Original article

Five versus seven days of nitrofurantoin for urinary tract infections in women with diabetes: a retrospective cohort study

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ABSTRACT

Objective: To compare the effectiveness of 5 versus 7 days of nitrofurantoin treatment for urinary tract infection (UTI) in women with diabetes.
Methods: Data were collected retrospectively from Dutch general practitioners between 2013 and 2020. Nitrofurantoin prescriptions with a duration of 5 days (5DN) or 7 days (7DN) in women with diabetes were included. Inverse propensity weighting was performed to calculate adjusted risk differences (RD) for treatment failure within 28 days. Secondary outcomes were 14-day treatment failure, severe treatment failure and 28-day treatment failure in defined risk groups.
Results: Nitrofurantoin was prescribed in 6866 episodes, 3247 (47.3%) episodes with 5DN and 3619 (52.7%) episodes with 7DN. Patients in the 7DN group had more co-morbidities, more diabetes-related complications and were more insulin-dependent. There were 517/3247 (15.9%) failures in the 5DN group versus 520/3619 (14.4%) in the 7DN group. The adjusted RD for failure within 28 days was 1.4% (95% CI −0.6 to 3.4).
Conclusion: We found no clinically significant difference in treatment failure in women with diabetes with UTI treated with either 5DN or 7DN within 28 days. A 5-day treatment should be considered to reduce cumulative nitrofurantoin exposure in DM patients. **Kelly D. Hendriks-Spoor, Clin Microbiol Infect 2022;28:377**

Introduction

Urinary tract infections (UTI) are the most common infections in patients with diabetes mellitus (DM) [1]. An epidemiological study showed an adjusted incidence for UTI per 1000 person-years in women with type 2 DM of 102.9 (95% CI 100.5—105.4) versus 76.2 (95% CI 74.2—78.2) in patients without DM [2]. There is little research on the optimal treatment duration of UTI in DM patients. Some guidelines suggest that patients with well-controlled diabetes may be considered to have an uncomplicated UTI [3]. This hypothesis is supported by an observational study in 259 women with DM that found no benefit of longer treatment duration

(≥5 days of treatment) on the recurrence of UTI within 30 days to 1 year of follow up [4]. Although this study stratified for the Charlson co-morbidity index, it did not correct for potential risk factors for clinical failure like age, glycaemic control and insulin use. Despite this, current guideline recommendations are still largely based on the expert opinion that UTI in DM patients should be treated as a complicated UTI. For example, the Dutch College of General Practitioners recommends treating UTI in patients with diabetes with 7 days of nitrofurantoin, instead of 5 days as recommended for UTI in healthy women, because of the supposed higher risk of recurrent UTI and complications [5].

Five instead of 7 days of nitrofurantoin might reduce cumulative use by 28% in a patient population that is already consuming large amounts of antibiotics because of a high incidence of infections [1]. Shorter duration might decrease the number of days with adverse effects due to nitrofurantoin, such as abdominal complaints (nausea or abdominal discomfort) and headaches, while increasing

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patient satisfaction, improving therapeutic compliance and cost-effectiveness [6—8]. Therefore, additional studies are necessary to address this problem. This study aimed to determine the effectiveness of 5 days of nitrofurantoin (5DN) compared with 7 days of nitrofurantoin (7DN) for UTI in women with DM.

Materials and methods

Data collection

Data were collected from the Julius General Practitioners' Network, containing information from 84 different primary care practices in the province of Utrecht in the Netherlands from January 2013 until September 2020 (Fig. 1). The database contains information on patient characteristics, diagnoses, prescriptions and laboratory results. Episodes of UTI were selected based on Anatomical Therapeutic Chemical (ATC) codes for nitrofurantoin and were additionally linked to International Classification of Primary Care (ICPC) codes for UTI.

