between populations. Under 100 mg and 50 mg, 82/551 (14.9%) and 199/1342 (14.8%) developed UTI and 46/551 (8.3%) and 81/1342 (6.0%) developed pyelonephritis, respectively. Adjusted HRs of 100 mg versus 50 mg were 1.01 (95% CI 0.78–1.30) on first UTI, 1.37 (95% CI 0.95–1.98) on first pyelonephritis episode, 1.82 (95% CI 1.20–2.74) on first consultation for cough, 2.68 for dyspnoea (95% CI 1.11–6.45) and 2.43 for nausea (95% CI 1.03–5.74).
Conclusion: Daily prophylaxis for recurrent UTI with 100 mg instead of 50 mg nitrofurantoin was associated with an equivalent hazard on UTI or pyelonephritis, and a higher hazard on cough, dyspnoea and nausea. We recommend 50 mg nitrofurantoin as daily prophylaxis. **Thijs ten Doesschate, Clin Microbiol Infect 2022;28:248**

Introduction

Nitrofurantoin is frequently used as prophylaxis for recurrent urinary tract infection (UTI) [1,2]. Although non-antimicrobial strategies to prevent UTI recurrences are preferable with regard to antimicrobial resistance and adverse events, the use of antimicrobial prophylaxis is still needed in daily practice [3–6].

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Nitrofurantoin is the first choice antimicrobial for uncomplicated UTI because of persisting low resistance rates among uropathogens [7–11]. The efficacy of nitrofurantoin as daily prophylaxis has been well established in multiple randomized controlled trials with an estimated reduction in the risk of UTI of more than 50% compared with placebo [8,9,11].

Nitrofurantoin as prophylaxis is sometimes used for years at a time [8]. The Dutch guideline advises prescription of nitrofurantoin for no longer than 12 months [1], because prolonged use seems to be associated with the occurrence of severe adverse events, including pulmonary toxicity [8,12,13].

International and Dutch guidelines make no distinction between their recommendation to use 50 mg or 100 mg normal-release macrocrystalline nitrofurantoin for continuous prophylaxis of UTI [1,2,14]. As a daily dose of 50 mg nitrofurantoin results in half the cumulative dose, we hypothesized that this might be accompanied by a better safety profile. The objective of this retrospective cohort study is to compare the effectiveness and safety of nitrofurantoin 100 mg versus 50 mg as continuous prophylaxis of recurrent UTI in women.

Materials and methods

Design and data collection

An extensive description of the methods can be found in the Supplementary material (Appendix S1). Data were retrospectively obtained from the Julius General Practitioners' Network, which comprises information on patient characteristics, diagnoses, prescriptions, requested investigations and laboratory values from general practitioner (GP) practices in the Netherlands [15]. Table S1 (Appendix 1) provides the classifications of episodes, end points and confounders that were used. Episodes were selected between January 2013 and November 2020. The article was written according to the CONSORT checklist for cohort studies (Appendix S2).

Study population

First episodes of nitrofurantoin prophylaxis in women of at least 12 years of age who had been prescribed nitrofurantoin (50 mg or 100 mg) every 24 hours for at least 15 days were eligible, according to the guideline [1].

End points

The first episode of UTI was defined as a registration of UTI for which appropriate antibiotics were prescribed. Therapeutic prescriptions with nitrofurantoin were excluded from the main analysis, but in a sensitivity analysis, nitrofurantoin prescriptions were included in the end point. First episode of pyelonephritis was defined as a registration of pyelonephritis with a therapeutic prescription. The safety end points consisted of first consultations for common or serious (adverse) events during nitrofurantoin use.

