

## Treatment of urinary tract infections with Canephron® in Germany: a retrospective database analysis

*Running title:* Canephron® and urinary tract infections

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### Abstract

*Objective:* The goal of the present study was to evaluate the treatment with Canephron® after the diagnosis of acute cystitis or urinary tract infection (UTI) with regards to the risk of a sporadic recurrent UTI, frequent recurrent UTIs, UTI associated sick leave, additional antibiotic prescriptions, and renal complications (pyelonephritis) compared to standard antibiotic treatment.

*Methods:* This retrospective cohort study was based on data from the IMS® Disease Analyzer database (IQVIA), and included outpatients in Germany with at least one diagnosis of acute cystitis or UTI with a prescription of either Canephron® or standard antibiotics between January 2016 and June 2019 in general practitioner (GP), gynecologist, or urologist practices from which data were obtained. Multivariable

regression models were used to investigate the association between Canephron® prescription and the amount of sporadic or frequent recurrent UTIs, as well as the duration of UTI associated sick leave, amount of additional antibiotic prescriptions, and cases of pyelonephritis. The effects of Canephron® were adjusted for age, sex, insurance status, and Charlson Comorbidity Score (CCI).

*Results:* 2,320 Canephron® patients and 158,592 antibiotic patients were available for analysis. Compared to antibiotic prescription, Canephron® prescription was significantly associated with less sporadic recurrences of UTI infections 30-365 days after the index date (odds ratio [OR]: 0.66; 95% confidence interval [CI]: 0.58–0.72), as well as with less frequent recurrences of UTI infections (OR: 0.61; 95% CI: 0.49–0.88), and with minor additional antibiotic prescription within 31-365 days (OR: 0.57; 95% CI: 0.52-0.63). No significant differences were observed between the Canephron® and antibiotic cohorts with regard to the likelihood of sick leave (OR: 0.99; 95% CI: 0.86–1.14), new antibiotic prescription within 1-30 days (OR: 1.01; 95% CI: 0.87-1.16) and occurrences of pyelonephritis (Hazard Ratio (HR): 1.00; 95% CI: 0.67-1.48).

*Conclusion:* These real world data show that Canephron® is an effective and safe symptomatic treatment for acute cystitis or UTI. It should be considered as an alternative treatment in particular also to strengthen antimicrobial stewardship strategies.

**Keywords:** Canephron, antibiotic, urinary tract infections, cohort study, herbal treatment

## Introduction

Worldwide, urinary tract infections (UTI) affect about 150 million people per year (Flores-Mireles et al., 2015) and are among the leading causes for treatment in adult primary care medicine (Schmiemann et al., 2010). According to Foxman, almost half of all women will experience one cystitis episode in their life and about one third of women will have experienced a cystitis episode by the age of 24 (Foxman 2002). Most UTIs are acute uncomplicated cystitis (Colgan & Williams, 2011) and current guidelines recommend antibiotics as first-line therapy (Bonkat et al., 2020; Kranz et al., 2018).

As response to the dramatic development of resistant bacteria, antibiotic stewardship calls for cautious use of antibiotics, if necessary, and for avoiding antibiotics when possible. In most cases of uncomplicated infections, the body's immune system is able to deal with pathogenic bacteria and thus, antibiotics are not necessarily indicated (Christiaens et al., 2002). Accordingly, the "EU guideline for the prudent use of antimicrobials in human health" (2017) generally recommend for prescribers to avoid antibacterial treatment when there is only evidence of viral infection or of a self-limiting bacterial infection. Based on this need to avoid antibiotics where possible non-antibiotic, symptomatic treatment have become an important treatment option for patients with uncomplicated UTI. So far, studies compared the efficacy of non-steroidal anti-inflammatory drugs (NSAIDs), e.g. ibuprofen (Gagyor et al., 2015; Bleidorn et al., 2016) or diclofenac (Kronenberg et al., 2017), with antibiotics. As these trials indicated sufficient efficacy, several guidelines nowadays recommend non-antibiotic treatment as well. According to the current EAU (European Association of Urology) guidelines (2020) as well as the German AWMF interdisciplinary S3 guideline (Kranz et al., 2018) antibiotics are still considered the first line treatment option for UTI but non-antibiotic, symptomatic treatment should be considered in cases of acute uncomplicated cystitis with mild or moderate symptoms. The administration of herbal preparations is also an appropriate non-antibiotic, approach for UTI treatment (Stange et al., 2017, Wawrysiuk et al., 2019). One of these products approved in 31 countries is Canephron<sup>®</sup>, which contains centaury herbs (*Centaurii herba*), lovage roots (*Levistici radix*) and rosemary leaves (*Rosmarini folium*) (Naber, 2013). Canephron<sup>®</sup> shows so-called "multi-target" properties including spasmolytic (Brenneis et al., 2012), diuretic (Haloui et al., 2000),

anti-oxidative (Nausch et al., 2015), anti-adhesive effects (Künstle et al., 2013), anti-inflammatory and anti-nociceptive (Nausch et al., 2019).