Study population

Index UTI episodes were selected from women ≥12 years of age with DM, either type 1 or type 2, based on ICPC code or the ATC code for DM medication, who received a nitrofurantoin prescription for 5 or 7 days in combination with an ICPC code for a UTI or UTI-related symptom. The duration of the prescription was calculated from the number and dosages of the nitrofurantoin tablets prescribed. The ICPC and ATC codes are provided in the Supplementary material (Table S1). Multiple episodes per patient were allowed in the analysis. Episodes with a presumed UTI 28 days before the index UTI episode were excluded from the analysis to distinguish between treatment failure and a new index UTI. Episodes from patients with a complicated UTI based on risk factors other than DM were excluded from the database, e.g. pregnancy, use of immunosuppressive drugs, kidney or bladder disease, an estimated glomerular filtration rate (eGFR) below 30 mL/min or three or more recurrent UTI in the last 6 months or prophylactic treatment in the last 6 months. Episodes with less than 28 days of follow up because of missing information from the general practitioner (GP) were excluded.

End points

The primary outcome measure of treatment failure was defined as a new prescription of nitrofurantoin, fosfomycin, trimethoprim, ciprofloxacin, trimethoprim-sulfamethoxazole or amoxicillin-clavulanic acid combined with an ICPC code for UTI or any symptom or sign correlated to UTI occurring within 28 days of the initial prescription. Secondary outcomes were 14-day treatment failure, severe treatment failure, defined as a new prescription for ciprofloxacin, trimethoprim-sulfamethoxazole or amoxicillin-clavulanic acid combined with an ICPC code for pyelonephritis, and 28-day treatment failure in defined risk groups. Studied risk groups were increased haemoglobin A1c (HbA1c), age and use of insulin.

Statistical analysis

Inverse propensity weighting (IPW) with clustering per patient to adjust for patients with repeated episodes, was used to estimate
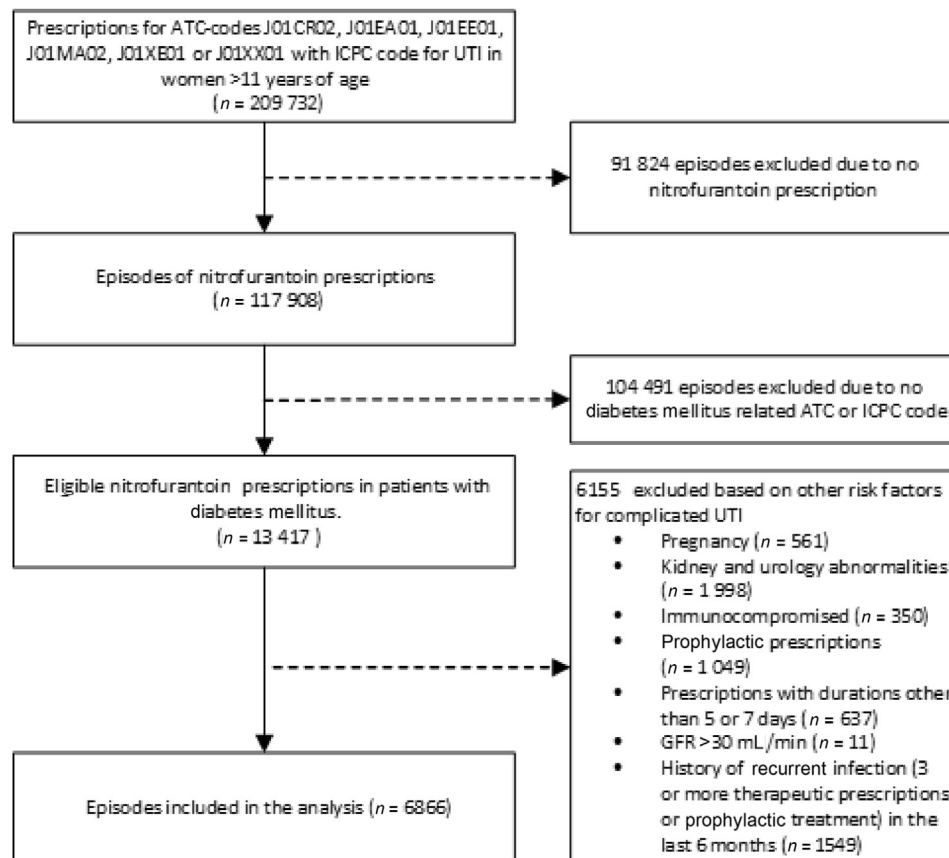