Duration of follow up

The patients' duration of follow up was estimated by the number of days between the start date of the first prescription to the end date of the last repeated prescription. Consecutive repeated prescriptions were included in follow up if the start date fell within 30 days of the end-date of the previous prescription. Because uncertainty exists about the estimated follow up duration, two sensitivity analyses were performed for the end points first episode

Table 1
Baseline characteristics in the population that received nitrofurantoin 100 mg or 50 mg as continuous prophylaxis for urinary tract infections in women

Patient characteristics	Prophylactic nitrofurantoin ($n = 1893$)		
	100 mg every 24 hours ($n = 551$)	50 mg every 24 hours ($n = 1342$)	p value
Age (years)			
Mean ± SD	57 ± 22	57 ± 23	0.74
Socio-economic status score[a]			
Not available, *n* (%)	1 (0)	2 (0)	
Mean ± SD	0.34 ± 1.2	0.25 ± 1.2	0.14
eGFR (mL/min)			
Not available, *n* (%)	306 (56)	714 (53)	
Mean ± SD	90 ± 22	92 ± 22	0.45
Pregnancy, *n* (%)	65 (12)	219 (16)	0.01
STD, *n* (%)	48 (9)	130 (10)	0.51
Use of OAC, *n* (%)	98 (18)	253 (19)	0.59
Diabetes mellitus (%)	101 (18)	194 (14)	0.04
Hba1C, mean ± SD	50 ± 15	54 ± 12	
Renal or urologic disorders[b], *n* (%)	19 (3)	58 (4)	0.38
Nephrolithiasis, *n* (%)	23 (4)	58 (4)	0.89
Immunosuppressive state, *n* (%)	18 (3)	23 (2)	0.04
No. of UTI episodes in previous year[c]			
Mean ± SD	2.6 ± 3.5	2.7 ± 2.8	0.57
No. of UTI episodes in previous half year[c]			
Mean ± SD	1.8 ± 2.2	1.9 ± 1.9	0.61
Recurrent UTI[d], *n* (%)	283 (51)	748 (56)	0.08
Obstructive lung disease[e], *n* (%)	61 (11)	156 (12)	0.73
IBD/peptic ulcer, *n* (%)	46 (8)	115 (9)	0.61

Abbreviations: eGFR, estimated glomerular filtration rate; IBD, inflammatory bowel disease; OAC, oral anticonception; SD, standard deviation; STD, sexually transmitted diseases; UTI, urinary tract infection.

[a] Socio-economic state ranges from −7 to +7 and is estimated on the neighbourhood the patient lives (postal code).

[b] Other than nephrolithiasis.

[c] Number of prescriptions for cystitis or pyelonephritis in the previous 183 or 365 days before the episode, respectively.

[d] Defined as having had three or more UTIs in the last year or two in the last 6 months.

[e] Asthma or chronic obstructive pulmonary disease.

of UTI and first episode of pyelonephritis, in which different follow-up durations were estimated, with an interval of, respectively, 1 and 75 days between the start date of a consecutive prescription and the end date of the previous prescription, instead of the above 30 days. For the end point first pulmonary event, a sensitivity analysis was performed with a fixed follow-up duration of 365 days after initiation of nitrofurantoin, irrespective of the estimated duration of use, because pulmonary toxicity can occur after discontinuation of nitrofurantoin.

Statistical analysis

Kaplan–Meier estimates were plotted for time to first UTI and for first pulmonary event for the populations that used 100 mg and 50 mg nitrofurantoin. Mixed effects Cox regression was used to calculate hazard ratios for all end points, using 50 mg nitrofurantoin as the reference category. The confounders that were used are described in the footnote of Table 2. A sensitivity analysis was conducted using propensity matching in which 551 patients using 50 mg nitrofurantoin were matched with 551 patients using 100 mg nitrofurantoin, on covariates that were either imbalanced between populations or that were associated with the end point. The covariates that were used for matching are described in the footnote of Table 2.

Ethics

The study was designated as not being subject to the Medical Research Involving Human Subjects Act by the ethics board of the University Medical Centre Utrecht, the Netherlands.

