Supplementary Online Content

Muanda FT, Sood MM, Weir MA, et al. Association of higher-dose fluoroquinolone therapy with serious adverse events in older adults with advanced chronic kidney disease. JAMA Netw Open. 2022;5(8):e2224892. doi:10.1001/jamanetworkopen.2022.24892

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This supplementary material has been provided by the authors to give readers additional information about their work.
### eTable 1. Recommended Dose of Oral Ciprofloxacin, Levofloxacin, and Norfloxacin Based on a Patient’s Kidney Function: Guidelines From UpToDate and the Product Monograph

### eTable 1a. Recommended dose of oral ciprofloxacin

| UpToDate Guidelines | Product Monograph |
|---------------------|-------------------|
| Creatinine clearance >50 to <130 mL/min | Creatinine clearance >50 to <130 mL/min |
| Oral Immediate Release: 500-750 mg every 12h Oral Extended Release: 1g every 24h | NA |
| Creatinine clearance 30 to 50 mL/min | Creatinine clearance 31 to 60 mL/min/1.73 m² |
| Oral Immediate Release: 250-500 mg every 12h Oral Extended Release: 1g every 24h | Maximum daily oral dose: 1000 mg |
| Creatinine clearance <30 mL/min | Creatinine clearance ≤30 mL/min/1.73 m² |
| Oral Dose: 500mg every 24hrs Oral Extended Release: 500 mg every 24h | Maximum daily oral dose: 500 mg |

Abbreviations: NA, not available.
### eTable 1b. Recommended dose of oral levofloxacin

| Creatinine clearance ≥ 50 mL/min | Creatinine clearance 50 to 80 mL/min |
|----------------------------------|-------------------------------------|
| No dosage adjustment required.    | No dosage adjustment required.      |

| Creatinine clearance 20 to <50 mL/min | Creatinine clearance 20 to 49 mL/min |
|---------------------------------------|-------------------------------------|
| If recommended dose is 250 mg every 24h: no dosage adjustment is required. | Initial dose: 500 mg, subsequent dose: 250 mg every 24h (acute sinusitis, acute bacterial exacerbation of chronic bronchitis, community-acquired pneumonia, uncomplicated skin and skin structure infections, chronic bacterial prostatitis). |
| If recommended dose is 500 mg every 24h: 500mg initial dose, then 250 mg every 24hrs. | Initial dose: 750 mg, subsequent dose 750mg every 48h (complicated skin and skin structure infections/nosocomial pneumonia/community acquired pneumonia/acute bacterial exacerbation of chronic bronchitis/acute sinusitis/complicated urinary tract infection/acute pyelonephritis). |
| If recommended dose is 750 mg every 24h: 750 mg every 48hr. | Initial dose: 750 mg, subsequent dose 750 mg every 48h (complicated skin and skin structure infections/nosocomial pneumonia/community acquired pneumonia/acute bacterial exacerbation of chronic bronchitis/acute sinusitis/complicated urinary tract infection/acute pyelonephritis). |

| Creatinine clearance <20mL/min | Creatinine clearance 10 to 19 mL/min |
|--------------------------------|-------------------------------------|
| If recommended dose is 250 mg every 24h: 250 mg every 48h (except for uncomplicated urinary tract infection, where no dosage adjustment necessary). | Initial dose: 500 mg, subsequent dose 250 mg every 48h (acute sinusitis, acute bacterial exacerbation of chronic bronchitis, community-acquired pneumonia, uncomplicated skin structure infections/nosocomial pneumonia, chronic bacterial prostatitis) |
| If recommended dose 500 mg every 24h: 500 mg initial dose, then 250mg every 48 h. | Initial dose: 250 mg, subsequent dose 250 mg every 48h (complicated urinary tract infection/acute pyelonephritis). |
| If recommended dose is 750 mg every 24h: 750 mg initial dose, then 500mg every 48h. | Initial dose: 750 mg, subsequent dose 500 mg every 48h (complicated skin structure infections/nosocomial pneumonia/nosocomial pneumonia/community acquired pneumonia/acute bacterial exacerbation of chronic bronchitis/acute sinusitis/complicated urinary tract infection/acute pyelonephritis). |
## eTable 1c. Recommended dose of oral norfloxacin

| UpToDate Guidelines<sup>5</sup> | Product Monograph<sup>6</sup> |
|---------------------------------|-------------------------------|
| **Creatinine clearance >30 mL/min/1.73m²** | **Creatinine clearance >30 mL/min/1.73m²** |
| No dose adjustment required: 400 mg twice daily | No dose adjustment required: 400 mg twice daily |
| **Creatinine clearance rate ≤30 mL/min/1.73m²** | **Glomerular filtration rate <30 mL/min/1.73 m²** |
| Recommended dose: 400 mg every 24h | Recommended dose: 400 mg every 24h |
**eTable 2. Literature Search**

**eTable 2a. A literature search in Medline (1946 to May 11, 2021)**

|   |   |
|---|---|
| 1 | exp Ciprofloxacin/ad, ae, pk, po, to [Administration & Dosage, Adverse Effects, Pharmacokinetics, Poisoning, Therapeutic Use, Toxicity] |
| 2 | ciprofloxacin*.ti,ab,kw. |
| 3 | ciprofloxacin*.tw. /freq=2 |
| 4 | exp Norfloxacin/ad, ae, pk, tu, to [Administration & Dosage, Adverse Effects, Pharmacokinetics, Therapeutic Use, Toxicity] |
| 5 | norfloxacin*.ti,ab,kw. |
| 6 | norfloxacin*.tw. /freq=2 |
| 7 | exp Levofoxacin/ad, ae, pk, tu, to [Administration & Dosage, Adverse Effects, Pharmacokinetics, Therapeutic Use, Toxicity] |
| 8 | levofloxacin*.ti,ab,kw. |
| 9 | levofloxacin*.tw. /freq=2 |
| 10 | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 |
| 11 | (((chronic$ or progressive or diabetic) adj (kidney or renal or nephro$ or glomerul$)) or dialy$ or h?emodia$).mp. or ckd.tw. or esrd.tw. or ((diabet$mp. or Disease Progression/ or Recurrence/) and nephropath$.mp.) or ur?emi$.mp. or m?croalbuminuri$.mp. or albuminuri$.mp. or proteinuri$.mp. or nephrosclerosis.mp. or glomerulosclerosis.mp. or glomerular sclerosis.mp. or *Glomerular Filtration Rate/ or (secondary adj2 hyperparathyroidism).mp. or ((tubulointerstitial or interstitial or renal or kidney) adj fibrosis).tw. or hyperphosphat?emia.tw. or vascular calcification$.tw. or alport$.mp. or denys- drash.mp. or glomerulopathy.tw. or hypoalbumin?emi$.mp. or multicystic kidney$.mp. or polycystic kidney$.mp. or cystic kidney$.mp. or calciphylaxis.mp. or tenckhoff.tw. or ((kidney or renal) adj (disease$ or failure$ or function$ or insufficien$ or disorder$ or dysfunction or replacement)).mp. or ((kidney or renal) and (ckf or crd or crf or eskd or esfk or esrf or hyperparathyroidism or end-stage or endstage or eGFR)).mp. or (((kidney or renal) adj transplant$) and (candidates or wait$ list$)).tw. or ((sclerosi$ or fibrosi$ or fibrotic).mp. and ((ureteral obstruction or nephritis or glomerulonephritis or nephrop$).mp. or (obstruct$ and (kidney$ or renal or nephropathy)).tw.)) |
| 12 | exp Renal Insufficiency, Chronic/co, dt, pc, th [Complications, Drug Therapy, Prevention & Control, Therapy] |
| 13 | exp Renal Replacement Therapy/ |
| 14 | 11 or 12 or 13 |
| 15 | 10 and 14 |
| 16 | exp "drug-related side effects and adverse reactions"/ or adverse.ti,ab,kf. or side effect?.ti,ab,kf. or adverse effects.fs. or exp drug overdose/ or overdose*.ti,ab,kf. or exp drug misuse/ or misus*.ti,ab,kf. or exp substance-related disorders/ or abus*.ti,ab,kf. or exp pregnancy/ or pregnan*.ti,ab,kf. or exp pregnancy complications/ or exp lactation/ or exp lactation disorders/ or exp breast feeding/ or (exp milk, human/ and exp secretion/) or exp fertility/ or exp infertility/ or exp reproduction/ or exp fetus/ or exp embryonic structures/ or terat*.ti,ab,kf. or drug efficacy.ti,ab,kf. or therapeutic efficacy.ti,ab,kf. or drug withdrawal.ti,ab,kf. or exp medication errors/ or exp death/ or death*.ti,ab,kf. or fatal*.ti,ab,kf. or exp drug interactions/ or exp carcinogens/ or carcinogen*.ti,ab,kf. or mutagen*.ti,ab,kf. or exp "off-label use"/ or exp occupational exposure/ or toxicity.fs. or toxic*.ti,ab,kf. or pharmacotox*.ti,ab,kf. or neurotox*.ti,ab,kf. or cardiotox*.ti,ab,kf. or nephrotox*.ti,ab,kf. or immunotox*.ti,ab,kf. or hepatotox*.ti,ab,kf. or cytotox*.ti,ab,kf. or immunocytox*.ti,ab,kf. or intoxicat*.ti,ab,kf. or exp "congenital, hereditary, and neonatal diseases and abnormalities"/ or drug treatment failure.ti,ab,kf. or drug toxicity.ti,ab,kf. or exp case |
|   |   |   |
|---|---|---|
| 17 | 15 and 16 | limit 17 to (english language and humans) |

**eTable 2b. Literature search in Embase (1947 to May 12, 2021)**

1. exp ciprofloxacin/ae, ct, ad, cm, do, dt, to, pv, tm [Adverse Drug Reaction, Clinical Trial, Drug Administration, Drug Comparison, Drug Dose, Drug Therapy, Drug Toxicity, Special Situation for Pharmacovigilance, Unexpected Outcome of Drug Treatment]
2. ciprofloxacin*.ti,ab,kw.
3. ciprofloxacin*.tw. /freq=2
4. exp norfloxacin/ae, ct, ad, cm, do, dt, to, pv, tm [Adverse Drug Reaction, Clinical Trial, Drug Administration, Drug Comparison, Drug Dose, Drug Therapy, Drug Toxicity, Special Situation for Pharmacovigilance, Unexpected Outcome of Drug Treatment]
5. norfloxacin*.ti,ab,kw.
6. norfloxacin*.tw. /freq=2
7. exp levofloxacin/ae, ct, ad, cm, do, dt, to, pv, tm [Adverse Drug Reaction, Clinical Trial, Drug Administration, Drug Comparison, Drug Dose, Drug Therapy, Drug Toxicity, Special Situation for Pharmacovigilance, Unexpected Outcome of Drug Treatment]
8. levofloxacin*.ti,ab,kw.
9. levofloxacin*.tw. /freq=2
10. (((chronic$ or progressive or diabetic) adj (kidney or renal or nephro$ or glomerul$)) or dialy$ or h?emodia$).mp. or ckd.tw. or esrd.tw. or (diabet$.mp. or Disease Progression/ or Recurrence/) and nephropath$.mp.) or ur?emi$.mp. or m?croalbuminuri$.mp. or albuminuri$.mp. or proteinuri$.mp. or nephrosclerosis.mp. or glomerulosclerosis.mp. or glomerular sclerosis.mp. or *Glomerular Filtration Rate/ or (secondary adj2 hyperparathyroidism).mp. or (tubulointerstitial or interstitial or renal or kidney) adj fibrosis).tw. or hyperphosphat?emia.tw. or vascular calcification$.tw. or alport$.mp. or denys- drash.mp. or glomerulopathy.tw. or hypoalbumin?emia.mp. or multicystic kidney$.mp. or polycystic kidney$.mp. or cystic kidney$.mp. or calciphylaxis.mp. or tenckhoff.tw. or ((kidney or renal) adj (disease$ or failure$ or dysfunction or replacement)).mp. or (k?idney or renal) and (ckf or crd or crf or eskf or esrf or hyperparathyroidism or end-stage or endstage or eGFR)).mp. or (((kidney or renal) adj transplant$) and (candidates or wait$ list$)).tw. or ((sclerosis$ or fibrosis$ or fibrotic).mp. and (ureteral obstruction or nephritis or glomerulonephritis or nephrop$.mp. or (obstruct$ and (kidney$ or renal or nephropathy))).tw.)
11. exp kidney disease/co, dm, dt, si, th [Complication, Disease Management, Drug Therapy, Side Effect, Therapy]
12. exp renal replacement therapy/ae [Adverse Drug Reaction]
13. 10 or 11 or 12
14. exp adverse drug reaction/ or adverse.ti,ab,kw. or side effect?.ti,ab,kw. or side effect.fs. or exp drug overdose/ or overdos*.ti,ab,kw. or exp drug misuse/ or misus*.ti,ab,kw. or exp drug abuse/ or exp substance abuse/ or abus*.ti,ab,kw. or exp pregnancy/ or pregnan*.ti,ab,kw. or exp pregnancy complications/ or exp lactation/ or exp breast feeding/ or (exp milk human/ and exp secretion/) or exp fertility/ or exp infertility/ or exp reproduction/ or exp fetus/ or exp embryo/ or terat*.ti,ab,kw. or exp drug efficacy/ or exp drug withdrawal/ or exp medication error/ or exp medication error.
|   |   |
|---|---|
| 15 | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 |
| 16 | 13 and 14 and 15 |
| 17 | limit 16 to (human and english language) |
Table 3. Summary of Studies of Fluoroquinolone-Associated Adverse Events in Patients With Chronic Kidney Disease