The effectiveness of Canephron® has been demonstrated by a number of clinical studies (Naber 2013, Davidov & Bunova, 2018, Davidov et al., 2019, Wagenlehner et al., 2018, Ivanov et al., 2015).

Recently Wagenlehner et al. (2018) showed in a randomized, double-blind, phase III trial, that the treatment of acute lower uUTIs in women with Canephron® was non-inferior to therapy with the antibiotic fosfomycin trometamol in terms of prevention of additional intake of antibiotics for the treatment in this indication.

According to Haynes (1999) the benefit risk assessment of medicinal products should not only be done under study conditions (“can it work?”) but should also be proven under real world conditions (“does it work?”, is it worth it?). Due to that the goal of the present study was to prove based on real world data the effectiveness of Canephron® monotherapy as symptomatic treatment for UTI under usual circumstances of healthcare practice and to confirm thereby clinical data from previous conducted interventional studies. Therefore, we evaluated the extent of Canephron® prescriptions (either Canephron® N or Canephron® UNO) as treatment after the diagnosis of acute cystitis or UTI and the need of additional antibiotic prescriptions compared to standard therapy with antibiotics. As the risk for recurrences, complications as well as the duration of the disease is a common reason for prescribing antibiotics, we also examined the effect of the Canephron® monotherapy on sporadic and frequent recurrent UTIs, pyelonephritis and the duration of UTI associated sick leave.

## **Materials and Methods**

### *Data source*

This analysis was based on data from the IMS® Disease Analyzer database, which contains case-based information provided by office-based physicians (both general practitioners (GPs) and specialists) in Germany. Information is available on patient demographics, drug prescriptions, concomitant medication, comorbid conditions, sick leave, and referrals to hospitals. Our data analyses only considered data from those sites that have continuously delivered data to the IMS®DA panel in the past. IMS®DA

contains data from more than 10 million patients, captured between 2015 and 2019. Information is provided by nearly 3,000 office-based physicians, representing approximately 3% of all German practices. The sample of practices included is geographically representative for Germany, covering eight major German regions. In Germany, the sampling methods used for the selection of physicians' practices are appropriate for obtaining a representative database of general and specialized practices (Rathmann et al., 2018).

German law allows the use of anonymous electronic medical records for research purposes under certain conditions. According to this legislation, it is not necessary to obtain informed consent from patients or approval from an institutional review board (IRB) for this type of observational study that contains no directly identifiable data. Because patients were only queried as aggregates and no protected health information was available for queries, no IRB approval was required for the use of this database or the completion of this study.

#### *Study population and covariables*

This retrospective cohort study includes patients with at least one diagnosis of acute cystitis (ICD-10: N30.0) or UTI (ICD-10: N39.0) between January 01, 2016 and June 30, 2019 in one of the GP, gynecologist, or urologist practices from which data were obtained. The first diagnosis documented during this period was considered the index date. Further inclusion criteria included at least 12 months of observation prior to this diagnosis, which was verified by the documentation of at least one visit to the physician in the period  $\geq 365$  days prior to the index date, and a prescription of either Canephron<sup>®</sup> N or Canephron<sup>®</sup> UNO or a standard antibiotic (ATC: J01) on the index date. Patients with an antibiotic prescription within 30 days prior to the index date, prescriptions of other herbal medications during the study period, and prescription of both Canephron<sup>®</sup> and any antibiotic drug together on the index date were excluded. Patients were categorized into one of two cohorts: the Canephron<sup>®</sup> cohort and antibiotic cohort; both cohorts were then compared with each other.