Results

Study population

Figure 1 provides the flowchart for inclusion. In the end, 551 patients receiving 100 mg and 1342 patients receiving 50 mg nitrofurantoin were eligible.

For the main analysis, 3333 consecutive prescriptions (42%) were excluded because the start-date fell more than 30 days after the previous prescription's stop date. The estimated median follow-up duration was 90 days (interquartile range (IQR) 30–152 days), which was equal between the 100 mg population (median 90 days, IQR 37–179 days) and the 50 mg population (median 90 days, IQR 30–146 days). For the sensitivity analysis with an interval of 1 day, 5023 (63%) prescriptions were disregarded, with a median follow-up duration of 89 days (IQR 30–90 days; 100 mg: 89 days, IQR 30–92 days, 50 mg: 89 days, IQR 30–90 days). For the sensitivity analysis with an interval of 75 days, 2518 (31%) prescriptions were

Table 2
All end points between the populations that were prescribed nitrofurantoin 100 mg or 50 mg as prophylaxis for urinary tract infections

	Prophylactic nitrofurantoin, *n* (%)		Crude HR 100 mg versus 50 mg (95% CI)	Adjusted HR 100 mg versus 50 mg (95% CI)	Propensity score matching HR 100 mg ($n = 551$) versus 50 mg ($n = 551$) (95% CI)[j]
	100 mg every 24 hours ($n = 551$)	50 mg every 24 hours ($n = 1342$)			
Urinary tract infection	82 (15)	199 (15)	1.00 (0.88–1.29)	1.01 (0.78–1.30)[a]	0.98 (0.72–1.33)
Pyelonephritis	46 (8)	81 (6)	1.37 (0.96–1.97)	1.37 (0.95–1.98)[a]	1.20 (0.78–1.85)
Any pulmonary consultation	60 (11)	80 (6)	1.68 (1.20–2.34)	1.75 (1.24–2.47)[b]	1.47 (0.97–2.23)[k]
Cough	42 (8)	51 (4)	1.84 (1.23–2.78)	1.82 (1.20–2.74)[b]	1.56 (0.94–2.60)[k]
Dyspnoea	9 (2)	12 (1)	2.99 (1.26–7.09)	2.68 (1.11–6.45)[b]	2.59 (0.84–8.04)[k]
Unspecified LRTI	17 (3)	24 (2)	1.56 (0.84–2.91)	1.75 (0.92–3.31)[b]	1.29 (0.61–2.76)[k]
Any gastrointestinal consultation	46 (8)	84 (6)	1.23 (0.86–1.76)	1.26 (0.88–1.81)[c]	1.29 (0.79–1.81)[l]
Nausea	11 (2)	10 (1)	2.45 (1.04–5.78)	2.43 (1.03–5.74)[c]	2.57 (0.82–8.08)[l]
Diarrhoea	7 (1)	20 (1)	0.76 (0.32–1.80)	0.78 (0.33–1.85)[c]	1.31 (0.42–4.13)[l]
Abdominal pain	25 (5)	44 (3)	1.26 (0.77–2.07)	1.32 (0.81–2.16)[c]	1.68 (0.88–3.24)[l]
Alopecia	2 (0)	5 (0)	0.89 (0.17–4.59)	1.56 (0.03–70.17)[d]	1.71 (0.16–18.87)[m]
(Candida) vaginitis	15 (3)	38 (3)	0.90 (0.49–1.63)	0.71 (0.38–1.31)[e]	0.87 (0.43–1.76)[n]
(Poly)neuropathy	6 (1)	13 (1)	0.99 (0.38–2.65)	0.58 (0.28–2.04)[f]	1.11 (0.34–3.64)[o]
Hepatotoxicity	3 (1)	5 (0)	1.35 (0.32–5.66)	2.05 (0.45–9.40)[g]	2.71 (0.28–26.10)[p]
Headache	9 (2)	22 (2)	0.90 (0.41–1.95)	0.97 (0.44–2.13)[h]	0.93 (0.37–2.35)[q]
Allergic reaction NOS	12 (2)	37 (3)	0.72 (0.38–1.38)	0.70 (0.36–1.34)[i]	0.78 (0.36–1.69)[r]

Abbreviations: HR, hazard ratio; LRTI, lower respiratory tract infection; NOS, not otherwise specified.