**eTable 3a. Case Reports**

| Author/year of publication | Age/sex | FQ administered | FQ dose (mg/day) | Degree of CKD, eGFR, or CrCl ml/min/1.73m² | Type of toxicity | Days to toxicity onset | Treatment | Naranjo score |
|----------------------------|---------|-----------------|-----------------|-------------------------------------------|-----------------|-----------------------|-----------|--------------|
| Abdalla 2013<sup>7</sup>   | 72/male | Ciprofloxacin   | 1000            | on hemodialysis                            | choreoathetosis | 3 days                | D/C drug  | 5            |
| Stroud 2020<sup>8</sup>    | 56/female| Ciprofloxacin   | 500             | 11                                         | delirium and hypoglycemia | 1 day     | D/C drug and HD      | 3         |
| Schwalm 2003<sup>9</sup>   | 73/male | Levofloxacin    | 250             | on hemodialysis                            | acute hepatitis | 21 days               | D/C drug  | 7            |
| Abo-salem 2011<sup>10</sup>| 92/female| IV Levofloxacin | 750             | on hemodialysis                            | Tdp arrhythmia  | 4 hours               | D/C drug  | 7            |
| Kawtharani 2016<sup>11</sup>| 70/male | Ciprofloxacin   | 1000            | A case of MCD/SCr=1.3-1.6                  | tendinopathy    | 4 days                | not mentioned | 6            |
| Denysenko 2011<sup>12</sup>| 60/female| IV Ciprofloxacin| 400             | on hemodialysis                            | neurotoxicity and catatonia | 1 day     | D/C drug  | 2            |
| Martin 2020<sup>13</sup>   | 76/male | Ciprofloxacin   | 1500            | Stage 2 CKD                                | acute renal failure | 9 days | D/C drug and supportive care for AKI | 6 |
| Sadlacek 2006<sup>14</sup> | 90/female| Ciprofloxacin   | 1500            | Stage 3 CKD                                | acute renal failure secondary to ciprofloxacin-induced crystal nephropathy | 8 days | D/C drug  | 7            |
| Reece 1996<sup>15</sup>    | 41/male | Ciprofloxacin   | 1000            | SCr =1.8                                   | AIN             | 3 days                | D/C drug, prednisolone administration | 7 |
| Striano 2007<sup>16</sup>  | 63/male | IV Ciprofloxacin| 200             | SCr =4                                     | myoclonus       | 2 days                | D/C drug and lorazepam  | 7 |
| Matoi 2021<sup>17</sup>    | 73/male | IV Ciprofloxacin| 400             | on hemodialysis                            | fatal hypoglycemia | 7 days                | not mentioned | 5 |
| Marti 1998<sup>18</sup>    | 55/male | Ciprofloxacin   | 500             | 22                                         | tendinopathy    | 3 days                | not mentioned | 5 |

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| Author/year of publication | Age/sex  | FQ administered | FQ dose (mg/day) | Degree of CKD, eGFR, or CrCl ml/min/1.73m² | Type of toxicity | Days to toxicity onset⁶ | Treatment | Naranjo score⁷ |
|---------------------------|---------|----------------|-----------------|---------------------------------------------|-----------------|----------------------|-----------|----------------|
| Takeda 2012¹⁹            | 58/female | Ciprofloxacin  | 500             | 40                                           |                 | 5 days               |           | 5              |
|                           | 37/male | Ciprofloxacin  | 500             | on hemodialysis                              |                 | 60 days              |           | 5              |
|                           | 74/male | Levofloxacin   | 400             | on hemodialysis                              |                 | 8 days               | D/C drug  | 7              |
|                           | 62/male | Levofloxacin   | 500 mg initial, then 250mg every 48 hrs | on hemodialysis | tendinopathy     | 2 days               | D/C drug  | 7              |
|                           | 76/male | Levofloxacin   | 500 mg initial, then 250mg every 48 hrs | on hemodialysis |                 | 3 days               | D/C drug  | 7              |
|                           | 66/male | Levofloxacin   | 500 mg initial, then 250mg every 48 hrs | on hemodialysis |                 | 1 day                | D/C drug  | 7              |
| Idrees 2019²⁰            | 82/female | IV Levofloxacin | 750             | on hemodialysis                              | myoclonus       | 1 day                | D/C drug and HD | 4              |
| Gkoufa 2020²¹            | 84/male | Ciprofloxacin  | 1000            | 37                                           | Henoch-Schönlein purpura | 2 days | D/C drug, Hydration and daily methylprednisolone | 5              |
| Korzets 2006²²           | 68/male | Levofloxacin   | 250             | 30                                           | rhabdomyolysis  | 10 days              | D/C drug  | 7              |
| Kato 2011²³              | 63/female | Levofloxacin  | 500 mg every two days | 8                                             | tendinopathy    | 3 days               | D/C drug  | 7              |
| Nishikubo 2019²⁴         | 68/male | Levofloxacin   | 500             | SCr =2.5                                     | neurotoxicity   | 11 days              | D/C drug and HD | 7              |
| Patil 2020²⁵             | 58/female | Levofloxacin  | 750             | stage 5 CKD                                  | hyperpigmented rash | 2 days | not mentioned but medication had not been stopped | 5              |
| Majda 2020²⁶             | 87/female | IV Levofloxacin | 500             | 23                                           | Hypoglycemia    | 3 days               | glucose injection, medication had not been stopped | 5              |
| Kelesidis 2010²⁷         | 65/female | Ciprofloxacin  | 500             | Mentioned by the authors as a case of CKD    | hypoglycemia    | a few hours           | dextrose and octreotide | 5              |

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| Author/year of publication | Age/sex | FQ administered | FQ dose (mg/day) | Degree of CKD, eGFR, or CrCl ml/min/1.73m² | Type of toxicity | Days to toxicity onset<sup>a</sup> | Treatment | Naranjo score<sup>b</sup> |
|----------------------------|---------|----------------|-----------------|---------------------------------|-----------------|---------------------------------|-----------|-----------------|
| Tsai 2014<sup>28</sup>     | 73/female | IV Levofloxacin | 750             | on hemodialysis                  | Tdp arrhythmia  | same day of first dose administration | cardioversion, replacing levofloxacin and HD | 5               |
| Kushner 2001<sup>29</sup>  | 75/female | Levofloxacin    | 500 mg on day 1 then 250 | SCr =1.5 | seizure | 3 days | D/C drug and seizure management with magnesium and fosphenytoin | 7               |
| Parra-Riffo 2012<sup>30</sup> | 72/male | Levofloxacin    | 250 mg every 48 hrs | on hemodialysis                  | hypoglycemia    | during the 2nd week after first dose | glucose administration | 7               |
| Proietti 2011<sup>31</sup> | 80/male | IV Levofloxacin | 500             | 27                              | Tdp arrhythmia  | 2 days | management of arrhythmia and D/C drug | 5               |

Abbreviations: CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; FQ, fluoroquinolone, D/C discontinue; HD, hemodialysis; IV, intravenous; tdp, torsades de pointes; Minimal Change Disease, MCD; SCr, serum creatinine.

<sup>a</sup>The median [IQR] time to toxicity was 3 (2-8) days after a fluoroquinolone initiation in these case reports.

<sup>b</sup>Naranjo Adverse Drug Reaction Probability Interpretation: ≥ 9 = definite ADR, 5-8 = probable ADR, 1-4 = possible ADR, 0 = doubtful ADR.
### Table 3b: Retrospective cohort study

| Author     | Study description                                                                 | Study procedure /exposure time                                                                 | Results                                                                                                                                                                                                 | Study limitation                                      | Quality score |
|------------|------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------|---------------|
| Assimon    | 264,968 patients (Medicare beneficiaries) receiving in-center maintenance hemodialysis (mean age 61 years) newly prescribed a study antibiotic between 200-2016 in the United States | Respiratory fluoroquinolone (levofloxacin or moxifloxacin) vs amoxicillin-based (amoxicillin or amoxicillin with clavulanic acid) antibiotic treatment. The primary outcome was sudden cardiac death within 5 days of outpatient initiation of a study antibiotic. Fracture was considered as a negative control outcome | Respiratory fluoroquinolone vs amoxicillin-based antibiotic treatment was associated with a higher 5-day risk of sudden cardiac death (weighted HR, 1.95; 95% CI, 1.57-2.41) Respiratory fluoroquinolone vs amoxicillin-based antibiotic treatment was not associated with the 5-day risk of fracture. | Residual confounding by indication                   | 26            |

Abbreviations: HR, hazard ratio; CI, confidence interval.

* We evaluated the quality of the using the Modified Downs and Black checklist for the assessment of the methodological quality of this retrospective cohort study. We gave a score from 0 to 28, grouped into the following four quality levels: excellent (26 to 28), good (20-25), fair (15-19) and poor (14 or less).
| Item No | Recommendation | Reported |
|---------|----------------|----------|
| **Title and abstract** | | |
| 1 | (a) Indicate the study's design with a commonly used term in the title or the abstract | Abstract |
| | (b) Provide in the abstract an informative and balanced summary of what was done and what was found | Abstract |
| **Introduction** | | |
| Background/rationale | | |
| 2 | Explain the scientific background and rationale for the investigation being reported | Introduction |
| Objectives | | |
| 3 | State specific objectives, including any prespecified hypotheses | Introduction |
| **Methods** | | |
| Study design | | |
| 4 | Present key elements of study design early in the paper | Methods - Study Design and Setting |
| Setting | | |
| 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | Methods - Study Design and Setting; Method - Data Sources; Patient’s selection and fluoroquinolone dosing |
| Participants | | |
| 6 | (a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | Methods – patient selection and fluoroquinolone dosing; Supplemental eFigure 1 |
| | (b) For matched studies, give matching criteria and number of exposed and unexposed | Statistical analysis; Results - Baseline Characteristics; Table 1; Supplemental eTable 11 |
| Variables | | |
| 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and | Methods - Data Sources; Methods - Outcomes. |

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| Item No | Recommendation |
|-----------------|------------------|
| **Data sources/measurement** | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group |
| **Bias** | Describe any efforts to address potential sources of bias |
| **Study size** | Explain how the study size was arrived at |
| **Quantitative variables** | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why |
| **Statistical methods** | (a) Describe all statistical methods, including those used to control for confounding |
|              | (b) Describe any methods used to examine subgroups and interactions |
|              | (c) Explain how missing data were addressed |
|              | (d) If applicable, explain how loss to follow-up was addressed |
|              | (e) Describe any sensitivity analyses |
| **Participants** | (a) Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed |
| **Reported** | Supplemental eTable 5; Table 1 |
|               | Methods - Data Sources. Supplemental eTable 5 |
|               | Methods – statistical analysis; additional analysis; Discussion |
|               | Not applicable; use of existing health records |
|               | Methods – Statistical Analysis and additional analysis |
|               | Methods – Statistical Analysis and additional analysis |
|               | Table 1; Supplemental eTable 11 |
|               | Not applicable |
|               | Methods – additional analyses; |
| Item No | Recommendation                                                                 | Reported                                                                 |
|---------|-------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| 14      | (b) Give reasons for non-participation at each stage                           | Supplemental eFigure 1                                                   |
|         | (c) Consider use of a flow diagram                                            | Supplemental eFigure 1                                                   |
| Descriptive data                                                                 |
| 14      | (a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders | Results - Baseline Characteristics. Table 1; Supplemental eTable 11     |
|         | (b) Indicate number of participants with missing data for each variable of interest | Methods - Data Sources; Table 1; Supplemental eTable 11                  |
|         | (c) Summarize follow-up time (e.g. average and total amount)                  | Results - Primary Outcomes, Secondary Outcomes                           |
| Outcome data                                                                 |
| 15      | Report numbers of outcome events or summary measures over time                | Results - Primary Outcomes; Table 2;                                     |
| Main results                                                                 |
| 16      | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. 95% confidence interval). Make clear which confounders were adjusted for and why they were included | Results - Primary Outcomes, Secondary Outcomes. Table 2                  |
|         | (b) Report category boundaries when continuous variables were categorized    | Not applicable                                                            |
|         | (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | Table 2                                                                  |
| Other analyses                                                                 |
| 17      | Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses | Results - Secondary Outcome. Table 2 and Additional analyses, Supplemental eTable 12-14 and Supplemental eFigure 2 |