The covariables used in this study included age, sex, health insurance coverage (private or statutory), physician specialty (GP, gynecologist, urologist), and Charlson Comorbidity Index (CCI). The CCI is a method for categorizing patient comorbidities

based on the International Classification of Diseases (ICD) and contains 19 categories. The higher the score, the more likely the predicted outcome result in mortality or higher resource use (Quan et al., 2005).

### *Statistical analyses*

The differences in proportions of patients (1) with a sporadic UTI recurrence defined as at least one renewed confirmed diagnosis of UTI (ICD-10: N39.0) or acute cystitis (ICD-10: N30.0) within 30-365 days after initial diagnosis, (2) with frequent recurrent UTIs defined as at least three diagnoses of urinary tract infections 2 - 365 days after initial diagnosis or at least two diagnoses of urinary tract infection 2 - 184 days after initial diagnosis, (3) with UTI associated sick leave defined as documented sick leave within one month following the diagnosis of a UTI, (4) with at least one antibiotic prescription 1-30 days after diagnosis or later (30-365 days), and (5) with an initial documentation of pyelonephritis (ICD-10: N10-12) within up to 3 years following the diagnosis of UTI, were estimated.

Multivariable logistic regression models were used to investigate the association between Canephron<sup>®</sup> prescription and a lower risk of either sporadic UTI recurrence, frequent recurrent UTIs, UTI associated sick leave, and antibiotic prescriptions. The effects of Canephron<sup>®</sup> were adjusted for age, sex, insurance status, and CCI. Multivariable regression models were also performed separately for men and women and for three age groups ( $\leq 40$ , 41-60,  $> 60$  years). A p-value of  $< 0.05$  was considered statistically significant.

The Kaplan-Meier method was used to estimate the differences between the Canephron<sup>®</sup> cohort and the antibiotic cohort in the percentages of patients with an initial documentation of pyelonephritis within up to 3 years following the diagnosis of a UTI. Patients with documented diagnoses of pyelonephritis prior to the index date were excluded from this analysis. A multivariable Cox regression model was used to investigate the association between Canephron<sup>®</sup> prescription and the probability of pyelonephritis, adjusted for age, sex, insurance status, and CCI.

## **Results**

### *Patient selection and baseline characteristics of the study patients*

Of the 232,875 patients diagnosed with UTI (ICD-10: N39.0) or acute cystitis (ICD-10: N30.0) and having an observation time of at least 365 days prior to the index date, either Canephron<sup>®</sup> N or Canephron<sup>®</sup> UNO was prescribed to 3,343 (0.014%) and antibiotics to 160,082 (68.74%) on the day of diagnosis. After the exclusion of patients with a combination therapy of Canephron<sup>®</sup> and antibiotic and patients who received other phytopharmaceuticals as UTI therapy as well as exclusion of those taking other UTI drugs (e.g., mannose, methionine or arbutin containing drugs) in the Canephron<sup>®</sup> cohort, a total of 2,320 Canephron<sup>®</sup> patients and 158,592 antibiotic patients were available for analysis (Figure 1).

Of the 69,450 patients not included in the analysis as they had been prescribed neither Canephron<sup>®</sup> nor an antibiotic on the index date, 93% were not prescribed any medication for UTI or acute cystitis, with only 7% receiving any prescription (3% analgesic, 3% arbutin containing drugs and less than 1% other drugs).

A total of 4% of patients in the Canephron<sup>®</sup> study cohort were also prescribed an analgesic, while in the antibiotic cohort, ~3% received analgesics and just 1% received prescriptions for other drugs (e.g., mannose, methionine or arbutin containing drugs).

Table 1 shows the baseline characteristics of the study patients. Canephron<sup>®</sup> patients were significantly younger (51.3 (SD: 19.9) vs. 55.0 (SD: 20.8) years) and had a slightly lower comorbidity index (1.6 vs. 1.7) than patients that were prescribed antibiotics. The proportions of female patients (81.2 vs. 90.8%) was significantly lower, and the proportion of privately insured patients (11.3% vs. 7.6%) was significantly higher among patients receiving Canephron<sup>®</sup> than among the antibiotic cohort. The majority of patients in both cohorts were treated by GPs (90.0% vs. 80.7%). The differences in baseline characteristics indicated the need for age- and sex-stratified analyses.