[a] Adjusted for age, socio-economic status, pregnancy, estimated glomerular filtration rate (eGFR), immunosuppressive state, the use of oral anticonception, urolithiasis, urological or renal diseases other than urolithiasis, diabetes mellitus, sexually transmitted disease, the number of UTIs within the 12 months prior to the episode.

[b] Adjusted for lung disease in the medical history or lung-related consultations within 12 months prior to the episode, smoking, the number of UTIs within 12 months prior to the episode.

[c] Adjusted for gastrointestinal disease in the medical history or gastrointestinally related consultations within 12 months prior to the episode and pregnancy.

[d] Adjusted for alopecia in the medical history, age.

[e] Adjusted for a consultation because of *Candida* vaginitis within 12 months prior to the episode, pregnancy and age.

[f] Adjusted for a consultation because of polyneuropathy within 12 months prior to the episode, diabetes mellitus and age.

[g] Adjusted for a consultation because of hepatotoxicity within 12 months prior to the episode, diabetes mellitus and age.

[h] Adjusted for a consultation because of headache within 12 months prior to the episode and age.

[i] Adjusted for a consultation because of allergy within 12 months prior to the episode and age.

[j] The populations were matched for age, socio-economic status, pregnancy, immunosuppressive state, diabetes mellitus, the number of UTI within 12 months prior to the episode.

[k] Additionally matched for lung disease in the medical history or lung-related consultations within 365 days prior to the episode, smoking.

[l] Additionally matched for gastrointestinal disease in the medical history or gastrointestinally related consultations within 12 months prior to the episode.

[m] Additionally matched for alopecia in the medical history.

[n] Additionally matched for candida vaginitis within 12 months prior to the episode.

[o] Additionally matched for polyneuropathy within 12 months prior to the episode.

[p] Additionally matched for hepatotoxicity within 12 months prior to the episode.

[q] Additionally matched for headache within 12 months prior to the episode.

[r] Additionally matched for allergy within 12 months prior to the episode.