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| Item No | Recommendation                                                                 | Reported     |
|---------|--------------------------------------------------------------------------------|--------------|
| **Discussion**                                                                 |
| Key results | Summarize key results with reference to study objectives                      | Discussion   |
| Limitations | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | Discussion   |
| Interpretation | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | Discussion   |
| Generalizability | Discuss the generalizability (external validity) of the study results | Discussion   |
| **Other information**                                                             |
| Funding | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | Article Information |
### eTable 5. Coding Definitions for Demographic and Comorbid Conditions

| Characteristic | Database | Codes              |
|----------------|----------|--------------------|
| **Demographics** |          |                    |
| Age            | RPDB     |                    |
| Sex            | RPDB     |                    |
| Location of residence — Rural status | Statistics Canada |                |
| Long-term care | ODB      | LTC                |
| Year of cohort entry | ODB    |                    |
| Socioeconomic Status (Neighbourhood Income Quintile) | Statistics Canada |                |
| LHIN\(^a\)    | RPDB     | LHIN               |
| Prescriber     | ODB      |                    |
| **Comorbidities (5 years prior the cohort entry date)** |          |                    |
| Acute kidney injury | CIHI-DAD | ICD-10: N17     |
| Anxiety disorder and depression | CIHI-DAD | ICD-10: F063, F064, F204, F313, F314, F315, F32, F33, F341, F400, F401, F402, F408, F409, F410, F411, F412, F413, F418, F419, F420, F421, F422, F428, F429, F430, F431, F432 |
|                  | OHIP     | OHIP DX: 311       |
|                  | OMHRS (DSM-IV) | 29189, 29284, 29289, 29383, 29384, 29620, 29621, 29622, 29623, 29624, 29625, 29626, 29629, 29631, 29632, 29639, 29635, 29636, 30000, 30001, 30002, 30012, 30021, 30022, 30023, 30029, 30039, 30040, 30113 |
| Anemia          | CIHI-DAD | ICD10: D50, D51, D52, D53, D55, D56, D570, D571, D58, D59, D60, D61, D62, D63, D64 |
|                  | OHIP     | OHIP dx: 280, 281, 282, 283, 284, 285 |
| Bipolar disorder | CIHI-DAD | ICD-10: F300, F301, F302, F308, F309, F310, F311, F312, F313, F314, F315, F316, F317, F318, F319 |
|                  | OHIP     | OHIP DX: 296       |
|                  | OMHRS (DSM-IV) | 29600, 29601, 29602, 29603, 29604, 29605, 29606, 29640, 29641, 29642, 29643, 29644, 29645, 29646, 29650, 29651, 29652, 29653, 29654, 29655, 29656, 29660, 29661, 29662, 29663, 29664, 29665, 29666, 29670, 29680, 29689 |
| Myocardial infarction | CIHI-DAD | ICD10: I21, I22 |
| Atrial fibrillation/flutter | CIHI-DAD | ICD10: I48 |
| Cancer           | CIHI-DAD | ICD-10: 80003, 80006, 80013, 80023, 80033, 80043, 80102, 80103, 80106, 80113, 80123, 802, 803, 80413, 80423, 80433, 80443, 80453, 80502, 80503, 80513, 80523, 807, 808, 80903, 80913, 80923, 80933, 80943, 80953, 81103, 81202, 81203, 81213, 81223, 81233, 81243, 81303, 81402, 81403, 81404, 81413, 81423, 81433, 81443, 81453, 81473, 81503, 81513, 81523, 81533, 81543, 81553, 81603, 81613, 81623, 81703,
| Characteristic                  | Database | Codes                                                                 |
|--------------------------------|----------|-----------------------------------------------------------------------|
|                                |          | 81713, 81803, 81903, 82003, 82102, 82103, 82113, 82203, 82213, 823, 82403, 82413, 82433, 82443, 82453, 82463, 82473, 82503, 82513, 82603, 82612, 82613, 82623, 82632, 82633, 82703, 82803, 82813, 82903, 83003, 83103, 83123, 83143, 83153, 83203, 83223, 83303, 83313, 83323, 83403, 83503, 83703, 83803, 83813, 83903, 84003, 84013, 84103, 84203, 84303, 84403, 84413, 84423, 84503, 84513, 84603, 84613, 84623, 84703, 84713, 84723, 84733, 84803, 84806, 84813, 849, 85002, 85003, 85012, 85013, 85023, 85032, 85033, 85042, 85043, 851, 852, 85303, 854, 85503, 85603, 85623, 857, 85803, 86003, 86203, 86303, 86403, 86503, 86803, 86933, 87003, 87103, 87202, 87203, 87213, 87223, 87233, 87303, 87403, 87412, 87413, 87422, 87423, 87433, 87443, 87453, 87613, 87703, 87713, 87723, 87733, 87743, 87803, 88003, 88006, 88013, 88023, 88033, 88043, 88103, 88113, 88123, 88133, 88143, 88303, 88323, 88333, 88403, 88503, 88513, 88523, 88533, 88543, 88553, 88583, 88903, 88913, 88943, 88953, 88963, 89003, 89013, 89023, 89033, 89103, 89133, 89143, 895, 89603, 89633, 89643, 897, 89803, 89913, 89903, 90003, 90023, 90043, 90413, 90423, 90433, 90443, 90503, 90513, 90523, 90533, 906, 90703, 90713, 90723, 90803, 90813, 90823, 90833, 90843, 90853, 90903, 91003, 91013, 91023, 91103, 91243, 91303, 91333, 91403, 91503, 91703, 91803, 91813, 91823, 91833, 91843, 91853, 91903, 92203, 92213, 92303, 92313, 92403, 92503, 92603, 92613, 92703, 92903, 93103, 93303, 93623, 93643, 93703, 93803, 93813, 93823, 93903, 93913, 93923, 940, 941, 942, 94303, 944, 945, 94603, 947, 948, 94903, 95003, 95013, 95023, 95033, 95043, 951, 952, 95303, 95393, 95403, 95603, 95613, 95803, 95813, 959, 965, 966, 967, 968, 969, 970, 971, 972, 973, 97403, 97413, 97603, 97613, 97623, 97633, 97643, 980, 982, 98303, 984, 98503, 986, 98703, 98803, 989, 99003, 99103, 993, 994, C00-C26, C30-C34, C37, C38-C86, C88, C90, C91-C97, D00-D09, Z85 |
| OHIP                          |          | OHIP DX: 140-165, 170-175, 179-208, 230-234 |

**Stroke, including TIA**

- **CIHI-DAD**
  - ICD-10: I62, I630, I631, I632, I633, I634, I635, I638, I639, I64, H341, I600, I601, I602, I603, I604, I605, I606, I607, I609, I61, G450, G451, G452, G453, G458, G459, H340

**Chronic liver disease**

- **CIHI-DAD**
  - ICD 10: B16, B17, B18, B19, B185, R17, R18, R160, R162, B942, Z225, E831, E830, K70, K713, K714, K715, K717, K721, K729, K73, K74, K753, K754, K758, K759, K76, K77

**OHIP**

- **OHIP DX:** 571, 573, 070
- **OHIP FEE:** Z551, Z554

**Coronary artery disease, with angina**

- **CIHI-DAD**
  - ICD-10: I20, I21, I22, I23, I24, I25, Z955, Z958, Z959, R931, T822
  - CI: I256, I217, 11J54, 1I1J5, 1J1J50, I1176
  - CCP: 4801, 4802, 4803, 4804, 4805, 481, 482, 483

**OHIP**

- **OHIP DX:** 410, 412, 413
- **OHIP FEE:** R741, R742, R743, G298, E646, E651, E652, E654, E655, G262, Z434, Z448

**Congestive heart failure**

- **CIHI-DAD**
  - ICD-10: I099, I420, I425, I426, I427, I428, I429, 1I43, 1I500, 1I501, 1I509, 1I255, J81
  - CCP: 4961, 4962, 4963, 4964
  - CI: 1HP53, 1HP55, 1HZ53GRFR, 1HZ53LAFR, 1HZ53SYFR

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| Characteristic          | Database     | Codes                                      |
|------------------------|--------------|--------------------------------------------|
|                        | OHIP         | OHIP DX: 428                               |
|                        |              | OHIP FEE: R701, R702, Z429                 |
| Epilepsy/seizure       | CIHI-DAD     | ICD-10: G40, G41, R5680, R5688             |
|                        | OHIP         | OHIP DX: 345, 780                          |
| Migraine               | CIHI-DAD     | ICD-10: G43                                |
|                        | OHIP         | OHIP DX: 346                               |
| Rheumatoid Arthritis   | CIHI-DAD     | ICD10: M05, M06                           |
|                        | OHIP         | OHIP DX: 714                               |
| Dyslipidemia           | CIHI-DAD     | ICD-10: E78                                |
|                        | OHIP         | OHIP DX: 272                               |
| Crohn disease          | CIHI-DAD     | ICD10: "K50"                               |
|                        | OHIP         | OHIP DX: 555                               |
| Parkinson’s disease    | CIHI-DAD     | ICD-9: 332                                 |
|                        |              | ICD-10: G20, F023                          |
| Peripheral vascular    | CIHI-DAD     | ICD 10: i700, i702, i708, i709, i731, i738, K551 |
| disease                |              | CCP: 5125, 5129, 5014, 5016, 5018, 5028, 5038, 5126, 5159 |
|                        |              | CCI: 1KA76, 1KA50, 1KE76, 1KG50, 1KG57, 1KG76ML, 1KG87, 1IA87LA, 1IB87LA, 1IC87LA, 1ID87, 1KA87LA, 1KE57 |
|                        | OHIP         | OHIP FEE: R787, R780, R797, R804, R809, R815, R936, R783, R784, R785, E626, R814, R786, R937, R860, R861, R855, R856, R933, R934, R791, E672, R794, R813, R867, E649 |
| Ulcerative colitis (UC)| CIHI-DAD     | ICD10: K51                                |
|                        | OHIP         | OHIP DX: 556                               |
| Osteoarthritis         | CIHI-DAD     | ICD10: M15, M16, M17, M18, M19, M47        |
| Gout                   | CIHI-DAD     | ICD10: M10                                 |
|                        | OHIP         | OHIP dx: 274                               |
| Hypercalcaemia         | CIHI-DAD     | ICD10: E835                                |
| Diabetes               | ODB          | Insulins, oral antihyperglycemic agents    |
| Hypertension           | ODB          | Antihypertensive agents                    |
| Ventricular arrhythmia | CIHI-DAD     | ICD10: I4900, I472                        |
| Dementia               | CIHI-DAD     | ICD10: F065, F066, F068, F069, F09, F00, F01, F02, F03, F051, G30, G31, R54 |
|                        | OHIP         | OHIP DX CODES: "290", "331", "797"         |
|                        | OMHRS (DSM-IV)| DSM-IV (OMHRS): "29040", "29041", "29042", "29043", "29120", "29282", "29410", "29411", "29480", "7809" |
| Hyponatremia           | CIHI-DAD     | ICD10: E871                               |

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| Characteristic                  | Database          | Codes                                                                 |
|--------------------------------|-------------------|----------------------------------------------------------------------|
| Schizophrenia                  | CIHI-DAD          | ICD-10: F060, F062, F105, F107, F115, F117, F125, F127, F135, F137, F145, F147, F155, F157, F165, F167, F175, F177, F185, F187, F195, F197, F200, F201, F202, F203, F204, "F205", "F206", F208, F209, F220, F228, F229, F230, F231, F232, F233, F238, F239, F24, F250, F251, F252, F258, F259, F28, F29 |
|                                | OHIP              | OHIP dx: 291, 292, 295, 297, 298                                      |
|                                |                   | OHIP fee: Q021                                                        |
|                                | OMHRS (DSM-IV)    | DSM-IV (OMHRS): 29130, 29150, 29211, 29212, 29381, 29382, 29510, 29520, 29530, 29540, 29560, 29570, 29590, 29710, 29730, 29880, 29890 |
| Alcohol misuse                 | CIHI-DAD          | ICD10: E24, E512, F10, G312, G621, G721, I426, K292, K70, K860, T510, X45, X65, Y15, Y573, Z502, Z714, Z721 |
|                                | OHIP              | OHIP dx: 303                                                          |
| hypotension                    | CIHI-DAD          | ICD10: I95                                                            |
| Arrhythmia                     | CIHI-DAD          | ICD10: I48, I44, I45, I47, I4900, I4901, I491, I492, I493, I494, I498, I499, R001 |
|                                |                   | OHIP fee: G178, G179, G249, G261, G259 ,Z443,Z431 Z437               |
| Urinary tract infection        | CIHI-DAD          | ICD10: N10, N11, N12, N136, N151, N159, N160, N300, N308, N309, N340, N390, N410, N411, N412, N413, N431, N45, T835 |
| Community acquired pneumonia   | CIHI-DAD          | ICD10: J12, J13, J14, J15, J16, J17, J18, P23                        |
| Prosthetic joint infection     | CIHI-DAD          | ICD-10: T845                                                          |
|                                | OHIP              | OHIP dx: 739                                                          |
| Other bacterial infections     | CIHI-DAD          | ICD-10: A49                                                          |
|                                | OHIP              | OHIP dx: 786, 136, 040, 039                                           |
| Gallstones /biliary stones     | CIHI-DAD          | ICD10: K80, K81, K82, K83, K87, K862, K863, K868, K869               |
|                                | OHIP              | OHIP DX: 574, 575, 576                                               |
| Sepsis                         | CIHI-DAD          | ICD10: A021, A392, A393, A394, A400, A401, A402, A408, A409, A410, A411, A412, A403, A414, A4159, A413, A4150, A4151, A4152, A4158, A4180" A4188, A427, A419 |
| Chronic obstructive pulmonary disease | CIHI-DAD          | ICD10: J41, J43, J44                                               |
| Gastroesophageal reflux disease | CIHI-DAD          | ICD10: K21                                                          |
|                                | OHIP              | OHIP dx: 530, 531, 532, 533, 534, 535 , 536 , 537 , 538 , 539            |
| Glaucoma                       | CIHI-DAD          | ICD-10: H40                                                          |
|                                |                   | CCP: 0926                                                            |
|                                | OHIP              | OHIP fee: "E123", "E133", "E214", "E983", "E984", "G819", "G820" |