Fig. 1. Flow chart of the study selection of nitrofurantoin prescriptions with a duration of 5 or 7 days from 84 Dutch GP practices between January 2013 and September 2020.

risk differences (RD) with 95% CI. IPW analysis redistributes patient groups based on available variables to form a standardized pseudo-population. There are three Assumptions for IPW: consistency, exchangeability and positivity [9–11]. The consistency assumption suggests that the individual's potential outcome under the observed exposure is the actual outcome. This is deemed plausible because the treatment for UTI is fairly standardized in the Netherlands. The assumption of exchangeability assumes that there is no unmeasured confounding. By using a database with a broad selection of variables, we aimed to reduce unmeasured confounding. The positivity assumption suggests that all patients have the chance of getting the exposure of interest, e.g. 5 or 7 days of nitrofurantoin, even those with uncommon co-variates. Based on the variation in the baseline table and the distribution of the 5DN and 7DN per primary care practice (see Supplementary material, Fig. S1), we do not expect the positivity assumption to be a problem.

IPW score was calculated to predict the probability of receiving 5DN or 7DN by using the following variables: age, antidiabetic medication, extended or normal release nitrofurantoin, eGFR (continuously from >30 mL/min), diabetic complications, urinary incontinence, urolithiasis, neuropsychiatric disorders, sexually transmitted disease, HbA1c values ($\leq$3 months), glucose values ($\leq$7 days), cardiovascular disease and related medication, antibiotic prescriptions for UTI in the previous 6 months (0, 1 or 2 previous prescriptions) and GP practice (see Supplementary material, Table S1). Weights derived from the IPW score were trimmed at the 1st and 99th centile to enhance the precision of the analysis [11].

We recoded eGFR, glucose values and HbA1c values, to account for missing values. The eGFR was calculated with the Chronic Kidney Disease Epidemiology (CKDepi) formula using age, gender and the most recent plasma creatinine value. Missing eGFR values were set to 60 mL/min, reflecting a normal eGFR. Glucose was recoded into four groups (<6 mmol/L, 6–11 mmol/L, >11 mmol/L, missing value) and HbA1c into three groups (<53 mmol/mol, >53 mmol/mol, missing value), reflecting clinically relevant thresholds. Missing information on the duration or dosage of prescribed nitrofurantoin was collected from the free text when possible.

We included a modified intention-to-treat analysis, excluding treatment failure within 6 days, because the intervention is identical during the first 5 days. We conducted a post-hoc analysis of stratifying for groups with a higher risk of UTI: suboptimal glycemic control (based on HbA1c levels), patients over 65 years of age and insulin use as a proxy for more severe DM.

Instrumental variable analysis was performed as a sensitivity analysis as an alternative to control for unobserved confounding. By using the GP practices as an instrumental variable, we were able to provide an estimation of the failure rates. There are three Assumptions to perform a valid instrumental variable analysis (Fig. 2). The relevance assumption was that the GP preference had an effect on treatment duration and would vary between practices. The exclusion restriction suggests that outcome is not affected by the instrumental variable other than through treatment. The last and third assumption is the exchangeability assumption. It assumes that GP practices were independent of patient characteristics. If possible these assumptions were checked using F-statistics.

R software version 1.1.456 was used for data analysis, with R package ipw to perform IPW and ivpack to perform the instrumental variable analysis.