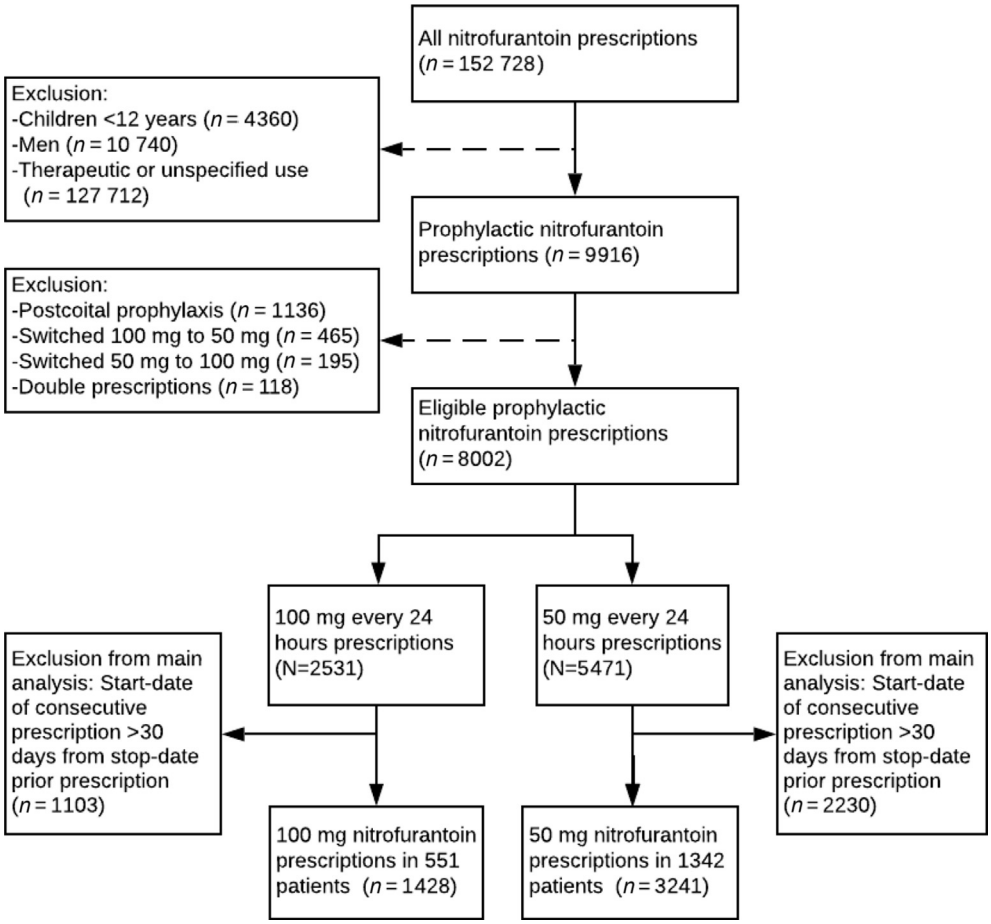

Fig. 1. Flowchart of nitrofurantoin (NF) as continuous prophylaxes from 84 Dutch GP practices between January 2013 and November 2020.

disregarded, with a median follow-up duration of 90 days (IQR 40–181 days; 100 mg: 90 days, IQR 40–197 days, 50 mg: 90 days, IQR 40–180 days). There was wide variation in the proportional use of 100 mg versus 50 mg nitrofurantoin prophylaxis per GP practice, illustrated in the Supplementary material (Fig. S1). The baseline characteristics of the study population are summarized in Table 1.

Effectiveness

Figure 2 represents the crude survival plot with the probability on first episode of UTI after initiation of 100 mg and 50 mg nitrofurantoin prophylaxis. After adjustment for confounders, the adjusted hazard ratio (aHR) on first episode of UTI when using 100 mg instead of 50 mg nitrofurantoin was 1.01 (95% CI 0.78–1.30) (Table 1). Factors that were associated with the hazard of UTI were increased age (aHR annually 1.02, 95% CI 1.01–1.02), having urological or renal co-morbidity (aHR 2.15, 95% CI 1.35–3.42), being immunocompromised (aHR 2.64, 95% CI 1.57–4.42) and an increased number of UTI within the previous year (aHR per UTI 1.04, 95% CI 1.02–1.06). The aHR on the occurrence of pyelonephritis between 100 mg and 50 mg was 1.37 (95% CI 0.95–1.98). Propensity-matched analyses resulted in similar hazard ratios (Table 2).

The sensitivity analysis in which nitrofurantoin prescriptions were included in the end point first UTI revealed an aHR of 100 mg versus 50 mg of 0.94 (95% CI 0.73–1.20). The sensitivity analysis with an interval period of 1 day resulted in aHRs of 0.83 (95% CI 0.59–1.17) on first UTI and 1.33 (95% CI 0.90–1.98) on first