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| Characteristic               | Database    | Codes                                      |
|-----------------------------|-------------|--------------------------------------------|
| Cataract                    | CIHI-DAD    | ICD-10 H25, H26, H27, H28                 |
|                             | OHIP        | OHIP fee: E214, E140, E141                |
| Syncope                     | CIHI-DAD    | ICD10: R55                                 |
| Prostate cancer             | CIHI-DAD    | ICD10: C61, D075                          |
|                             | OHIP        | OHIP DX: 185                              |
| Prostatitis                 | CIHI-DAD    | ICD10: N410, N411, N412                   |
|                             | OHIP        | OHIP DX: 601                              |
| Prostatic hyperplasia       | CIHI-DAD    | ICD10: N40                                |
|                             | OHIP        | OHIP DX: 600                              |
| Macular degeneration        | CIHI-DAD    | ICD-10 H35                                |
|                             | OHIP        | OHIP Fee: E154, E125, E126, E1            |
| Obesity                     | CIHI-DAD    | ICD10: E660, E661, E662, E668, E669       |
|                             | OHIP        | OHIP DX: 278                              |
| Inflammatory bowel disease  | CIHI-DAD    | ICD10: "K50", "K51"                       |
| Hypothyroidism              | CIHI-DAD    | ICD-10: E030, E031, E032, E033, E034, E035, E038, E039, E890 |
|                             | OHIP        | OHIP DX: 243, 244                         |
| Hypoglycemia                | CIHI-DAD    | ICD10: E15, E160, E161, E162, E1063, E1163, E1363, E1463 |
| Pain                        | CIHI-DAD    | ICD-10: F454, "M081", "M2550", "M2551", "M2555", "M2556", "M2557", "M432", "M433", "M434", "M435", "M436", "M45", "M461", "M466", "M469", "M47", "M480", "M481", "M488", "M489", "M508", "M509", "M51", "M531", "M532", "M533", "M538", "M539", "M54", "M608", "M609", "M633", "M790", "M791", "M792", "M796", "M797", "M961", "G500", "G530" |
| Cirrhosis/liver damage      | CIHI-DAD    | ICD10: K702, K703, K704, K709, K740, K741, K742, K743, K744, K745, K746 |
|                             | OHIP        | OHIP DX: 571, 573                         |
| Chronic lung disease        | CIHI-DAD    | ICD10: I272, I278, I279, I40, I41, I42, I43, I44, I45, I47, I60, I61, I62, I63, I64, I66, I67, I68, I701, I703, I704, I708, I709, J82, J84, J92, J941, J949, J953, J961, J969, J984, "J988", J989, J99 |
|                             | OHIP        | OHIP DX: 491, 492, 493, 494, 496, 501, 502, 515, 518, 519 |
|                             |             | OHIP FEE: J889, J689                      |
| Hypokalemia                 | CIHI-DAD    | ICD10: E876                               |
|                             | OHIP        | OHIP dx: 579                              |
| Urinary retention           | CIHI-DAD    | ICD10: R33                               |

Medication use (120 days before cohort entry)

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## Characteristic

| Characteristic | Database          | Codes                                      |
|----------------|-------------------|--------------------------------------------|
| All medications | ODB               |                                            |
| **Healthcare Use (1 year prior to the cohort entry date)** |                   |                                            |
| GP/FP visits   | OHIP, IPDB        | Mainspeciality = “GP/FP” or “F.P./EMERGENCY MEDICINE” |
| Nephrologist visits | OHIP, IPDB        | Mainspeciality = “NEPHROLOGY”             |
| Number of any hospitalizations | CIHI-DAD         | "ddate"                                   |
| Number of any ER visits | NACRS           | "regdate"                                 |
| Number of serum creatinine tests | OLIS             | OBSERVATIONCODE: 14682-9                  |
| TSH            | OHIP              | OHIP FEE: G016, L341                       |
| CT head        | OHIP              | OHIP FEE: X188, X400, X401, X402, X405, X408 |
| CT abdomen     | OHIP              | OHIP FEE: X126, X409, X410                |
| CT extremities | OHIP              | OHIP FEE: X127, X412, X413                |
| CT neck        | OHIP              | OHIP FEE: X124, X403, X404                |
| CT pelvis      | OHIP              | OHIP FEE: X128, X415, X416                |
| CT spine       | OHIP              | OHIP FEE: X231, X232, X233                |
| CT thorax      | OHIP              | OHIP FEE: X125, X406, X407                |
| Chest x-ray    | OHIP              | OHIP FEE: X090, X091, X092, X195          |
| Echocardiography | CIHI-DAD         | CCP: 0282, CCI: 3IP30                      |
|                | OHIP              | OHIP FEE: G560, G561, G562, G566, G567, G568, G570, G571, G572, G574, G575, G576, G577, G578, G581 |
| Carotid ultrasound | CIHI-DAD         | CCP: 0281, CCI: 3JE30, 3JG30               |
|                | OHIP              | OHIP FEE: J201, J501, J190, J191, J490, J491, J492 |
| Cardiac catheterization | CIHI-DAD      | CCP: 4995, 4996, 4997, 4892, 4893, 4894, 4895, 4896, 4897, 4898 |
|                | OHIP              | OHIP FEE: G296, G297, G299, G300, G301, G304, G305, G306, G297, G509 |
| Coronary angiogram | CIHI-DAD        | CCP: 4892, 4893, 4894, 4895, 4896, 4897, 4898 |
|                | OHIP              | OHIP FEE: G297, G509                       |
| Holter monitoring | CIHI-DAD      | CCP: 0354, CCI: 2HZ24JAKH                  |

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| Characteristic                               | Database                  | Codes                                                                 |
|---------------------------------------------|---------------------------|-----------------------------------------------------------------------|
| Cardiac stress test                         | CIHI-DAD                  | CCP: 0341, 0342, 0343, 0344, 0605                                      |
|                                              |                           | CCI: 2H208, 3IP70                                                     |
|                                              | OHIP                      | OHIP FEE: G315, G174, G111, G112, G319, G582, G583, G584, J607, J608, J807, J808, J809, J866, J609, J666 |
| Coronary revascularization                  | CIHI-DAD                  | CCP: 481, 482, 483, 480                                              |
|                                              |                           | CCI: 1U50, 1U26, 1U27, 1U57, 1U76, 1U57GQ, 1U54GQAZ                  |
|                                              | OHIP                      | OHIP FEE: R741, R742, R743, E651, E652, E654, E646, G298, Z434, G262 |
| Electrocardiography                         | CIHI-DAD                  | CCI: 2HZ24JAKE                                                        |
|                                              | OHIP                      | OHIP FEE: G310, G313                                                  |
| Colorectal cancer screening                 | OHIP                      | OHIP FEE: G004, L179, L181, Q043, Q152, X112, X113, Z535, Z536, Z555, Z580 |
| Cervical cancer screening                   | OHIP                      | OHIP FEE: E430, G365, G394, L713, L812                                |
| Prostate-specific antigen test              | OHIP                      | OHIP FEE: Q005, Q118, Q119, Q120, Q121, Q122, Q123, Q133             |
| Mammography                                 | OHIP                      | OHIP FEE: X172, X178, X184, X185, X201                                |
| Influenza vaccination                       | OHIP                      | OHIP FEE: G590, G591                                                 |
| Bone mineral density test                   | OHIP                      | OHIP FEE: J654, J688, J854, J888, X149, X152, X153, X155, Y654, Y688, Y854, Y888 |
| Hearing test                                | OHIP                      | OHIP FEE: G153, G154, G440, G441, G442, G443, G448, G450, G451, G452, G525, G526, G529, G530, G533, G815, G816 |
| Cystoscopy                                  | OHIP                      | OHIP FEE: Z606, Z607, Z628, Z632, Z633, Z634                          |
| Pulmonary function test                     | OHIP                      | OHIP FEE: L354, L358                                                  |
| At-home physician service                   | OHIP                      | OHIP FEE: A901, B960, B961, B962, B963, B964, B966, B990, B992, B993, B994, B996, B997, B998 |
| Sputum                                      | OHIP                      | OHIP Fee: L629                                                       |
| Vaginal smear                               | OHIP                      | OHIP Fee: L625                                                       |
| Throat swab                                 | OHIP                      | OHIP Fee: L640, L636                                                 |
| Urinalysis                                  | OHIP                      | OHIP FEE: L253, L254, L255, L633, G009, G010                          |
| Serum creatinine value*                     | OLIS                      | OBSERVATIONCODE: 14682-9                                             |
| Urine albumin-to-creatinine ratio*          | OLIS                      | OBSERVATIONCODE: 14959-1, 30000-4, 32294-1, XON10383-8 and XON12394-3 |

*Assessed in the 365-day period before the cohort entry date."
**eTable 6. Justification for Using the CKD-EPI Equation to Estimate Patients’ Glomerular Filtration Rate in This Study**

| The best equation to estimate GFR to guide drug-dosing adjustments in patients with chronic kidney disease remains controversial. While the Cockcroft-Gault equation, expressed in mL/min, is a popular formula used to guide drug dosing, this equation requires information on body weight, which was not available in our data sources. However, the United States Kidney Disease Education program indicates that GFR equations that express results in mL/min per 1.73 m² or mL/min are appropriate to adjust drug doses in most adults. CKD-EPI eGFR <30 mL/min per 1.73 m² will usually also identify patients with a Cockcroft-Gault eGFR < 30mL/min. |

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eTable 7. Median Dose of Fluoroquinolone Dispensed to Adults Aged 66 and Older With an Estimated Glomerular Filtration Rate <30 mL/min/ 1.73 m² in Ontario, Canada (2008 to 2020)

| Fluoroquinolone | No. patients | Median dose, mg/day (range) |
|-----------------|--------------|-----------------------------|
| Ciprofloxacin   | 7614         | 500 (500 to 1000)           |
| Levofloxacin    | 2492         | 500 (250 to 750)            |
| Norfloxacin     | 1811         | 800 (400 to 800)            |

* Estimated with the chronic kidney disease–epidemiology equation.³⁵
**eTable 8. Operating Characteristics of Hospital Diagnosis Codes Used to Define the Primary and Secondary Outcomes**

| Outcome                                                                 | Outcome component                                      | ICD-10/CCI/OHIP/ORGD codes in this study | ICD-10 /CCI/OHIP/ORGD codes used in the validation study | Reference Standard                                                                 | Operating Characteristics, % (95% CI)                                                                 | Study |
|-------------------------------------------------------------------------|--------------------------------------------------------|------------------------------------------|----------------------------------------------------------|------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|-------|
| **Hospital visit with nervous system and/or psychiatric disorders** a   | Delirium, not induced by alcohol and other psychoactive substance | ICD-10 codes: F050, F051, F058, F059, G934 | ICD-10 codes: F05, F10121, F10221, F10231, F10921, F11121, F11921, F12121, F12221, F12921, F13121, F13231, F13921, F13931, F14121, F14221, F14921, F15121, F15221, F15921, F16121, F16221, F16921, F18121, F18221, F18921, F19121, F19221, F19921, F19231, F19931, A812, E512, G0430, G0431, G0432, G0439, G92, G9340, G9341, G9349, I673, I674, I6783, J1081, J1181, P9160, P9161, P9163 | Identification of delirium in a cohort of patients undergoing a cardiac surgery through interviews by geriatricians or trained research assistants | 18 (10-30) 98 (93-100) 80 (52-96)                                                                 | Kim 2017<sup>36</sup> |
| Disorientation unspecified                                               | ICD-10 code: R410                                      |                                          |                                                          |                                                                                      |                                                                                                 |       |
| Transient alteration of awareness                                       | ICD-10 codes: R4180, R4188                            |                                          |                                                          |                                                                                      |                                                                                                 |       |
| Agitation and nervousness                                                | ICD-10 codes: R451, R450                              |                                          |                                                          |                                                                                      |                                                                                                 |       |
| Somnolence                                                              | ICD-10 code: R400                                     |                                          |                                                          |                                                                                      |                                                                                                 |       |

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| Outcome | Outcome component | ICD-10/CCI/OHIP/ORGD codes in this study | ICD-10 /CCI/OHIP/ORGD codes used in the validation study | Reference Standard | Operating Characteristics, % (95% CI) | Study |
|---------|-------------------|------------------------------------------|--------------------------------------------------------|-------------------|----------------------------------------|-------|
| Hospital visit with nervous system and/or psychiatric disorders<sup>a</sup> | Dizziness and giddiness | ICD-10 code: R42 | | | | |
| | Peripheral neuropathy | ICD-10 codes: G603, G608, G611, G620 | | | | |
| Hospital visit with hypoglycemia | | ICD-10 codes: E15, E160, E161, E162, E1063, E1163, E1363, E1463 | ICD-10 codes: E15, E160, E161, E162, E1063, E1163, E1363, E1463 | Positive predicted value: hypoglycemia in adults aged ≥65 on chart review defined as blood glucose <4 mmol/L or physician diagnosis  
Sensitivity: hypoglycemia in adults aged ≥65 using healthcare databases with plasma glucose <4 mmol/L during hospital visit | 13 (12-14) | 94 (89-97) | Hodge 2017<sup>17</sup> |
| Outcome                                      | Outcome component                  | ICD-10/CCI/OHIP/ORGD codes in this study | ICD-10 /CCI/OHIP /ORGD codes used in the validation study | Reference Standard | Operating Characteristics, % (95% CI) | Study                        |
|----------------------------------------------|------------------------------------|------------------------------------------|-----------------------------------------------------------|---------------------|--------------------------------------|------------------------------|
| Hospital visit with a collagen-associated event<sup>c</sup> | Achilles’ tendon rupture<sup>b</sup> | ICD 10 codes: S8600, S8608. CCI codes: 1WT80 OHIP fee codes: R587, R589 | ICD-10 code: I713 CCI codes: 1KA76, 1KA80 OHIP fee codes: R802, R817, R877, R875, E627 | Abdominal aortic aneurysm rupture in two academic tertiary hospitals on chart review by vascular surgeons | ICD-10 code I713 83 (75,89) CCI codes 1KA76 100 (74,100) 1KA80 100 (63,100) OHIP fee codes R802 100 (97,100) R817 100 (97,100) R875 98 (94,100) E627 90 (83,96) R877 100 (88,100) | Salata 2018<sup>8</sup> |
| Hospital visit with sepsis<sup>d</sup>       |                                    | ICD-10 codes: A021, A392, A393, A394, A400, A401, A402, A408, A409, A410, A411, A412, A403, A414, A4159, A413, A4150, A4151, A4152, A4158, A4180, A4188, A427, "A419 |                                            |                                            |                                            |                              |
| Hospital visit with retinal detachments      |                                    | ICD-10 codes: H330, H331, H332, H333, H334, H335 |                                            |                                            |                                            |                              |
| Outcome                          | Outcome component | ICD-10/CCI/OHIP/ORGD codes in this study | ICD-10 /CCI/OHIP/ORGD codes used in the validation study | Reference Standard | Operating Characteristics, % (95% CI) | Study     |
|---------------------------------|-------------------|------------------------------------------|--------------------------------------------------------|--------------------|---------------------------------------|-----------|
|                                 |                   |                                          |                                                        |                    | Sensitivity                          | Specificity | Positive predictive value |         |
| Hospital visit with other tendinopathies |                   | OHIP fee codes: E152A, E148A, E142A, E936 |                                                        |                    |                                       |            |                          |         |
| Sudden cardiac death            |                   | ORGD code: LCD_34, LCD_35, LCD_38, LCD_39, LCD_40, LCD_41, LCD_43 |                                                        |                    |                                       |            |                          |         |
| Death                           |                   |                                          |                                                        |                    | 98                                    | 100        |                          | Jha P 1996 |