Ethics

Ethical approval was obtained from the medical ethics committee of the University Medical Centre Utrecht, the Netherlands, with a waiver for informed consent. Individuals are not traceable because all data were anonymized.
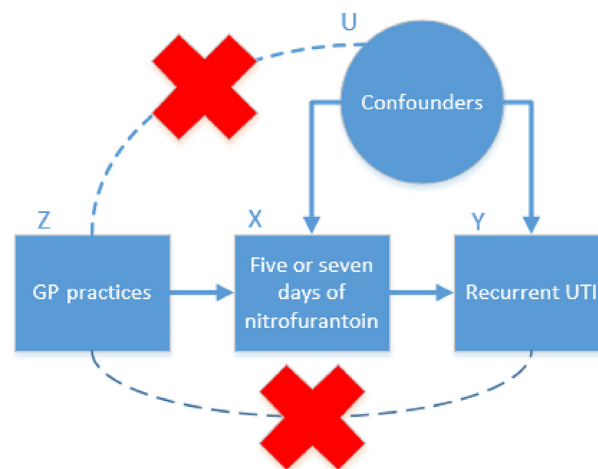

Fig. 2. Graphical representation of the model and the assumption for instrumental variable analysis. Assumption 1—Relevance. The instrumental variable Z has an effect on the exposure X. Assumption 2—Exclusion restriction. The instrumental variable Z does not affect the outcome Y. Assumption 3—Exchangeability. The confounders (U) are independent of the instrumental variable Z. Instrumental variable analysis is assumed to be unbiased if GP practice preference affects clinical failure only through prescription of 5 days or 7 days of nitrofurantoin ($\times$) and they have no direct effect on the outcome of clinical failure (Y) and do not differ in the type of patients (U) for whom they prescribe either 5 days or 7 days of nitrofurantoin.

Results

Patient selection

A total of 14 352 nitrofurantoin prescriptions in individuals with DM were found during the study period. After the exclusion of 6527 episodes, we analysed 6866 episodes in 3681 unique individuals, consisting of 3247 (47.3%) episodes of 5DN and 3619 (52.7%) of 7DN (Fig. 1).

Baseline characteristics

The 7DN group had more co-morbidities, and received insulin treatment more often or a combination of insulin and oral medication, but were comparable in age to the 5DN group (Table 1). Although HbA1c levels were higher in the 7DN group, the average glucose levels were similar. The 7DN group had been treated for UTI more frequently in the previous 6 months.

Assumptions instrumental variable

The preference for treatment duration was highly variable between GP practices (see Supplementary material, Fig. S1), while population age and outcome between the practices did not differ (see Supplementary material, Fig. S2). As both age and outcome were independent of GP practice, we assumed that the Assumptions necessary for the instrumental variable analysis were met. Using the GP practice to predict the treatment duration gave an F-statistic of $1.77 \, e^{+27}$, which confirms the appropriateness of the instrumental variable.

Primary analysis

Of the 3247 individuals who were treated with 5DN, 15.9% received a new prescription within 28 days, whereas in the 7DN, 14.4% of the 3619 received a new prescription (Table 2). Using the IPW analysis, the adjusted RD was 1.4% (95% CI −0.6 to 3.4).

Table 1
Baseline characteristics in the study population that received nitrofurantoin for either 5 days or 7 days to treat cystitis in women with diabetes