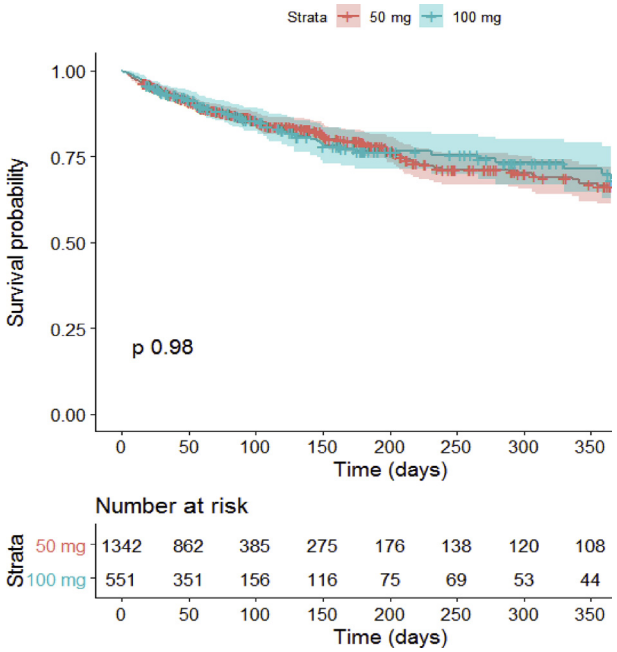

Fig. 2. Crude survival plot containing a point-wise 95% CI of time to first episode of urinary tract infection after the first prescription of 100 mg or 50 mg nitrofurantoin as continuous daily prophylaxis.

pyelonephritis. The sensitivity analysis with an interval period of 75 days provided aHRs of 0.88 (95% CI 0.65–1.21) on first UTI and 1.02 (95% CI 0.65–1.61) on first pyelonephritis.

Safety

The use of 100 mg instead of 50 mg was associated with an increased hazard on a consultation because of cough (aHR 1.82, 95% CI 1.20–2.74), dyspnoea (aHR 2.68, 95% CI 1.11–6.45) and nausea (aHR 2.43, 95% CI 1.03–5.74). Fig. 3 provides the crude survival plot with the probability of first pulmonary event. Factors that were associated with an increased hazard for first pulmonary event were the number of UTI in the previous 12 months before the episode (aHR per UTI 1.05, 95% CI 1.02–1.08) and pulmonary disease in the medical history or lung-related consultation within 365 days before the episode (aHR 2.33, 95% CI 1.68–3.25). The sensitivity analysis for the end-point first pulmonary event with a fixed duration of follow up of 365 days resulted in a hazard ratio of 1.35 (95% CI 1.06–1.71). Table 2 describes all safety end points.

Discussion

The results of this study constitute an important indication that the use of 100 mg compared with 50 mg nitrofurantoin is associated with an increased hazard for pulmonary (adverse) events and nausea, but an equivalent hazard for first UTI or pyelonephritis.

To our knowledge, no head-to-head comparisons have been made between the effectiveness or safety of 100 mg and 50 mg nitrofurantoin as UTI prophylaxis. A meta-analysis of controlled trials that compared nitrofurantoin with placebo made an indirect comparison between 100 mg and 50 mg, which yielded no difference in UTI incidence [8]. A randomized crossover study compared the pharmacokinetic profile of macrocrystalline normal-release nitrofurantoin and found a significantly higher dose-normalized area under the curve in urine after using 50 mg every 6 hours instead of 100 mg every 8 hours, which suggests that the availability of nitrofurantoin into urine is saturable [18]. This could explain why an increased dose would not improve its effectiveness as prophylaxis.