### *Sporadic recurrent urinary tract infection*

At least one renewed confirmed diagnosis of UTI was documented within 30-365 days after the index date in 12.3% of patients with Canephron<sup>®</sup> prescription and 17.2% of patients with antibiotic prescription. Canephron<sup>®</sup> prescription was associated with significantly lower odds of at least one renewed confirmed diagnosis of UTI within 30-

365 days after the index date (odds ratio [OR]: 0.66; 95% confidence interval [CI]: 0.58–0.72;  $p < 0.001$ ). This association was observed in men and women, and also in different age groups (Figure 2).

#### *Frequent recurrent urinary tract infections*

At least three diagnoses of UTI 2 - 365 days after initial diagnosis or at least two diagnoses of UTI 2 - 184 days after initial diagnosis were documented in 3.1% of patients with Canephron® prescription and 5.0% of patients with antibiotic prescription. Canephron® prescription was associated with significantly lower odds of frequent recurrent UTIs (OR: 0.61; 95% CI: 0.49–0.88;  $p < 0.001$ ). This association was observed significantly or tendentially in men and women, and occurred in all age groups (Figure 3).

#### *Sick leave associated with a urinary tract infection*

In total, 16.9% of patients with Canephron® prescription and 18.2% of patients with antibiotic prescription took at least 3 days of sick leave due to UTI. There was no significant association between Canephron® prescription and the odds of taking sick leave (OR: 0.99; 95% CI: 0.86–1.14;  $p = 0.931$ ), nor was any such association observed in the subgroups analyzed (Figure 4). As a sensitivity analysis, the association between Canephron® prescription and the probability of sick leave of at least 7, 10, or 14 days was analyzed. No significant associations were observed in the multivariable regression models, and no differences were found between Canephron® and antibiotic cohort (OR: 1.01 (95%CI: 0.85-1.19;  $p = 0.949$ ) for  $\geq 7$  days: OR: 1.04 (95% CI: 0.86-1.25;  $p = 0.703$ ) for  $\geq 10$  days, OR: 1.06 (95% CI: 0.86-1.31;  $p = 0.584$ ) for  $\geq 14$  days.

#### *Additional antibiotic prescriptions after the index date*

At least one new (further) antibiotic prescription was issued 31-365 days after the index date for 23.4% of patients with Canephron® prescription and 32.8% of patients with antibiotic prescription. Canephron® prescription was associated with significantly lower odds of antibiotic prescription 31-365 days after the index date (OR: 0.57; 95% CI: 0.52-0.63;  $p < 0.001$ ). This association was observed in all subgroups investigated

(Figure 5). There was, however, no association between Canephron® prescription and antibiotic prescription 1-30 days after the index date (OR: 1.01; 95% CI: 0.87-1.16;  $p=0.921$ ).

### *Incidence of pyelonephritis*

Pyelonephritis occurred relatively rarely up to 3 years after the index date. Pyelonephritis was initially documented in 1.6% of Canephron® patients and 1.5% of antibiotic patients, and no significant association was observed in the multivariable Cox regression analysis (Hazard Ratio (HR): 1.00; 95% CI: 0.67-1.48;  $p=0.954$ ).

## **Discussion**

To the best of our knowledge, this is the first non-interventional real-world study in Germany proving that Canephron® monotherapy does work as a symptomatic treatment for UTI. The data support the important role Canephron® plays in reducing antibiotic use and antibiotic resistance.

The presented results are not surprising, since Canephron® is a well-studied approved medicinal product. Wagenlehner et al. (2018) performed a Phase III, non-inferiority trial including 659 women and found a non-inferior difference between patients treated with Canephron® N and those receiving antibiotics with regard to the proportion of women requiring additional antibiotics. In the present study, the additional antibiotic prescription was analyzed for two periods (1-30 and 31-365 days after UTI diagnosis). There was no significant difference between Canephron® and antibiotic therapy in the period of 1-30 days. This result confirms the outcome of the clinical trial of Wagenlehner et al. (2018) in a real world setting. For the time 31-365 days the use of additional antibiotic prescriptions was significantly lower after Canephron® as compared to antibiotic therapy.

A further clinical trial conducted by Davidov & Bunova (2018) compared the efficacy and safety of monotherapy with Canephron® N and antibiotic therapy with Ciprofloxacin in the treatment of mild acute cystitis in 160 women. After 6 days of treatment clinical symptoms completely disappeared in 66 (82.5%) patients of the Canephron® N group and in 68 (85.0%) patients in the antibiotic group. A relapse of cystitis within one year

was observed in 5% of Canephron® N patients and 12.5% of antibiotic patients (Davidov & Bunova 2018). Interestingly, RWD show, that Canephron® was not only associated with a significantly lower risk of sporadic UTI recurrence but even with a significantly lower risk of frequent recurrent UTIs in all patients.