	5DN	7DN	p value
N	3247	3619	
Age (years), mean ± SD	66.81 ± 15.54	67.86 ± 14.17	0.003
Use of insulin, n (%)	760 (23.4)	1162 (32.1)	< 0.001
Use of oral antidiabetic medication, n (%)	2337 (72.0)	2864 (79.1)	< 0.001
Biguanides (A10BA)	2211 (68.1)	2709 (74.9)	
Sulphonylureas (A10BB)	1097 (33.8)	1470 (40.6)	
Combinations (A10BD)	13 (0.4)	16 (0.4)	
α-glucosidase inhibitors (A10BF)	24 (0.7)	12 (0.3)	
Thiazolidinediones (A10BG)	17 (0.5)	41 (0.4)	
DPP-4 inhibitors (A10BH)	116 (3.6)	200 (5.5)	
GLP-1 analogues (A10BJ)	72 (2.2)	122 (3.4)	
SGLT2 inhibitors (A10BK)	20 (0.6)	35 (1.0)	
Other blood glucose lowering drugs (A10BX)	26 (0.8)	35 (1.0)	
Combination insulin and oral antidiabetic medication, n (%)	546 (16.8)	872 (24.1)	< 0.001
Glucose level, median (IQR)[a]	7.7 (6.3—9.0)	7.7 (6.8—8.9)	0.407
Glucose categorical, n (%)			< 0.001
Hyperglycaemic (> 11.9 mmol/L)	82 (2.5)	139 (3.8)	
Hypoglycaemic (< 6.0 mmol/L)	338 (10.4)	314 (8.7)	
Normal (> 5.9 but < 12.0 mmol/L)	1136 (35.0)	1515 (41.9)	
Missing	1691 (52.1)	1651 (45.6)	
HbA1c (mmol/mol), median (IQR)[b]	53 (47—61)	54 (49—63)	< 0.001
Hb1Ac categorical, n (%)			< 0.001
High(>53.0 mmol/mol)	347 (10.7)	589 (16.3)	
Normal (< 53.1 mmol/mol)	356 (11.0)	491 (13.6)	
Missing	2544 (78.3)	2539 (70.2)	
Diabetic complications, n (%)	195 (6.0)	426 (11.8)	< 0.001
Retinopathy	98 (3.0)	274 (7.6)	
Glomerulopathy	5 (0.2)	5 (0.1)	
Neuropathy	100 (3.1)	183 (5.1)	
GFR (mL/min), mean ± SD[c]	101 ± 24	102 ± 20	0.291
Missing, n (%)	600 (18.5)	507 (14.0)	
Received antibiotics for UTI in the last 6 months, n (%)	650 (20.0)	822 (22.7)	< 0.001
Use of hormones,[d] n (%)	221 (6.8)	170 (4.8)	< 0.001
History of neuropsychiatric diseases,[e] n (%)	625 (19.2)	687 (19.0)	0.804
History of cardiovascular risk factors,[f] n (%)	2638 (81.2)	3172 (87.6)	< 0.001
History of cardiovascular disease,[g] n (%)	179 (5.5)	302 (8.3)	< 0.001

Abbreviations: 5DN, 5 days of nitrofurantoin; 7DN, 7 days of nitrofurantoin; GFR, glomerular filtration rate; GP, general practitioner; HbA1c, haemoglobin A1c; ICPC, International Classification of Primary Care; IQR, interquartile range; UTI, urinary tract infection.
[a] Most recent level within 7 days before UTI episode.
[b] Most recent level within 30 days before UTI episode.
[c] Most recent measurement within 365 days to UTI episode.
[d] This category includes GP prescriptions for oral contraception, estrogen and progesterone.
[e] This category includes ICPC codes for cognitive impairment, dementia and depressions.
[f] This category includes GP prescriptions of medication for hypercholesterolaemia, and antihypertensive and anti-thrombotic medication.
[g] This category includes ICPC codes for previous acute myocardial infarction and ischaemic heart disease.

Table 2
End point for primary and secondary outcomes in the populations that were prescribed either 5 or 7 days of nitrofurantoin as treatment for uncomplicated UTI in women with diabetes[a]