Abbreviations: ICD-10, International Classification of Diseases, Tenth Revision; CCI code, Canadian Classification of Health Interventions code; OHIP codes, Ontario Health Insurance Program; Office of the registrar General Deaths (ORGD).

a The algorithm used to identify delirium and transient ischaemic attack has high specificity and high positive predicted value but low sensitivity. ICD-10 code algorithms to capture other components of encephalopathy were not validated. As such, we expected some outcome misclassification, but there is no reason to believe that misclassification occurred differentially between exposure groups.

b ICD-10 codes for falls were not validated. Therefore, outcome misclassification cannot be ruled out, but it is unlikely that this misclassification differ between comparison groups.

c ICD-10 codes and CCI codes for Achilles’ tendon rupture have not been validated. We have also used OHIP fee codes to identify Achilles’ tendon rupture. As such, we expect this outcome to be recorded accurately because Achilles’ tendon rupture is linked to remuneration, and fee-for-service codes generally have high sensitivity and specificity.

d ICD-10 code algorithms to capture sepsis were not validated. As such, we expected some outcome misclassification, but there is no reason to believe that misclassification occurred differentially between exposure groups.
### Table 9. Variables Included in the Propensity Score Model

| Category          | Variables                                                                                           |
|-------------------|------------------------------------------------------------------------------------------------------|
| **Demographics**  | Age, sex, year of cohort entry, neighborhood income quintile, long-term residence, location, Local Health Integration Network, prescriber type |
| **Comorbidities** | Acute kidney injury, alcoholism, angina, bipolar disorder, chronic liver disease, chronic obstructive pulmonary disease, hyperkalemia, coronary artery disease (minus angina), dementia, diabetes, anemia, glaucoma, arrhythmia, congestive heart failure, hypertension, hypokalemia, hyponatremia, hypothyroidism, migraine, acute myocardial infarction, obesity, Parkinson disease, peripheral vascular disease, schizophrenia, hypoglycemia, seizure, ischemic stroke, hemorrhagic stroke, unipolar depression and/or anxiety disorder, rheumatoid arthritis, syncope, inflammatory bowel disease, cancer, prostatic hyperplasia, prostatitis, hypertension, ulcerative colitis, Crohn disease, acute urinary retention, macular degeneration, dyslipidemia, gastroesophageal reflux disease, osteoarthritis, transient ischemic stroke, Gallstones /biliary stones, gout, ventricular arrhythmia, community-acquired pneumonia, urinary tract infection, sepsis, modified Charlson comorbidity index |
| **Medications**   | Alpha-adrenergic blocking agents, anti-arrhythmic, allopurinol, other antibiotics, anticoagulants, anticonvulsants, aspirin, antiplatelet agents, anticholinergics agent, bone calcium regulators, benzodiazepine, bisphosphonates, beta-agonists, calcium, chemotherapeutic drugs, cholinesterase inhibitors, glucocorticoid, nitrates, NSAIDs (excluding aspirin), opioids, overactive bladder medication, antipsychotics, proton pump inhibitors, 5 alpha reductases, selective serotonin reuptake inhibitors, statins, number of unique drug names, number of unique dns |
| **Health Care Use** | Emergency department visit, family physician visit, hospitalization |
| **Investigations**| Serum creatinine tests, TSH test, at home physician service, Bone mineral density test, cardiac catheterization, cardiac stress test, carotid ultrasound, chest-X ray, cataract surgery, cervical cancer screening, colorectal cancer screening, cholesterol test (total cholesterol, HDL), CT abdomen, CT extremities, CT head, CT neck, CT pelvis, CT spine, CT thorax, echocardiography, flu shot, cystoscopy, hearing test, mammography, prostate-specific antigen (PSA) test, Holter monitoring, parathyroid hormone testing, pulmonary function test, urinalysis, eGFR value, ACR |

Abbreviations: ACR, urine albumin-to-creatinine ratio; ACE inhibitor, angiotensin-converting-enzyme inhibitor; CT, computed tomography; eGFR, estimated glomerular filtration rate.
eTable 10. Dose and Duration of Continuous Fluoroquinolone Dispensing in Older Adults With Advanced Chronic Kidney Disease Newly Prescribed a Fluoroquinolone in Ontario, Canada (2008-2020)

| Dose and duration of continuous fluoroquinolone dispensing | Higher dose n=5482 (46.0%) | Lower dose n=6435 (54.0%) |
|-------------------------------------------------------------|-----------------------------|---------------------------|
| Median daily dose, mg (IQR)                                |                             |                           |
| Ciprofloxacin                                              | 1000 (525 to 1000)          | 500 (500 to 500)          |
| Levofloxacin                                               | 750 (523 to 750)            | 500 (250 to 500)          |
| Norfloxacin                                                | 800 (457 to 800)            | 400 (400 to 400)          |
| Median duration, a days (IQR)                             |                             |                           |
| Ciprofloxacin                                              | 7 (7-10)                    | 7 (6-10)                  |
| Levofloxacin                                               | 7 (5-8)                     | 8 (7-10)                  |
| Norfloxacin                                                | 7 (6-9)                     | 7 (5-10)                  |

Abbreviations: IQR, interquartile range.

*Defined as consecutive prescription claims within a period equivalent to 150% of the days supplied for the previous prescription.
| Demographics                        | Unweighted data (N = 11,917) | Weighted data (N = 10,998) |
|------------------------------------|------------------------------|-----------------------------|
|                                    | Higher dose (n = 5,482)     | Lower dose (n = 6,435)     | Higher dose (n = 5,482) | Lower dose (n = 5,516) |
| Age at cohort entry                | Mean ± SD (n = 5,482)       | Median (IQR) (n = 5,482)   | Mean ± SD (n = 5,516)   | Median (IQR) (n = 5,516) |
|                                    | 82 ± 8.0                    | 83 (76-88)                  | 82 ± 8.0                  | 82 (76-88)                  |
| 66-70                              | 493 ± 9.0%                  | 433 (6.7%)                  | 493 ± 9.0%                | 512 (9.3%)                  |
| 70-75                              | 706 ± 12.9%                 | 664 (10.3%)                 | 706 ± 12.9%               | 753 (13.7%)                 |
| 75-80                              | 944 ± 17.2%                 | 898 (14.0%)                 | 944 ± 17.2%               | 908 (16.5%)                 |
| 80-85                              | 1234 ± 22.5%                | 1376 (21.4%)                | 1234 ± 22.5%              | 1255 (22.7%)                |
| 85-90                              | 1178 ± 21.5%                | 1438 (22.3%)                | 1178 ± 21.5%              | 1095 (19.9%)                |
| 90+                                | 927 ± 16.9%                 | 1626 (25.3%)                | 927 ± 16.9%               | 994 (18.0%)                 |
| Sex                                | F 3287 ± 4151               | M 2195 ± 2284               | F 3287 ± 4151             | M 2195 ± 2284               |
|                                    | 60.0% ± 64.5%               | 40.0% ± 35.5%               | 60.0% ± 64.5%             | 40.0% ± 35.5%               |
| Year of cohort entry               | 2008 395 ± 332              | 2009 664 ± 672              | 2008 395 ± 332            | 2009 664 ± 672              |
|                                    | 7.2% ± 5.2%                 | 12.1% ± 10.4%               | 7.2% ± 5.2%               | 12.1% ± 10.4%               |
|                                    | 2010 718 ± 796              | 2011 626 ± 690              | 2010 718 ± 796            | 2011 626 ± 690              |
|                                    | 13.1% ± 12.4%               | 11.4% ± 10.7%               | 13.1% ± 12.4%             | 11.4% ± 10.7%               |
|                                    | 2012 553 ± 614              | 2013 481 ± 534              | 2012 553 ± 614            | 2013 481 ± 534              |
|                                    | 10.1% ± 9.5%                | 8.8% ± 8.3%                 | 10.1% ± 9.5%              | 8.8% ± 8.3%                 |
|                                    | 2014 434 ± 586              | 2015 373 ± 502              | 2014 434 ± 586            | 2015 373 ± 502              |
|                                    | 7.9% ± 9.1%                 | 6.8% ± 7.8%                 | 7.9% ± 9.1%               | 6.8% ± 7.8%                 |
|                                    | 2016 319 ± 433              | 2017 256 ± 401              | 2016 319 ± 433            | 2017 256 ± 401              |
|                                    | 5.8% ± 6.7%                 | 4.7% ± 6.2%                 | 5.8% ± 6.7%               | 4.7% ± 6.2%                 |
|                                    | 2018 291 ± 431              | 2019 308 ± 375              | 2018 291 ± 431            | 2019 308 ± 375              |
|                                    | 5.3% ± 6.7%                 | 5.6% ± 5.8%                 | 5.3% ± 6.7%               | 5.6% ± 5.8%                 |
|                                    | 2020 64 ± 69                | 2020 64 ± 69                | 64 ± 1.2%                 | 64 ± 1.2%                  |
| Location                           | Urban 4846 ± 5724           | Rural 636 ± 711             | Urban 4846 ± 5724         | Rural 636 ± 711             |
|                                    | 88.4% ± 89.0%               | 11.6% ± 11.0%               | 88.4% ± 89.0%             | 11.6% ± 11.0%               |

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Unweighted data (N = 11,917)  
Weighted data (N = 10,998)

| Residence | Long-term care | Higher dose (n = 5,482) | Lower dose (n = 6,435) | Standardized difference | Higher dose (n = 5,482) | Lower dose (n = 5,516) | Standardized difference |
|-----------|----------------|-------------------------|------------------------|------------------------|-------------------------|------------------------|------------------------|
| Residence | Long-term care | 697 12.7% 1450 22.5%   | 26%                    | 697 12.7% 686 12.4%    | 1%                     |
| LHIN      | 1              | 377 6.9% 366 6%         | 5%                     | 377 6.9% 368 6.7%      | 1%                     |
| LHIN      | 2              | 544 9.9% 566 9%         | 4%                     | 544 9.9% 528 9.6%      | 1%                     |
| LHIN      | 3              | 292 5.3% 466 7%         | 8%                     | 292 5.3% 296 5.4%      | 0%                     |
| LHIN      | 4              | 758 13.8% 1144 18%     | 11%                    | 758 13.8% 754 13.7%    | 0%                     |
| LHIN      | 5              | 243 4.4% 251 4%        | 3%                     | 243 4.4% 244 4.4%      | 0%                     |
| LHIN      | 6              | 311 5.7% 332 5%        | 2%                     | 311 5.7% 316 5.7%      | 0%                     |
| LHIN      | 7              | 349 6.4% 340 5%        | 5%                     | 349 6.4% 353 6.4%      | 0%                     |
| LHIN      | 8              | 671 12.2% 636 10%      | 8%                     | 671 12.2% 710 12.9%    | 2%                     |
| LHIN      | 9              | 652 11.9% 636 10%      | 6%                     | 652 11.9% 668 12.1%    | 1%                     |
| LHIN      | 10             | 221 4.0% 290 5%        | 2%                     | 221 4.0% 238 4.3%      | 2%                     |
| LHIN      | 11             | 510 9.3% 729 11%       | 7%                     | 510 9.3% 500 9.1%      | 1%                     |
| LHIN      | 12             | 194 3.5% 210 3%        | 1%                     | 194 3.5% 197 3.6%      | 1%                     |
| LHIN      | 13             | 265 4.8% 337 5%        | 2%                     | 265 4.8% 258 4.7%      | 0%                     |
| LHIN      | 14             | 95 1.7% 135 2%         | 3%                     | 95 1.7% 88 1.6%        | 1%                     |

Socio-economic status

| Socio-economic status | Higher dose (n = 5,482) | Lower dose (n = 6,435) | Standardized difference | Higher dose (n = 5,482) | Lower dose (n = 5,516) | Standardized difference |
|-----------------------|-------------------------|------------------------|------------------------|-------------------------|------------------------|------------------------|
| Socio-economic status | 1                       | 1244 22.7% 1563 24%    | 4%                     | 1244 22.7% 1265 22.9%   | 0%                     |
| Socio-economic status | 2                       | 1224 22.3% 1434 22%    | 0%                     | 1224 22.3% 1225 22.2%   | 0%                     |
| Socio-economic status | 3                       | 1147 20.9% 1274 20%    | 3%                     | 1147 20.9% 1164 21.1%   | 0%                     |
| Socio-economic status | 4                       | 1001 18.3% 1138 18%    | 2%                     | 1001 18.3% 994 18.0%    | 1%                     |
| Socio-economic status | 5                       | 866 15.8% 1026 16%     | 0%                     | 866 15.8% 869 15.7%     | 0%                     |