Canephron® is not only effective in the treatment of UTI, but it is also well tolerated (Ivanov et al., 2015). Unlike antibiotics, this herbal medicinal product does not affect the gut microbiota compared to fosfomycin or nitrofurantoin (Naber et al., 2017). This effect is particularly notable as research into the urinary microbiome showed that asymptomatic bacteriuria appears to have a protective effect on UTIs (Cai et al., 2016) and might be considered as a preventive treatment strategy in recurrent infections (Wullt et al., 2016). The results presented confirm this conclusion as antibiotic therapy was associated with a significantly higher likelihood of further antibiotic prescriptions in the period of 31-365 days.

Within the last years several non-antibiotic treatment options such as non-steroidal anti-inflammatory drugs (NSAIDs) (Gagyor et al., 2015; Bleidorn et al., 2016; Kronenberg et al., 2017) or as well as further herbal substances like Angocin® (Stange et al., 2017) have been investigated in order to reduce the number of antibiotic prescriptions. The present retrospective study showed that there is an acceptance for non-antibiotic treatment options, as in clinical practice almost one third of the patients (31.3%) received no antibiotic therapy. Over 2,320 of these cases were treated with a Canephron® monotherapy. GPs have prescribed Canephron® more often than gynecologists or urologists reflecting that patients in Germany suffering from a uUTI go first to a GP.

Pyelonephritis can occur as complication in 0.3 – 0.5 % of the lower urinary tract infections (Gagyor et al., 2015; Kronenberg et al., 2017). Although higher rates of pyelonephritis have been reported for alternative treatment options than for antibiotics (Gagyor et al., 2015; Kronenberg et al., 2017; Wagenlehner et al., 2018), a retrospective long-term follow-up analysis showed that non-antibiotic treatment has no negative impact on pyelonephritis (Bleidorn et al., 2016). In the present study, there was also no significant association between Canephron® and the incidence of pyelonephritis. In addition, the duration of UTI associated sick leave under Canephron® therapy was as long as under antibiotic treatment.

The strengths of this study include the large dataset (over 2,300 patients receiving Canephron® and more than 158,000 antibiotic patients), which includes both female and male patients as well as different age groups and physician specialties. Furthermore, our study used the German IMS®DA database whose reliability has been validated in several medical studies and consequently supports the reliability of our findings (Rathmann et al., 2018; Martin et al., 2020).

The IMS®DA database used exhibits specific characteristics which have to be considered. First, assessments rely on ICD codes entered by GPs, urologists, or gynecologists. These codes are checked and validated by the owner of IMS®DA (IQVIA). Nevertheless ICD codes allow no differentiation between complicated and uncomplicated diagnoses. Second, the number of patients treated with Canephron® was markedly lower as compared to the number of patients treated with antibiotics. The lower number of prescriptions for the herbal medicinal product may be due to the regulatory status in Germany, which is over the counter (OTC), whereas antibiotics are Rx. The database does not include data on the use of herbal medicines that patients buy without prescriptions. The same applies to NSAIDs. In addition, no data were available on socioeconomic status and lifestyle-related risk factors (smoking, alcohol, physical activity). Moreover, patients can only be observed in a single practice; if they receive a diagnosis or prescription from another physician, such prescriptions are not documented.

To reduce a potential bias, regression models were fitted separately for three age groups, for men and for women in addition to the adjustment include in the regression models.

In conclusion, this study revealed that Canephron® is already used as monotherapy for treating UTI in a real-world setting. Moreover, despite limitations due to the database used the results demonstrate that symptomatic treatment with Canephron® as monotherapy is successful and safe. The rates of sporadic and frequent UTI recurrences were even significantly lower with Canephron® as compared with antibiotic. Therefore, symptomatic treatment of uncomplicated lower UTI with Canephron®, an herbal medicinal product, is recommended to reduce prescriptions of antibiotics in this indication.

## **Conclusion**

These real world data show that Canephron® is an effective and safe symptomatic treatment for acute cystitis or UTI. Long-term additional antibiotic prescriptions and UTI recurrences after Canephron® therapy were even significantly lower than after antibiotic therapy. Therefore, Canephron® should be considered as an alternative treatment in particular also to strengthen antimicrobial stewardship strategies.