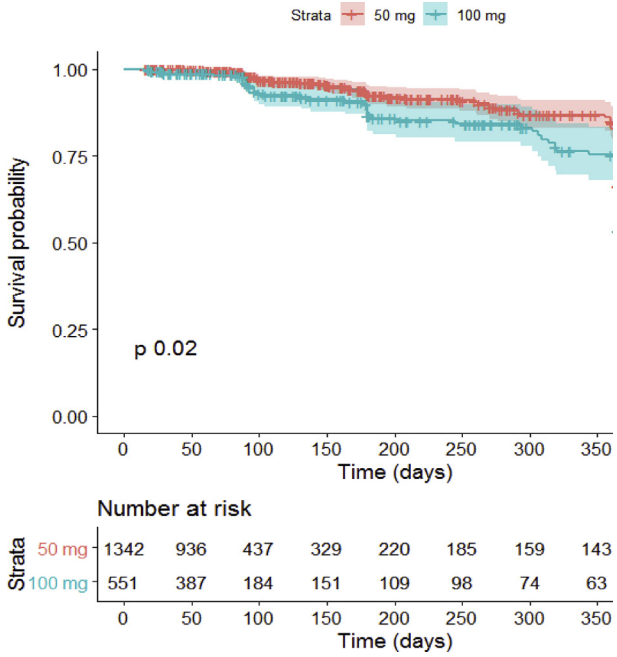

Fig. 3. Crude survival plot containing a point-wise 95% CI of time to first pulmonary event, defined as any pulmonary-related consultation, in the populations that used 100 mg or 50 mg nitrofurantoin as continuous prophylaxis.

The use of 100 mg over 50 mg nitrofurantoin as continuous prophylaxis was associated with a clinically relevant hazard for pulmonary events, mainly consisting of cough and dyspnoea. The number of patients needed to prevent one pulmonary event by using a daily dose of 50 mg instead of 100 mg nitrofurantoin was 20. The nature, severity and prognosis of these events is unfortunately unknown. The high percentage of patients with pulmonary events in our study (7.4%) is not consistent with the low incidence of severe pulmonary toxicity in a meta-analysis (0.001%–0.2%), and we assume that most pulmonary events in our study were mild and self-limiting [8]. Pulmonary events in our study were not necessarily related to the use of nitrofurantoin but could rather have been the expression of underlying lung disease. In another cohort of 3400 mainly short-term nitrofurantoin users 641 pulmonary or hepatic adverse events (18.6%) were recorded, using International Classification of Diseases 9th revision codes, but after manual chart inspection 89% were not considered to be related to the use of nitrofurantoin [13]. Nevertheless, the comparable populations and the adjusted analysis in our study make it plausible that the observed higher incidence of pulmonary events is attributable to the higher daily dose of nitrofurantoin, through a higher systemic availability and/or an increased cumulative dose. To monitor and objectify these pulmonary events and to estimate their nature, severity and prognosis we recommend educating patients about the risk of pulmonary toxicity. A wide variety of pulmonary syndromes has been attributed to the use of nitrofurantoin in literature and pharmacovigilance databases, the most common being acute pulmonary hypersensitivity, which typically arises within 1 month after the start of nitrofurantoin with fever (82%), dyspnoea (60%) and cough (43%), and chronic pneumonitis, which is rarer and normally develops after 12 months of use with dyspnoea (73%), dry cough (63%) and fatigue (37%). Given our relatively short follow-up period, we may have missed consultations for chronic pneumonitis. If recognized early with discontinuation of nitrofurantoin, prognosis of both entities is on average good; however, serious irreversible lung damage could also occur and fatalities have been described [19,20].

It was already known that macrocrystalline nitrofurantoin prophylaxis is associated with a higher incidence of gastrointestinal adverse events when compared with other antimicrobials, with relative ratios of 2.24 (95% CI 1.77–2.83) and 2.17 (95% CI 1.34-3.50) in two meta-analyses [8,9,21]. We found that more nausea occurred after using 100 mg instead of 50 mg nitrofurantoin with a low but probably underestimated incidence. No differences were observed between 100 mg and 50 mg regarding other adverse or serious adverse events, for example, hepatotoxicity, polyneuropathy or headache.