Prescriber information

| Prescriber information | Higher dose (n = 5,482) | Lower dose (n = 6,435) | Standardized difference | Higher dose (n = 5,482) | Lower dose (n = 5,516) | Standardized difference |
|------------------------|-------------------------|------------------------|------------------------|-------------------------|------------------------|------------------------|
| General practitioner   | 4234 77.2% 5120 79.6%   | 6%                     | 4234 77.2% 4241 76.9%   | 1%                     |
| Internal medicine      | 42 0.8% 94 1.5%        | 7%                     | 42 0.8% 44 0.8%         | 0%                     |
| Nephrology             | 73 1.3% 293 4.6%       | 20%                    | 73 1.3% 73 1.3%         | 0%                     |
| Urologist              | 402 7.3% 177 2.8%      | 21%                    | 402 7.3% 427 7.7%       | 2%                     |
| Other                  | 343 6.3% 263 4.1%      | 10%                    | 343 6.3% 346 6.3%       | 0%                     |
| Comorbidities | Unweighted data (N = 11,917) | Weighted data (N = 10,998) |
|---------------|-------------------------------|---------------------------|
|               | Higher dose (n = 5,482) | Lower dose (n = 6,435) | Standardized difference | Higher dose (n = 5,482) | Lower dose (n = 5,516) | Standardized difference |
| Missing       | 388 | 7.1% | 488 | 7.6% | 2% | 388 | 7.1% | 385 | 7.0% | 0% |
| Acute kidney injury | 1130 | 20.6% | 1492 | 23.2% | 6% | 1130 | 20.6% | 1151 | 20.9% | 1% |
| Alcoholism    | 71 | 1.3% | 77 | 1.2% | 1% | 71 | 1.3% | 70 | 1.3% | 0% |
| Angina        | 1396 | 25.5% | 1601 | 24.9% | 1% | 1396 | 25.5% | 1425 | 25.8% | 1% |
| Atrial fibrillation/flutter | 754 | 13.8% | 1030 | 16.0% | 6% | 754 | 13.8% | 761 | 13.8% | 0% |
| Bipolar disorder | 136 | 2.5% | 158 | 2.5% | 0% | 136 | 2.5% | 128 | 2.3% | 1% |
| Chronic liver disease | 233 | 4.3% | 233 | 3.6% | 4% | 233 | 4.3% | 234 | 4.2% | 0% |
| Anemia        | 2170 | 39.6% | 2652 | 41.2% | 3% | 2170 | 39.6% | 2217 | 40.2% | 1% |
| Coronary artery disease (minus angina) | 2264 | 41.3% | 2725 | 42.3% | 2% | 2264 | 41.3% | 2306 | 41.8% | 1% |
| Congestive heart failure | 1885 | 34.4% | 2511 | 39.0% | 10% | 1885 | 34.4% | 1903 | 34.5% | 0% |
| Cirrhosis     | 142 | 2.6% | 154 | 2.4% | 1% | 142 | 2.6% | 152 | 2.8% | 1% |
| Chronic obstructive pulmonary disease | 1577 | 28.8% | 2102 | 32.7% | 8% | 1577 | 28.8% | 1606 | 29.1% | 1% |
| Dementia      | 1344 | 24.5% | 2158 | 33.5% | 20% | 1344 | 24.5% | 1350 | 24.5% | 0% |
| Dyslipidemia  | 1225 | 22.3% | 1357 | 21.1% | 3% | 1225 | 22.3% | 1228 | 22.3% | 0% |
| Glaucoma      | 400 | 7.3% | 479 | 7.4% | 0% | 400 | 7.3% | 400 | 7.3% | 0% |
| Hypertension  | 5036 | 91.9% | 5944 | 92.4% | 2% | 5036 | 91.9% | 5096 | 92.4% | 2% |
| Hypokalemia   | 209 | 3.8% | 261 | 4.1% | 2% | 209 | 3.8% | 213 | 3.9% | 1% |
| Hyponatremia  | 148 | 2.7% | 216 | 3.4% | 4% | 148 | 2.7% | 147 | 2.7% | 0% |
| Hypothyroidism| 623 | 11.4% | 751 | 11.7% | 1% | 623 | 11.4% | 617 | 11.2% | 1% |
| Hypoglycemia  | 146 | 2.7% | 207 | 3.2% | 3% | 146 | 2.7% | 154 | 2.8% | 1% |
| Thyrotoxicosis | 13 | 0.2% | 21 | 0.3% | 2% | 13 | 0.2% | 15 | 0.3% | 2% |
| Migraine      | 130 | 2.4% | 178 | 2.8% | 3% | 130 | 2.4% | 126 | 2.3% | 1% |
| Acute myocardial infarction | 446 | 8.1% | 574 | 8.9% | 3% | 446 | 8.1% | 458 | 8.3% | 1% |
| Obesity       | 305 | 5.6% | 304 | 4.7% | 4% | 305 | 5.6% | 326 | 5.9% | 1% |
| Parkinson disease | 131 | 2.4% | 170 | 2.6% | 1% | 131 | 2.4% | 125 | 2.3% | 1% |
| Condition                              | Unweighted data (N = 11,917) | Weighted data (N = 10,998) |
|----------------------------------------|-------------------------------|---------------------------|
|                                        | Higher dose (n = 5,482) | Lower dose (n = 6,435) | Standardized difference | Higher dose (n = 5,482) | Lower dose (n = 5,516) | Standardized difference |
| Peripheral vascular disease            | 189 3.4%                    | 228 3.5%                  | 1%                      | 189 3.4%                  | 185 3.4%                  | 0%                      |
| Schizophrenia                          | 218 4.0%                    | 348 5.4%                  | 7%                      | 218 4.0%                  | 215 3.9%                  | 1%                      |
| Seizure                                | 36 0.7%                     | 56 0.9%                   | 2%                      | 36 0.7%                   | 37 0.7%                   | 0%                      |
| Hemorrhagic stroke                     | 13 0.2%                     | 20 0.3%                   | 2%                      | 13 0.2%                   | 13 0.2%                   | 0%                      |
| Ischemic stroke                        | 195 3.6%                    | 256 4.0%                  | 2%                      | 195 3.6%                  | 194 3.5%                  | 1%                      |
| Depression                             | 532 9.7%                    | 679 10.6%                 | 3%                      | 532 9.7%                  | 544 9.9%                  | 1%                      |
| Ventricular arrhythmia                 | 40 0.7%                     | 41 0.6%                   | 1%                      | 40 0.7%                   | 36 0.7%                   | 0%                      |
| Rheumatoid arthritis                   | 332 6.1%                    | 371 5.8%                  | 1%                      | 332 6.1%                  | 340 6.2%                  | 0%                      |
| Syncope                                | 134 2.4%                    | 217 3.4%                  | 6%                      | 134 2.4%                  | 141 2.6%                  | 1%                      |
| Inflammatory bowel disease             | 47 0.9%                     | 43 0.7%                   | 2%                      | 47 0.9%                   | 44 0.8%                   | 1%                      |
| Major Cancer                           | 2337 42.6%                  | 2597 40.4%                | 4%                      | 2337 42.6%                | 2379 43.1%                | 1%                      |
| Prostatic hyperplasia                  | 931 17.0%                   | 770 12.0%                 | 14%                     | 931 17.0%                 | 968 17.5%                 | 1%                      |
| Prostatitis                            | 179 3.3%                    | 162 2.5%                  | 5%                      | 179 3.3%                  | 184 3.3%                  | 0%                      |
| Hypotension                            | 178 3.2%                    | 252 3.9%                  | 4%                      | 178 3.2%                  | 180 3.3%                  | 1%                      |
| Community acquired pneumonia           | 472 8.6%                    | 758 11.8%                 | 11%                     | 472 8.6%                  | 470 8.5%                  | 0%                      |
| Coeliac disease                        | 17 0.3%                     | 13 0.2%                   | 3%                      | 17 0.3%                   | 13 0.2%                   | 2%                      |
| Ulcerative colitis                     | 99 1.8%                     | 75 1.2%                   | 2%                      | 99 1.8%                   | 95 1.7%                   | 1%                      |
| Crohn’s disease                        | 63 1.1%                     | 60 0.9%                   | 5%                      | 63 1.1%                   | 65 1.2%                   | 1%                      |
| Acute urinary retention                | 302 5.5%                    | 313 4.9%                  | 2%                      | 302 5.5%                  | 316 5.7%                  | 1%                      |
| Gallstones/biliary stones              | 296 5.4%                    | 342 5.3%                  | 3%                      | 296 5.4%                  | 299 5.4%                  | 0%                      |
| Macula degeneration                    | 384 7.0%                    | 461 7.2%                  | 0%                      | 384 7.0%                  | 388 7.0%                  | 0%                      |
| Gastroesophageal reflux disease        | 1377 25.1%                  | 1556 24.2%                | 1%                      | 1377 25.1%                | 1414 25.6%                | 1%                      |
| Arrhythmia                             | 1016 18.5%                  | 1353 21.0%                | 2%                      | 1016 18.5%                | 1028 18.6%                | 0%                      |
| Osteoarthritis                         | 387 7.1%                    | 420 6.5%                  | 6%                      | 387 7.1%                  | 399 7.2%                  | 0%                      |
| Hyperkaliema                           | 240 4.4%                    | 327 5.1%                  | 2%                      | 240 4.4%                  | 243 4.4%                  | 0%                      |
| Prostate cancer                        | 356 6.5%                    | 325 5.1%                  | 3%                      | 356 6.5%                  | 372 6.7%                  | 1%                      |

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| Condition                      | Higher dose (n = 5,482) | Lower dose (n = 6,435) | Standardized difference | Higher dose (n = 5,482) | Lower dose (n = 5,516) | Standardized difference |
|-------------------------------|-------------------------|------------------------|-------------------------|-------------------------|------------------------|-------------------------|
| Diabete                       | 2107                    | 2353                   | 6%                      | 2107                    | 2157                   | 1%                      |
| Urinary tract infection       | 998                     | 1266                   | 4%                      | 998                     | 1030                   | 1%                      |
| Sepsis                        | 188                     | 183                    | 3%                      | 188                     | 196                    | 1%                      |
| Transient ischemic stroke    | 61                      | 112                    | 5%                      | 61                      | 58                     | 1%                      |
| Gout                          | 881                     | 969                    | 3%                      | 881                     | 898                    | 1%                      |
| Other bacterial infections    | 2117                    | 2618                   | 4%                      | 2117                    | 2145                   | 1%                      |
| Prosthetic joint infection    | 766                     | 854                    | 2%                      | 766                     | 764                    | 0%                      |
| Prior fluoroquinolone associated adverse events | 1517 | 2043 | 9% | 1517 | 1622 | 4% |
| Modified Charlson comorbidity index | Mean ± SD           | 3.2 ± 1.9             | 6%                      | 3.2 ± 1.9              | 3.2 ± 1.8             | 1%                      |
|                               | Median (IQR)            | 2 (2-4)                |                         | 2 (2-4)                | 2 (2-4)                |                         |
| Medication use (120-day look back) | Alpha adrenergic blocking agents | 486 | 8.9% | 550 | 8.5% | 1% | 486 | 8.9% | 501 | 9.1% | 1% |
|                               | Anti-arrhythmic         | 374                    | 6.8%                    | 374                     | 379                    | 0%                      |
|                               | Other Antibiotics       | 1097                   | 20.0%                   | 1097                    | 1129                   | 1%                      |
|                               | Ace inhibitor           | 1741                   | 31.8%                   | 1741                    | 1761                   | 0%                      |
|                               | Anticoagulants          | 784                    | 14.3%                   | 784                     | 777                    | 1%                      |
|                               | Anticonvulsants         | 125                    | 2.3%                    | 125                     | 127                    | 0%                      |
|                               | Angiotensin II receptor blockers | 1436 | 26.2% | 1579 | 24.5% | 4% | 1436 | 26.2% | 1423 | 25.8% | 1% |
|                               | Aromatase inhibitors   | 34                     | 0.6%                    | 34                      | 35                     | 0%                      |
|                               | Aspirin                 | 172                    | 3.1%                    | 172                     | 180                    | 1%                      |
|                               | Antiplatelet agents    | 643                    | 11.7%                   | 643                     | 664                    | 1%                      |
|                               | Anticholinergic agents | 480                    | 8.8%                    | 480                     | 485                    | 0%                      |
|                               | Beta blockers           | 2564                   | 46.8%                   | 2564                    | 2572                   | 0%                      |
|                               | Bone calcium regulators | 54                     | 1.0%                    | 54                      | 52                     | 1%                      |
|                               | Benzodiazepine          | 953                    | 17.4%                   | 953                     | 950                    | 1%                      |