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## **Author Contributions**

Karel Kostev contributed to the design of the study, performed the statistical analyses, managed the literature searches, wrote the first draft of the manuscript, and corrected the manuscript. Martina Höller, Hubert Steindl, Dimitri Abramov-Sommariva, Florian Wagenlehner, Kurt G. Naber contributed to the design of the study, managed the literature searches and corrected the manuscript. All authors contributed to and have approved the final manuscript.

## **Conflict of Interest**

Martina Höller, Hubert Steindl, Dimitri Abramov-Sommariva are employees of Bionorica SE; Karel Kostev is an employee of IQVIA without other conflicts of interests. Kurt G. Naber reports personal fees from Bionorica, as well as personal fees from Adamed, personal fees from Allecra, personal fees from Apogepha, personal fees from Enteris Biopharma, personal fees from Galenus, personal fees from GlaxoSmithKline, personal fees from Hermes, personal fees from Leo, personal fees from Medice, personal fees from MerLion, personal fees from MSD SHARP& DOHME, personal fees from Paratek, personal fees from Roche, personal fees from Rosen, personal fees from Saxonia, personal fees from Vifor, outside the submitted work. FW reports personal fees from Bionorica, as well as personal fees and other from Achaogen, personal fees from AstraZeneca, other from Enteris BioPharma, other from Helperby Therapeutics Ltd., personal fees from Janssen, personal fees from LeoPharma, personal fees from MerLion, personal fees from MSD, personal fees from OM Pharma/Vifor Pharma, personal fees from Pfizer, personal fees from RosenPharma, personal fees and other from Shionogi, personal fees from VenatoRx, personal fees from GSK, outside the submitted work.

## **Ethics Statements**

German law allows the use of anonymous electronic medical records for research purposes under certain conditions. According to this legislation, it is not necessary to obtain informed consent from patients or approval from an institutional review board (IRB) for this type of observational study that contains no directly identifiable data. Because patients were only queried as aggregates and no protected health information was available for queries, no IRB approval was required for the use of this database or the completion of this study.