		Follow-up duration	5DN	Failure rate, n (%)	7DN	Failure rate, n (%)	Crude RD (95% CI)	IPW RD (95% CI)	IV RD (95% CI)
Primary outcome	Overall failure	Day 0–28	3247	517 (15.9%)	3619	520 (14.4%)	1.6 (−0.1 to 3.3)	1.4 (−0.6 to 3.4)	1.6 (−2.6 to 5.8)
Secondary outcome	Overall failure	Day 0–14	3338	368 (11.0%)	3749	348 (9.3%)	1.7 (0.3–3.1)	1.5 (0.0–3.1)	2.0 (−1.5 to 5.5)
	m-ITT	Day 6–28	3247	416 (12.8%)	3619	426 (11.8%)	0.9 (−1.0 to 2.7)	0.9 (−0.9 to 2.7)	1.8 (−2.0 to 5.7)
	Severe failure	Day 0–28	3247	28 (0.9%)	3619	36 (1.0%)	-0.3 (−0.8 to 0.2)	−0.3 (−0.8 to 0.2)	0.2 (−1.0 to 1.3)

Abbreviations: 5DN, 5 days of nitrofurantoin; 7DN, 7 days of nitrofurantoin; IPW, inverse propensity weighting; IV, instrumental variable; m-ITT, modified intention-to-treat; RD, risk difference.
[a] An RD > 0 is in favour of 7 days of nitrofurantoin treatment.

Similarly, the sensitivity instrumental variable analysis yielded an RD of 1.6% (95% CI −2.6 to 5.8).

Secondary analyses

The crude failure rate of recurrence of UTI within 14 days was slightly higher in the 5DN group, but the RD was not statistically significant (Table 2). Also, the modified intention-to-treat analysis

and the severe failure end point did not yield a statistically significant RD between treatment groups.

Subgroup analysis

Independent of treatment duration, patients with an HbA1c > 53 mmol/mL had an increased failure rate compared with those with HbA1C < 53 mmol/mL and patients >65 years of age had

Table 3
Subgroup analyses for overall failure within 28 days after prescription[a]

Subgroup	5DN	Failure rate, n (%)	7DN	Failure rate, n (%)	Crude RD (95% CI)	IPW RD (95% CI)	IV RD (95% CI)
HbA1c > 53 mmol/mL	374	49 (14.1%)	589	84 (14.3%)	−0.1 (−4.8 to 4.5)	−1.8 (−6.8 to 3.4)	0.7 (−7.9 to 9.4)
HbA1c < 53 mmol/mL	356	46 (12.9%)	491	63 (12.8%)	0.1 (−4.5 to 4.7)	1.1– 4.2 to 6.4)	−4.4 (−13.4 to 4.6)
Patients >65 years	1908	276 (14.5%)	2310	305 (13.2%)	1.3 (−0.8 to 3.5)	1.5 (−1.4 to 4.4)	0.0 (−4.5 to 4.4)
Patients <65 years	1339	140 (10.5%)	1309	121 (9.2%)	1.2 (−1.1 to 3.5)	1.5 (−1.4 to 4.3)	3.8 (−2.7 to 10.2)
Insulin-using patients	760	106 (13.9%)	1162	174 (15.0%)	−1.0 (−4.0 to 2.0)	−0.7 (−4.5 to 3.1)	−2.3 (−8.7 to 4.2)
Non-insulin-using patients	2487	411 (16.5%)	2457	346 (14.1%)	1.8– 0.1 to 3.6)	2.4 (0.0–4.8)	2.3 (−2.2 to 6.8)

Abbreviations: 5DN, 5 days of nitrofurantoin; 7DN, 7 days of nitrofurantoin; HbA1c, haemoglobin A1c; IPW, inverse propensity weighting; IV, instrumental variable; RD, risk difference.
[a] An RD > 0 is in favour of 7 days of nitrofurantoin treatment.

an increased failure rate compared with those who were younger (Table 3). However, the adjusted RD of 5DN compared with 7DN was not statistically significant for subgroups based on HbA1c > 53 mmol/mL or <53 mmol/mL, age >65 or <65 years, or insulin use versus no insulin use (Table 3).

Discussion

Our study demonstrates that 5DN to treat UTI in women with DM does not lead to a significantly increased risk of treatment failure compared with the guideline-advised 7DN. This was found in both the IPW and the sensitivity analyses of the primary outcome as well as in the subgroups and secondary outcomes.