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| Drug Category                        | Unweighted data (N = 11,917) | Weighted data (N = 10,998)
|-------------------------------------|------------------------------|-----------------------------|
|                                     | Higher dose (n = 5,482) | Lower dose (n = 6,435) | Standardized difference | Higher dose (n = 5,482) | Lower dose (n = 5,516) | Standardized difference |
| Bisphosphonates                     | 652 (11.9%)                | 766 (11.9%)               | 0%                     | 652 (11.9%)                | 660 (12.0%)               | 0%                     |
| Beta agonist                        | 521 (9.5%)                 | 930 (14.5%)               | 15%                    | 521 (9.5%)                 | 525 (9.5%)                | 0%                     |
| Calcium                             | 68 (1.2%)                  | 85 (1.3%)                 | 1%                     | 68 (1.2%)                  | 70 (1.3%)                 | 1%                     |
| Calcium channel blocker             | 2558 (46.7%)               | 3070 (47.7%)              | 2%                     | 2558 (46.7%)               | 2658 (48.2%)              | 3%                     |
| Chemotherapeutic drugs              | 84 (1.5%)                  | 104 (1.6%)                | 1%                     | 84 (1.5%)                  | 88 (1.6%)                 | 1%                     |
| Cholinesterase inhibitors           | 387 (7.1%)                 | 551 (8.6%)                | 6%                     | 387 (7.1%)                 | 393 (7.1%)                | 0%                     |
| Glucocorticoid                       | 1621 (29.6%)               | 1912 (29.7%)              | 0%                     | 1621 (29.6%)               | 1651 (29.9%)              | 1%                     |
| Loop diuretics                      | 2389 (43.6%)               | 3185 (49.5%)              | 12%                    | 2389 (43.6%)               | 2443 (44.3%)              | 1%                     |
| Nitrates                            | 764 (13.9%)                | 1093 (17.0%)              | 9%                     | 764 (13.9%)                | 782 (14.2%)               | 1%                     |
| NSAIDS (excluding ASA)              | 406 (7.4%)                 | 351 (5.5%)                | 8%                     | 406 (7.4%)                 | 412 (7.5%)                | 0%                     |
| Opioids                             | 1186 (21.6%)               | 1453 (22.6%)              | 2%                     | 1186 (21.6%)               | 1214 (22.0%)              | 1%                     |
| Over-active bladder medication      | 247 (4.5%)                 | 263 (4.1%)                | 2%                     | 247 (4.5%)                 | 261 (4.7%)                | 1%                     |
| Insulin                             | 1086 (19.8%)               | 1322 (20.5%)              | 2%                     | 1086 (19.8%)               | 1168 (21.2%)              | 3%                     |
| Anti-psychotics                     | 425 (7.8%)                 | 607 (9.4%)                | 6%                     | 425 (7.8%)                 | 432 (7.8%)                | 0%                     |
| Proton pump inhibitors              | 2372 (43.3%)               | 3018 (46.9%)              | 7%                     | 2372 (43.3%)               | 2380 (43.2%)              | 0%                     |
| Oral prednisone                     | 296 (5.4%)                 | 401 (6.2%)                | 3%                     | 296 (5.4%)                 | 342 (6.2%)                | 3%                     |
| 5 alpha reductases                  | 239 (4.4%)                 | 276 (4.3%)                | 0%                     | 239 (4.4%)                 | 249 (4.5%)                | 0%                     |
| Selective serotonin reuptake inhibitors | 710 (13.0%)               | 1085 (16.9%)              | 11%                    | 710 (13.0%)               | 694 (12.6%)               | 1%                     |
| Statins                             | 3266 (59.6%)               | 3646 (56.7%)              | 6%                     | 3266 (59.6%)               | 3330 (60.4%)              | 2%                     |
| Thiazide diuretics                  | 913 (16.7%)                | 945 (14.7%)               | 5%                     | 913 (16.7%)                | 915 (16.6%)               | 0%                     |
| Allopurinol                         | 1035 (18.9%)               | 1079 (16.8%)              | 5%                     | 1035 (18.9%)               | 970 (17.6%)               | 3%                     |
| Oral antidiabetics                  | 1397 (25.5%)               | 1465 (22.8%)              | 6%                     | 1397 (25.5%)               | 1360 (24.6%)              | 2%                     |
| Number of unique drug names         | Mean ± SD: 9.8 ± 4.6       | Median (IQR): 9 (7-12)    | 11%                    | Mean ± SD: 9.8 ± 4.6       | Median (IQR): 9 (7-12)    | 2%                     |
|                                     | Mean ± SD: 9.8 ± 4.6       | Median (IQR): 9 (7-12)    | 11%                    | Mean ± SD: 9.8 ± 4.6       | Median (IQR): 9 (7-12)    | 2%                     |

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|                                      | Unweighted data (N = 11,917) |                      | Weighted data (N = 10,998) |                      |
|--------------------------------------|-----------------------------|----------------------|-----------------------------|----------------------|
|                                      | Higher dose                | Lower dose           | Standardized differencec   | Higher dose          | Lower dose           | Standardized differencec   |
|                                      | (n = 5,482)                | (n = 6,435)          |                             | (n = 5,482)          | (n = 5,516)          |                             |
| Number of unique dins                | Median (IQR)               | 10 (7-14)            | 11 (7-15)                   | 10 (7-14)            | 10 (7-14)            |                             |
| Healthcare use (365-day look back)j |                             |                      |                             |                      |                      |                             |
| GP/FP visits                         | Mean ± SD                  | 12.7                 | 12.7                        | 12.7                 | 12.7                 | 12.8                        | 11.2                        | 1%                          |
|                                      | Median (IQR)               | 9 (5-15)             | 9 (5-15)                    | 9 (5-15)             | 9 (5-15)             |                             |                             |                             |
| Nephrology Visits                   | Mean ± SD                  | 1.4                  | 2.5                         | 1.4                  | 2.5                  | 1.5                         | 2.5                         | 4%                          |
|                                      | Median (IQR)               | 0 (0-2)              | 0 (0-2)                     | 0 (0-2)              | 0 (0-2)              |                             |                             |                             |
| Number of hospitalizations           | Mean ± SD                  | 0.36                 | 0.8                         | 0.4                  | 0.8                  | 0.36                        | 0.77                        | 0%                          |
|                                      | Median (IQR)               | 0 (0-0)              | 0 (0-0)                     | 0 (0-0)              | 0 (0-0)              |                             |                             |                             |
| Number of emergency departments visits | Mean ± SD                  | 0.96                 | 1.57                        | 0.99                 | 1.6                  | 0.96                        | 1.57                        | 1%                          |
|                                      | Median (IQR)               | 0 (0-1)              | 0 (0-1)                     | 0 (0-1)              | 0 (0-1)              |                             |                             |                             |
| Number of serum creatinine tests     | Mean ± SD                  | 4.1                  | 3.8                         | 4.4                  | 3.9                  | 4.1                         | 3.8                         | 1%                          |
|                                      | Median (IQR)               | 3 (2-5)              | 3 (2-6)                     | 3 (2-5)              | 3 (2-5)              |                             |                             |                             |
| TSH test                             |                             | 3787                 | 69.1%                       | 4428                 | 68.8%                | 3810                        | 69.1%                       | 0%                          |
| At home physician service            |                             | 457                  | 8.3%                        | 640                  | 9.9%                 | 453                         | 8.2%                        | 0%                          |
| Bone mineral density test            |                             | 295                  | 5.4%                        | 311                  | 4.8%                 | 299                         | 5.4%                        | 0%                          |
| Cardiac catheterization              |                             | 77                   | 1.4%                        | 74                   | 1.1%                 | 78                          | 1.4%                        | 0%                          |
| Cardiac stress test                  |                             | 563                  | 10.3%                       | 628                  | 9.8%                 | 561                         | 10.2%                       | 0%                          |
| Carotid ultrasound                   |                             | 312                  | 5.7%                        | 349                  | 5.4%                 | 318                         | 5.8%                        | 0%                          |
| Chest-X ray                          |                             | 2458                 | 44.8%                       | 3293                 | 51.2%                | 2455                        | 44.5%                       | 1%                          |
| Cataract surgery                     |                             | 264                  | 4.8%                        | 273                  | 4.2%                 | 259                         | 4.7%                        | 0%                          |
| Cervical cancer screening            |                             | 92                   | 1.7%                        | 88                   | 1.4%                 | 84                          | 1.5%                        | 2%                          |

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| Procedure                                      | Higher dose (n = 5,482) | Lower dose (n = 6,435) | Standardized difference | Higher dose (n = 5,482) | Lower dose (n = 5,516) | Standardized difference |
|-----------------------------------------------|------------------------|------------------------|-------------------------|------------------------|------------------------|-------------------------|
| Colorectal cancer screening                   | 702 (12.8%)            | 672 (10.4%)            | 8%                      | 702 (12.8%)            | 689 (12.5%)            | 1%                      |
| Cholesterol test                               | 3503 (63.9%)           | 3894 (60.5%)           | 7%                      | 3503 (63.9%)           | 3566 (64.7%)           | 2%                      |
| CT abdomen                                     | 715 (13.0%)            | 711 (11.0%)            | 6%                      | 715 (13.0%)            | 733 (13.3%)            | 1%                      |
| CT extremities                                 | 56 (1.0%)              | 49 (0.8%)              | 2%                      | 56 (1.0%)              | 60 (1.1%)              | 1%                      |
| CT head                                        | 662 (12.1%)            | 883 (13.7%)            | 5%                      | 662 (12.1%)            | 666 (12.1%)            | 0%                      |
| CT neck                                        | 46 (0.8%)              | 42 (0.7%)              | 1%                      | 46 (0.8%)              | 50 (0.9%)              | 1%                      |
| CT pelvis                                      | 685 (12.5%)            | 686 (10.7%)            | 6%                      | 685 (12.5%)            | 699 (12.7%)            | 1%                      |
| CT spine                                       | 109 (2.0%)             | 127 (2.0%)             | 0%                      | 109 (2.0%)             | 114 (2.1%)             | 1%                      |
| CT thorax                                      | 311 (5.7%)             | 379 (5.9%)             | 1%                      | 311 (5.7%)             | 314 (5.7%)             | 0%                      |
| Echocardiography                               | 1401 (25.6%)           | 1625 (25.3%)           | 1%                      | 1401 (25.6%)           | 1404 (25.5%)           | 0%                      |
| Flu shot                                       | 2660 (48.5%)           | 2838 (44.1%)           | 9%                      | 2660 (48.5%)           | 2717 (49.3%)           | 2%                      |
| Cytoscopy                                      | 429 (7.8%)             | 374 (5.8%)             | 8%                      | 429 (7.8%)             | 454 (8.2%)             | 0%                      |
| Hearing test                                   | 234 (4.3%)             | 244 (3.8%)             | 3%                      | 234 (4.3%)             | 231 (4.2%)             | 0%                      |
| Mammography                                    | 272 (5.0%)             | 262 (4.1%)             | 4%                      | 272 (5.0%)             | 259 (4.7%)             | 1%                      |
| Prostate specific antigen (PSA) test           | 62 (1.1%)              | 51 (0.8%)              | 3%                      | 62 (1.1%)              | 55 (1.0%)              | 1%                      |
| Holter monitoring                              | 376 (6.9%)             | 466 (7.2%)             | 1%                      | 376 (6.9%)             | 374 (6.8%)             | 0%                      |
| Parathyroid hormone testing                    | 1491 (27.2%)           | 1779 (27.6%)           | 1%                      | 1491 (27.2%)           | 1512 (27.4%)           | 0%                      |
| Pulmonary function test                        | 433 (7.9%)             | 585 (9.1%)             | 4%                      | 433 (7.9%)             | 433 (7.9%)             | 0%                      |
| Vaginal smear                                  | 38 (0.7%)              | 50 (0.8%)              | 1%                      | 38 (0.7%)              | 34 (0.6%)              | 1%                      |
| Throat swab                                    | 64 (1.2%)              | 73 (1.1%)              | 1%                      | 64 (1.2%)              | 54 (1.0%)              | 2%                      |
| Sputum                                         | 18 (0.3%)              | 34 (0.5%)              | 3%                      | 18 (0.3%)              | 23 (0.4%)              | 2%                      |
| Urine culture                                  | 3833 (69.9%)           | 4189 (65.1%)           | 10%                     | 3833 (69.9%)           | 3896 (70.6%)           | 2%                      |

**Healthcare use (7-day look back)**

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### Unweighted data (N = 11,917)

| Procedure                  | Higher dose (n = 5,482) | Lower dose (n = 6,435) | Standardized difference$^c$ |
|----------------------------|-------------------------|------------------------|-----------------------------|
| CT abdomen                 | 29 (0.5%)               | 38 (0.7%)              | 1%                          |
| Chest-X ray                | 195 (3.6%)              | 318 (5.8%)             | 15%                         |
| Urine culture              | 981 (17.9%)             | 936 (17.0%)            | 3%                          |

### Weighted data (N = 10,998)$^b$

| Procedure                  | Higher dose (n = 5,482) | Lower dose (n = 5,516) | Standardized difference$^c$ |
|----------------------------|-------------------------|------------------------|-----------------------------|
| CT abdomen                 | 29 (0.5%)               | 38 (0.7%)              | 3%                          |
| Chest-X ray                | 195 (3.6%)              | 318 (5.8%)             | 10%                         |
| Urine culture              | 981 (17.9%)             | 936 (17.0%)            | 2%                          |

### Laboratory measurements

| Procedure                  | Mean ± SD | Median (IQR) | Median (IQR) | Median (IQR) |
|----------------------------|-----------|--------------|--------------|--------------|
| eGFR$^d$                   | 23.9 ± 5.0| 23.3 (21-28) | 23.9 (21-28) | 23.9 (21-28) |
| Most recent eGFR value     | 25 (21-28)| 24 (20-28)   | 25 (21-28)   | 25 (21-28)   |
| Urine ACR available        | 23 (21-28)| 24 (20-28)   | 25 (21-28)   | 25 (21-28)   |
| Baseline ACR categories, μg/mg | 2366 ± 43.2 | 2604 (40.5%) | 2366 (43.2%) | 2412 (43.7%) |
| Missing                    | 3116 (56.8%)  | 3831 (59.5%) | 3116 (56.8%) | 3104 (56.3%) |
| <30                        | 683 (12.5%)   | 682 (10.6%)   | 683 (12.5%)   | 655 (11.9%)   |
| 30-300                     | 947 (17.3%)   | 1033 (16.1%)  | 947 (17.3%)   | 961 (17.4%)   |
| >300                       | 736 (13.4%)   | 889 (13.8%)   | 736 (13.4%)   | 796 (14.4%)   |

Abbreviations: eGFR, estimated glomerular filtration rate; IQR, interquartile range; LHIN, Local Health Integration Network; ACR, urine albumin-to-creatinine ratio.

$^a$ Unless otherwise specified in the footnotes, baseline characteristics were assessed on the date the patient filled a fluoroquinolone prescription—the cohort entry date.

$^b$ Weighted using inverse probability of exposure weighting based on propensity scores. The propensity score was estimated using multivariable logistic regression with 121 covariates chosen a priori (defined in eTable 9 in the Supplement). Patients in the reference group were weighted as [propensity score/ (1 - propensity score)]. $^{40,42}$ This method produces a weighted pseudo-sample of patients in the reference group with the same distribution of measured covariates as the exposure group. $^{40,41}$

$^c$ The difference between the groups divided by the pooled SD; a value greater than 10% is interpreted as a meaningful difference. $^{43}$

$^d$ Income was categorized into fifths of average neighborhood income on the cohort entry date.

$^e$ Baseline comorbidities were assessed in the 5-year period before the cohort entry date.