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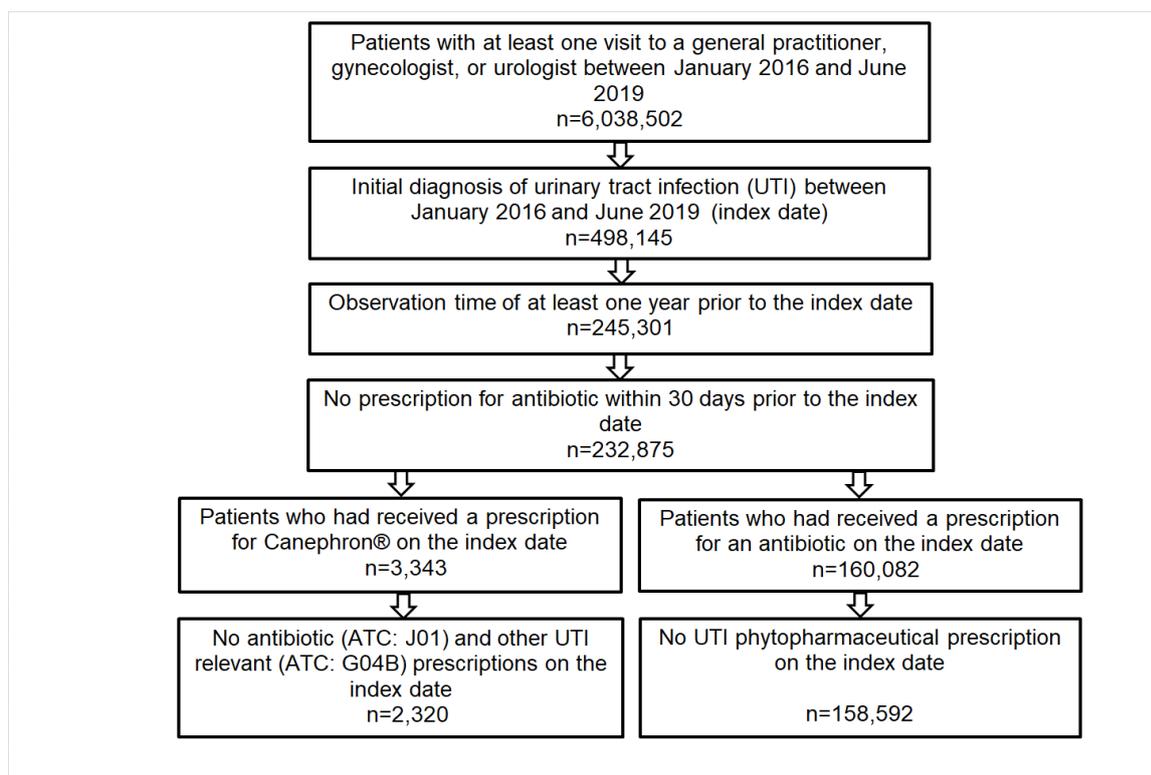
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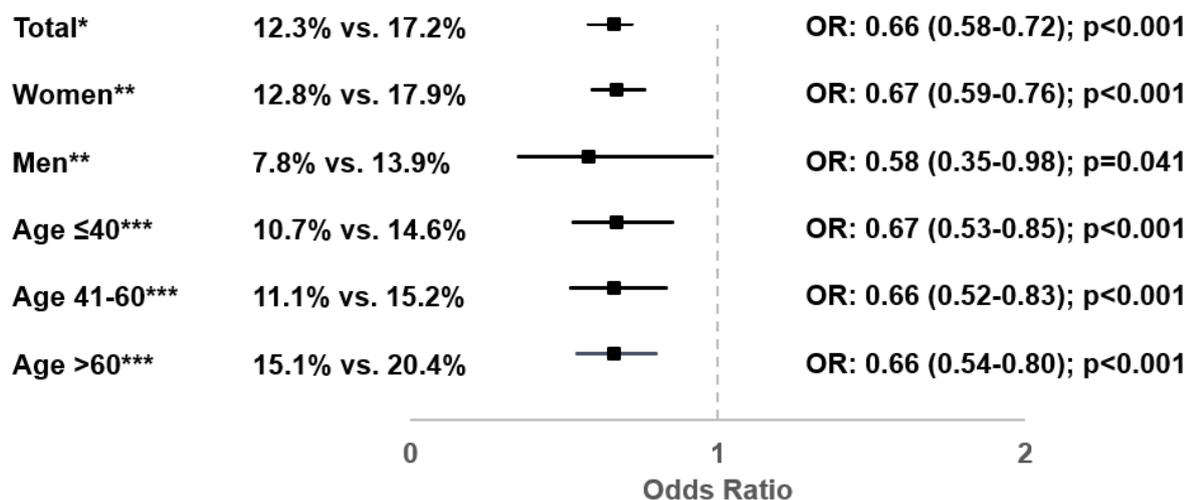
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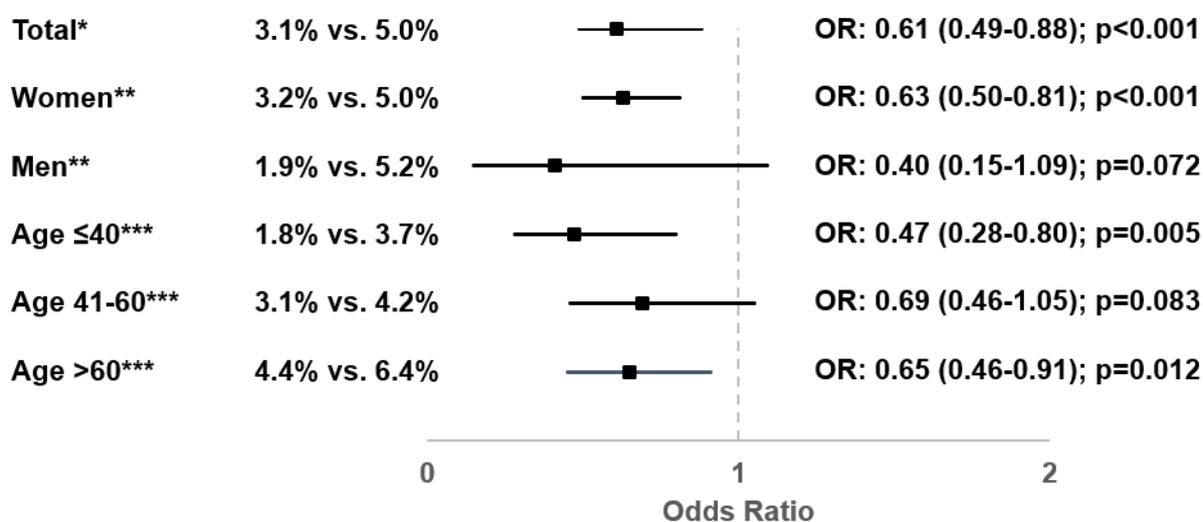
**Figure 1.** Selection of study patients