According to our main analysis, a risk difference of over 3.4% in favour of 7DN is unlikely. There is no consensus concerning a clinically relevant risk difference that would justify an additional 2 days of nitrofurantoin treatment. For example, if the true risk difference were 5%, we could prevent one antibiotic prescription for recurrent UTI by treating 20 patients for an extra 2 days (i.e. 40 treatment days to prevent one antibiotic prescription of 5–10 days). Hence we conclude that our study is sufficiently powered to exclude a clinically relevant risk difference.

The high percentage of GP practices that prescribed 5DN in women with DM was an unexpected finding and illustrates the need for studies on this subject. This is in contrast with earlier research showing that compliance with the UTI guideline had increased [12].

The crude failure rate of UTI treatment for patients with DM remains high. Earlier research has shown that antimicrobial resistance is not higher in patients with DM, so this is not likely to play a role. More treatment failure is probably a result of an impaired immune response, though studies have been contradictory on the subject [13,14]. Risk factors for recurrent UTI in women with diabetes are often related to worse glycaemic control and diabetic complications. However, we did not find that 7DN reduces treatment failure in patients with a high HbA1c. Similarly, stratifying for age >65 years or insulin use, neither resulted in a relevant difference between 5DN and 7DN outcomes.

Two observational studies have shown that the number of new UTI within 30 days was not affected by treatment duration, though they did not correct for common risk factors such as medication or glycaemic control [5,14]. To our knowledge, this study is the first to find a lack of effect of longer treatment for uncomplicated UTI in women with DM, while correcting for bias by using an IPW analysis.

Antimicrobial therapy duration should always be shortened if deemed safe. Although only 2% of patients discontinue the treatment because of adverse effects, 28%–49% of women experience common adverse effects during their treatment, like nausea and headaches [8,15]. We presume that a shorter treatment duration could also shorten the duration of adverse effects, although there is no literature to support this. Second, longer treatments decrease

cost-effectiveness and therapeutic compliance [16]. Third, although it is unproven that a reduction of 2 days would cause less selective pressure on the microbiome and reduce antimicrobial resistance, nitrofurantoin prescription independent of the dosage has been associated with antibiotic-resistant infections, and shorter duration, if safe, is generally recommended to reduce antibiotic resistance development [17–19].

There are several limitations to the study. First, as we do not have information on severity of the complaints, residual confounding by indication is still a possibility. Non-adherence to the UTI guidelines by Dutch GPs could be associated with non-adherence to guidelines in general, such as lifestyle advice preventing UTI, and might result in a higher rate of recurrence.

Second, our outcomes were based on retrospective prescription data and lack data on microbiology cultures, which can lead to misclassification. However, GP included in this database spend extra care in providing correct information and the database has been studied before and appears to provide reliable data [20].

Third, the end point of clinical failure was based on a new prescription for UTI. Failures could have been missed because of out-of-office prescriptions or patients admitted to hospital. This group is expected to be small and unlikely to differ in size in both groups.

Based on this study and possible persistent residual confounding, we think a clinical trial on this topic is needed. Although outside our study domain, it could also be interesting to study different antimicrobial options, because treatment failure in women with DM is still far higher than in healthy women (15.9% versus 4.1%) [21].

In conclusion, there was no significant difference in treatment failure between 5DN and 7DN for uncomplicated UTI in patients with DM after 28 days, because we do not think a difference of a few per cent to be clinically relevant. Furthermore, switching standard therapy to 5DN could reduce the number of antibiotic days in patients with DM.

Transparency declaration

The authors have stated that there are no conflicts of interest to declare.

Author contributions

TtD and FW conceived the study; TtD, FW, KDH-S and CHW performed the methodology, including software, analysis and data curation; KDH-S and FW wrote the orginal draft and all authors contributed to reviewing and editing the article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2021.06.034.

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