The population that used continuous prophylaxis consisted of mostly postmenopausal women, with a relatively high incidence of diabetes mellitus and urological disorders. Few differences existed in baseline characteristics between the populations that used 100 mg and 50 mg nitrofurantoin, probably as a consequence of the fact that the Dutch guideline does not distinguish between both. Together with the large variation in proportional use of 100 mg to 50 mg that we observed between GP practices, this indicates that the GP preference is based on habitual or logistical factors instead of patient characteristics, which diminishes the risk of confounding bias. Naturally, confounding by indication cannot be excluded. GPs that prescribe 100 mg nitrofurantoin instead of 50 mg may have informed patients better about the risk of pulmonary toxicity, or they could have monitored these patients more intensively. On the other hand, physicians that are aware of this risk of lung toxicity are probably more likely to prescribe

50 mg instead of 100 mg nitrofurantoin. So if there were to be confounding by indication it is unclear whether this underestimated or overestimated the true effect.

Most limitations of this study result from its retrospective nature. Data from the Julius General Practitioners' Network provides reliable quantitative estimates of demographic data, drug prescriptions (ATC: Anatomical Therapeutic Chemical Classification codes), complaints, symptoms and entities (ICPC: International Classification of Primary Care codes) and laboratory values [15]. Nevertheless, data have not been collected for the purposes of this study, and assumptions needed to be made on the actual presence of UTI episodes, end points and confounder estimates. The exact motive to prescribe prophylaxis was unknown, although it is reassuring that the majority of the population suffered from recurrent UTI [15]. The presence of UTI was not confirmed with urine culture or with urinalysis because these data were lacking in the Julius General Practitioners' Network database, which may have increased the risk of misclassification. This risk is lowered by the fact that Dutch GPs usually confirm the presence of a UTI using a dipstick before prescribing antimicrobials [1,15,22]. We had no access to prescriptions from hospitals or out-of-office GP services, as a result of which end points may have been underestimated. Only 6% of total antimicrobial prescriptions in primary care occur out of office hours in the Netherlands, diminishing this risk [23]. For the estimation of the safety end points we relied on ICPC registrations of complaints, symptoms and entities by GPs. As mentioned, the ICPC encoding system does not contain sufficient detail to draw inferences on the incidence, nature or severity of adverse events. Unfortunately, we lacked data and were not able to adjust the calculation of the estimated glomerular filtration rate on the ethnicity of patients. Only a small minority in the Netherlands are of African descent. Next, the follow-up duration was difficult to estimate. Repeated prescriptions did not always follow previous prescriptions consecutively because these were acquired with delay as a probable consequence of varying treatment adherence. To capture these effects on the effectiveness, we performed two sensitivity analyses with different intervals, which revealed similar results. Other limitations resulted from our statistical approach. We used right-censoring if we estimated that prophylaxis was discontinued. This could have occurred for several reasons, for example because of the intended end of use, because of treatment non-adherence, as a result of unregistered failure or as a result of adverse events. Theoretically, reasons for censoring could have differed between 100 mg and 50 mg, although we expected that this would also have led to differences in the estimated follow-up durations, which we did not observe. The propensity-matched analyses pointed towards the same direction as the crude and multivariable analyses. Significance was not reached because of the smaller sample size and insufficient power.

In conclusion, the use of 100 mg instead of 50 mg nitrofurantoin as daily prophylaxis for UTI is associated with an increased hazard on pulmonary events and nausea but an equivalent hazard on clinical failure. The findings in this study emphasize existing concerns about pulmonary toxicity after prophylactic nitrofurantoin use [8,24]. A randomized controlled trial with close and in-depth monitoring of pulmonary toxicity would yield an unbiased result in terms of efficacy and safety. Until that time, we would recommend the use of 50 mg nitrofurantoin as prophylaxis for recurrent UTI with close monitoring of pulmonary signs and symptoms.

Transparency declaration

The authors declare that they have no conflicts of interest.
No funding was received.

Author contributions

TD, KH, CW, EH, TP, IG, AM, AH, MB and SG contributed to the design of the study. TD, HW and KH did the data extraction and analysis. TD and SG wrote the original draft and were responsible for the conceptualization; and TD, KH, CW, EH, TP, IG, AM, AH, MB and SG contributed to reviewing and editing. All authors read and approved the final version. TD and KH had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2021.05.048.

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