**Figure 2.** Association between Canephron® prescription and renewed sporadic confirmed diagnosis of UTI within 30-365 days after the index date [Canephron® versus antibiotic]



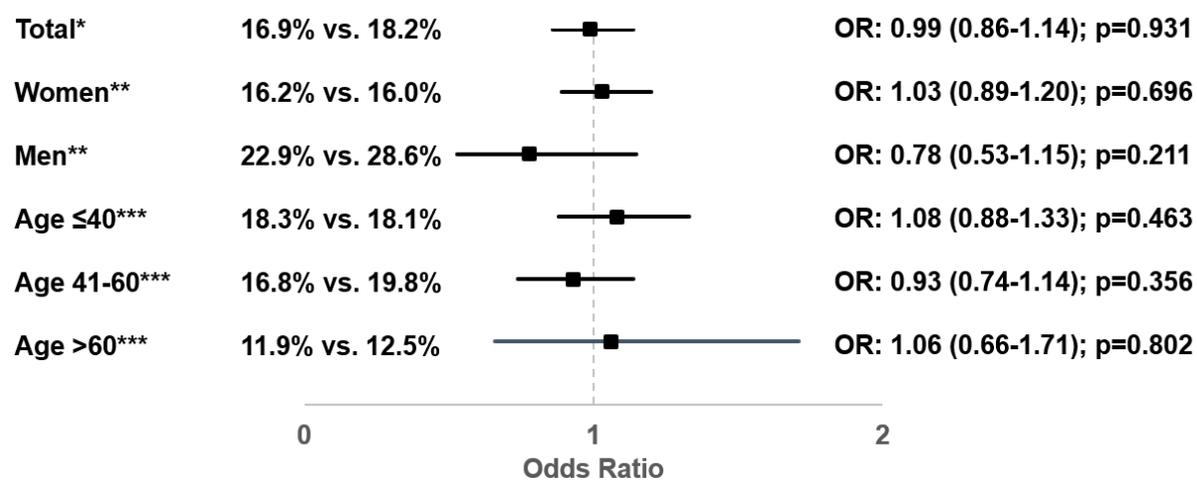
\*Multivariable logistic regression adjusted for age, sex, health insurance coverage, practice specialty, CCI \*\* Multivariable logistic regression adjusted for age, health insurance coverage, practice specialty, and CCI \*\*\* Multivariable logistic regression adjusted for sex, health insurance coverage, practice specialty, and CCI

**Figure 3.** Association between Canephron® prescription and probability of frequent recurrent UTIs [Canephron® versus antibiotic]



\*Multivariable logistic regression adjusted for age, sex, health insurance coverage, practice specialty, CCI \*\* Multivariable logistic regression adjusted for age, health insurance coverage, practice specialty, and CCI \*\*\* Multivariable logistic regression adjusted for sex, health insurance coverage, practice specialty, and CCI

**Figure 4.** Association between Canephron® prescription and probability of sick leave of at least 3 days [Canephron® versus antibiotic]



\* Multivariable logistic regression adjusted for age, sex, health insurance coverage, practice specialty, CCI  
 \*\* Multivariable logistic regression adjusted for age, health insurance coverage, practice specialty, and CCI  
 \*\*\* Multivariable logistic regression adjusted for sex, health insurance coverage, practice specialty, and CCI



**Table 1.** Basic characteristics of study patients

Variable	Patients with Canephron® prescription	Patients with antibiotic prescription	P-value
N	2,320	158,592	
Age (mean, SD)	51.3 (19.9)	55.0 (20.8)	<0.001
≤40 years (%)	33.2	29.5	<0.001
41-60 years (%)	32.3	28.6	
>60 years (%)	34.5	41.9	
Sex: female (%)	81.2	90.8	<0.001
CCI (mean, SD)	1.6 (2.3)	1.7 (2.4)	0.019
Private health insurance coverage (%)	11.3	7.6	<0.001
Therapy by general practitioners	90.0	80.7	<0.001
Therapy by gynecologists	7.1	14.1	
Therapy by urologists	2.9	5.2	