$^f$ Cancer includes the following types of cancer: skin, mouth (lip, tonsil, etc), throat, stomach, small/large intestine, liver, gall bladder, pancreas, breast, male/female reproductive organs, heart, lung, bone, urinary system (kidney, bladder, etc), endocrine glands, as well as leukemias and lymphomas.

$^g$ Presence of kidney disease is a variable in the Charlson comorbidity index, which automatically results in all individuals receiving a minimum score of 2. Individuals with a Charlson comorbidity index of 0 were given a score of 2, and individuals with a score of 1 were given a score of 3.

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Medication use was examined in the 120-day period before the cohort entry date (the Ontario Drug Benefit program dispenses a maximum 100-day supply).

Glucocorticoids included many medications regardless of their route of administration such as hydrocortisone acetate, dexamethasone, beclomethasone dipropionate, prednisone, hydrocortisone, flumetasone pivalate, clobetasol propionate, prednisone & betamethasone valerate, betamethasone, triamcinolone acetonide, triamcinolone diacetate, triamcinolone, flurandrenolide, betamethasone & dexamethasone sodium phosphate, cortisone acetate, dexamethasone tebulate, prednisolone, dexamethasone, corticotrophin, prednisolone acetate, fluocinolone acetonide, hydrocortisone sodium succinate, methylprednisolone sodium succinate, methylprednisolone acetate, methylprednisolone disodium phosphate, methylprednisolone, fluocinolone, betamethasone disodium phosphate, medrysone & polyvinyl alcohol, prednisolone acetate & sulfacetamide sodium, dexamethasone & neomycin sulfate & polymyxin b sulfate, clobetasol propionate & acetic acid & benzethonium chloride & hydrocortisone, clobetasol propionate & gentamycin sulfate, fluocinolone acetonide, dexamethasone & neomycin sulfate, hydrocortisone & lidocaine hcl & neomycin sulfate, haemorrhoidal veinous plexus, prednisone & pheniramine maleate & inositol & phosphatidyl choline & vitamin a & vitamin d2& vitamin e, chloramphenicol & hydrocortisone acetate, haemorrhoidal veinous plexus, dexamethasone & framycetin sulfate & gramicidin, dibucaine hcl & esculin & framycetin sulfate & hydrocortisone, betamethasone valerate & neomycin sulfate, betamethasone valerate & gentamicin sulfate, prednisolone acetate & sulfacetamide sodium, ascorbic acid & chlorpheniramine maleate & prednisolone acetate, neomycin sulfate & prednisolone acetate & sulfacetamide sodium, gramicidin & neomycin sulfate & triamcinolone acetonide, methylprednisolone, acetylsalicylic acid & methyltestosterone, methylprednisolone sulfate & neomycin sulfate, hydrocortisone acetate & neomycin sulfate, aluminum chlorohydrate & methylprednisolone acetate & neomycin sulfate & sulfur, gramicidin & neomycin sulfate & nystatin & triamcinolone acetonide, hydrocortisone acetate & zinc oxide, hydrocortisone acetate & pramoxine hcl & zinc sulfate, aluminum chlorohydrate & methylprednisolone acetate & sulfur, hydrocortisone acetate & zinc oxide, hydrocortisone acetate & pramoxine hcl & zinc sulfate, desonide, clobetasol propionate, beclomethasone dipropionate & clobetasol, bacitracin zinc & hydrocortisone & neomycin sulfate & polymyxin b sulfate, hydrocortisone & neomycin sulfate & polymyxin b sulfate, gramicidin & neomycin sulfate & nystatin & triamcinolone acetonide, flurometholone & polyvinyl alcohol, aluminum chloride & methylprednisolone acetate & sulfur, flurometholone, lidocaine hcl & methylprednisolone acetate, flumetasone pivalate & salicylic acid, fluorometholone, lidocaine hcl & methylprednisolone acetate, aclometasone dipropionate, allantoin & chloramphenicol & hydrocortisone, amcinonide, atropine sulfate & prednisolone acetate, bacitracin & hydrocortisone & neomycin sulfate & polymyxin b sulfate, benzalkonium & dexamethasone & tobramycin, benzocaione & hydrocortisone acetate & zinc sulfate, betamethasone & sulfacetamide sodium, betamethasone acetate & betamethasone sodium phosphate, betamethasone benzoate, betamethasone dipropionate, betamethasone dipropionate & calcipotriene, betamethasone dipropionate & clotrimazole, betamethasone dipropionate & gentamicin sulfate, betamethasone dipropionate & salicylic acid, betamethasone disodium phosphate, betamethasone valerate & salicylic acid, betamethasone valerate & gentamicin sulfate, betamethasone valerate & neomycin sulfate, budesonide, camphor & hydrocortisone & menthol, chlorbutol & dexamethasone & tobramycin, ciclesonide.

Total number of healthcare visits/tests in the 12-month period before the cohort entry date.

Total number of healthcare visits/tests in the 7-day period before the cohort entry date.

The most recent eGFR measurement in the 365 day period before the cohort entry date; eGFR was calculated using the Chronic Kidney Disease (CKD)—Epidemiology (EPI) equation: $\text{eGFR} = 141 \times \min[\text{serum creatinine concentration in } \mu\text{mol}/L/88.4]/\alpha,\ 1]^{1.209} - 0.993 \times 0.7 \times 1.159 \times 0.85$ if female and under 0.9 if male; $\alpha=0.329$ if female and -0.411 if male; min=the minimum of serum creatinine concentration/x or 1; max=the maximum of serum creatinine concentration/x or 1. All patients were assumed not to be of African-Canadian race; African-Canadians represented less than 5% of the population of Ontario in 2006.

eTable 12. Post Hoc Survival Analysis in Older Adults With Advanced Chronic Kidney Disease Within 14 Days of Starting a New Prescription for a Higher- Vs Lower-Dose Fluoroquinolone: Risk of a Hospital Visit With Nervous System and/or Psychiatric Disorders, Hypoglycemia, or a Collagen-Associated Event

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| Fluoroquinolone dose | Unweighted | Weighted<sup>a</sup> |
|----------------------|------------|----------------------|
|                      | No. patients | No. events (%) | Event rate per 1000 person-years | No. patients | No. events (%) | Event rate Per 1000 person-years | Hazard ratio (95% CI) |
| Exposure             | Higher-dose<sup>b</sup> | 5482 | 68 (1.2) | 327.8 | 5482 | 68 (1.2) | 327.8 | 1.45 (1.01 to 2.09)<sup>c</sup> |
| Referent             | Lower-dose<sup>b</sup> | 6435 | 67 (1.0) | 276.7 | 5516 | 47 (0.85) | 225.0 | |

<sup>a</sup>Inverse probability of treatment weighting on the propensity score was used to balance comparison groups on indicators of baseline health. The propensity score was estimated using multivariable logistic regression with 121 covariates chosen <i>a priori</i> (defined in eTable 9 in the Supplement). Patients in the reference group were weighted as [propensity score/ (1 - propensity score)]. This method produces a weighted pseudo-sample of patients in the reference group with the same distribution of measured covariates as the exposed group.<sup>40,41</sup>

<sup>b</sup>Higher-dose: ciprofloxacin 501 to 1000 mg/day, levofloxacin 501 to 750 mg/day, or norfloxacin 401 to 800 mg/day. Lower-dose fluoroquinolone: ciprofloxacin 500 mg/day, levofloxacin 250 to 500 mg/day, or norfloxacin 400 mg/day.

<sup>c</sup>We used a Cox proportional hazards regression (with 14-day follow-up censoring on death) to estimate the 14-day risk of a hospital admission or emergency department visit with nervous system and/or psychiatric disorders, hypoglycemia, or a collagen-associated event.

<sup>eTable 13</sup>. Risk of Heart Failure in Older Adults With Advanced Chronic Kidney Disease Within 14 Days of Starting a New Prescription for a Higher-vs Lower-Dose Fluoroquinolone<sup>a</sup>
| Outcome                                      | Unweighted No. events (%) fluoroquinolone dose | Weighted<sup>b</sup> No. events (%) fluoroquinolone dose | Risk difference, % (95% CI) | Risk ratio (95% CI) |
|----------------------------------------------|-----------------------------------------------|--------------------------------------------------------|-----------------------------|---------------------|
| Higher dose                                 | Lower dose                                    |                                                        |                             |                     |
| (n = 5,482)                                  | (n = 6,435)                                   | (n = 5,482)                                             | (n = 5,516)                 |                     |
| Hospital admission with heart failure (main diagnosis) | 22 (0.40)                                     | 27 (0.42)                                              | 22 (0.40)                   | 21 (0.37)           | 0.03 (-0.20 to 0.26) | 1.07 (0.59 to 1.95) |

<sup>a</sup> Higher-dose: ciprofloxacin 501 to 1000 mg/day, levofloxacin 501 to 750 mg/day, or norfloxacin 401 to 800 mg/day. Lower-dose fluoroquinolone: ciprofloxacin 500 mg/day, levofloxacin 250 to 500 mg/day, or norfloxacin 400 mg/day.

<sup>b</sup>The propensity score was estimated using multivariable logistic regression with 121 covariates chosen <em>a priori</em> (defined in eTable 9 in the Supplement).<sup>40-42</sup> Patients in the reference group were weighted as [propensity score/(1 - propensity score)].<sup>40-42</sup> This method produces a weighted pseudo-sample of patients in the reference group with the same distribution of measured covariates as the exposed group.<sup>40,41</sup> Weighted risk ratios and 95% CIs were obtained using modified Poisson regression<sup>44</sup> and weighted risk differences and 95% CIs were obtained using a binominal regression model with an identity link function.
**eTable 14.** Risk of a Hospital Visit With Nervous System and/or Psychiatric Disorders, Hypoglycemia, or a Collagen-Associated Event in Older Adults With Advanced Chronic Kidney Disease Within 14 Days of Starting a New Prescription for a Higher- vs Lower-Dose Fluoroquinolone<sup>a</sup> Using Fine Stratification Weighting<sup>b</sup>

| Outcome                                                                 | Unweighted No. events (%) | Weighted No. events (%) | Risk difference, % (95% CI) | Risk ratio (95% CI) |
|-------------------------------------------------------------------------|---------------------------|-------------------------|-----------------------------|--------------------|
| Higher dose fluoroquinolone dose                                        | Higher dose               | Lower dose              | Higher dose                 | Lower dose         |
| (n = 5,482)                                                             | (n = 6,435)               | (n = 5,480)             | (n = 6,411)                 |                    |
| Hospital visit with nervous system and/or psychiatric disorders, hypoglycemia, or a collagen-associated event | 68 (1.2)                  | 67 (1.0)                | 68 (1.2)                    | 54 (0.84)          | 0.39 (0.02 to 0.77) | 1.47 (1.02 to 2.11) |

<sup>a</sup> Higher dose: ciprofloxacin 501 to 1000 mg/day, levofloxacin 501 to 750 mg/day, or norfloxacin 401 to 800 mg/day. Lower-dose fluoroquinolone: ciprofloxacin 500 mg/day, levofloxacin 250 to 500 mg/day, or norfloxacin 400 mg/day.

<sup>b</sup> This weighting method does not use the propensity score directly to calculate weights; instead, propensity scores are used to create fine stratum after ranking only the exposed patients (ciprofloxacin 501 to 1000 mg/day, levofloxacin 501 to 750 mg/day, or norfloxacin 401 to 800 mg/day) based on the propensity score and assigning unexposed patients (ciprofloxacin 500 mg/day or levofloxacin 250 to 500 mg/day or norfloxacin 400 mg/day) to these strata based on their propensity score. The weights for the exposed group are set to 1 and reference patients are re-weighted based on the number of exposed patients residing within their stratum, so that unexposed patients contribute proportionally to the relative number of total patients within a stratum. Patients in the unexposed group are weighted as \((\frac{N_{exposed \ in \ PS \ stratum}}{N_{total \ exposed}}) / (\frac{N_{unexposed \ in \ PS \ stratum}}{N_{total \ unexposed}})\). This weighting creates a pseudo-population in which confounder distribution concordance is achieved between the exposed and unexposed groups, to the extent that it is achieved within each stratum. As a result, extreme weights due to propensity scores that are very close to 0 or 1 are unlikely. This method calculates a treatment effect estimate similar to the propensity score matching estimate (i.e., an average treatment effect among the treated population, ATT).45,46

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eFigure 1. Flow Diagram of Cohort Build

**Source population** (N = 1,277,043)
Older adults in Ontario newly prescribed an oral fluoroquinolone as outpatients from January 1, 2008, to March 17, 2020

**Patients excluded from the study** (N = 1,265,126)
- Died on the fluoroquinolone dispensing date, or non-Ontario resident (data cleaning), n = 1282
- Age less than 66 years on the fluoroquinolone dispensing date, n = 55,229
- Prescription for any fluoroquinolone in the prior 180 days, n = 278,627
- Prescription of unusual dose of fluoroquinolone (ciprofloxacin <500 mg/day or >1000 mg/day; norfloxacin <400 mg/day or >800 mg/day; levofloxacin <250 mg/day or >750 mg/day), n = 21,860
- Prescription of more than one fluoroquinolone on index date, n = 158
- Kidney failure, n = 14,990
- Hospital discharge or emergency department visit in the 2-day period before the fluoroquinolone dispensing date, n = 229,930
- Patients without an outpatient baseline serum creatinine value in the year before the fluoroquinolone dispensing date, n = 302,629
- Baseline eGFR ≥ 30 mL/min per 1.73m², n = 360,421

**Patients included in the study** (N = 11,917)
Older adults with an eGFR < 30 mL/min per 1.73m² newly prescribed an oral fluoroquinolone
Higher dose, N = 5,482 (46.0%)
Lower dose, N = 6,435 (54.0%)

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**Figure 2.** e-Value Analysis to Assess the Extent of Unmeasured Confounding That Would Be Required to Negate the Observed Results

E-value for point estimate: 2.26 and for confidence interval: 1.11
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