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# BMJ Open

## Oral fluoroquinolone type and risk of serious ventricular arrhythmia: a population-based study in Korea

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4 **Oral fluoroquinolone type and risk of serious ventricular arrhythmia: a population-based study**  
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## Abstract

**Objective:** To evaluate whether oral ciprofloxacin, levofloxacin, ofloxacin, and moxifloxacin increase the risk of ventricular arrhythmia in the general population of Korea.

**Design:** Population-based cohort study using administrative claims data on a national scale in Korea

**Setting:** Korean nationwide study from January to December 2015

**Participants:** Patients who were prescribed the relevant study medications at outpatient visits

**Primary outcome measures:** Each group of patients prescribed ciprofloxacin, levofloxacin, ofloxacin, and moxifloxacin was compared with the group prescribed cefixime to assess the risk of serious ventricular arrhythmia (ventricular tachycardia, fibrillation, flutter and cardiac arrest). Using logistic regression analysis with inverse probability treatment weighting, odds ratios and 95% confidence intervals for serious ventricular arrhythmia were calculated during days after the commencement of antibiotic use.

**Results:** During the study period, 4,888,890 of patients were prescribed the study medications. They included 1,466,133 users of ciprofloxacin, 1,141,961 users of levofloxacin, 1,830,786 users of ofloxacin, 47,080 users of moxifloxacin and 402,930 users of cefixime. There was no evidence of increased serious ventricular arrhythmia related to the prescription of ciprofloxacin, levofloxacin and ofloxacin, whereas the odds ratio of serious ventricular arrhythmia after the prescription of moxifloxacin was 1.87 (95% confidence interval, 1.15-3.11) compared to cefixime.

**Conclusions:** Ciprofloxacin, levofloxacin, and ofloxacin were not associated with increased risk of serious ventricular arrhythmia. Moxifloxacin increased the risk of serious ventricular arrhythmia.

**Strengths and limitations of this study**

- This study is a nationwide population-based study including 4,888,890 of patients who were prescribed oral fluoroquinolone or cefixime.
- This is the largest study to date evaluating the association between oral fluoroquinolone use and serious ventricular arrhythmia
- This study adjusted the underlying characteristics and indications of antibiotics of both fluoroquinolone and cefixime groups using propensity score weighting.
- This study did not reflect baseline health information such as laboratory data or ECG because we used health claims data.
- Number of deaths that occurred in the follow up period could not be investigated.

## Introduction

Fluoroquinolone is a broad-spectrum antibiotic prescribed for various infectious diseases. Common adverse effects of fluoroquinolones include gastrointestinal symptoms such as diarrhea and nausea, and central nervous system side effects, such as headache and dizziness.[1] These side effects are mild and fluoroquinolone is mostly used safely. However, rare but serious adverse effects that have been reported include tendon rupture, retinal detachment, aortic aneurysm, and aortic dissection.[2–8]

Fluoroquinolone also has cardiac side effects. Several studies have reported QT interval increases after fluoroquinolone use,[9–14] which can lead to ventricular arrhythmia. Case reports of torsades de pointes occurrence associated with fluoroquinolone use have also been reported.[15–19] Several population based studies also reported that fluoroquinolone increases the risk of ventricular arrhythmia or sudden cardiac death.[20–22] Despite these reports, the association of fluoroquinolones with arrhythmia remains contentious. A recent observation study in Denmark and Sweden reported that oral fluoroquinolone treatment was not associated with the risk of serious arrhythmia.[23] This study compared 909,656 fluoroquinolone users with 909,656 penicillin V users and obtained statistical power. However, most prescribed fluoroquinolone was ciprofloxacin and risk of arrhythmia according to the antibiotic type was not determined. Previous studies have reported the risk of arrhythmia by type of fluoroquinolone, but the results differed for each study.

To provide clarity to this issue, we exploited a large general population database in Korea to examine whether oral ciprofloxacin, levofloxacin, ofloxacin, and moxifloxacin increase the risk of ventricular arrhythmia compared to cefixime.

## Methods

### *Study design*

The population-based cohort study involved patients who had been prescribed oral

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4 fluoroquinolones (ciprofloxacin, levofloxacin, ofloxacin, moxifloxacin) or cefixime in the outpatient  
5 department from 01 January 2015 to 31 December 2015. To reduce potential confounding by  
6 indication, oral cefixime was used as a control. Both fluoroquinolones and cefixime are frequently  
7 prescribed for respiratory diseases and urinary tract infections in Korea. Cefixime is a medication  
8 without any pro-arrhythmic effects and is not in the list of drug-induced QT prolongation or torsades  
9 de pointes.[24–29]  
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### 19 *Data Source and Ethics*

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22 We analyzed the claim data of Health Insurance and Review Assessment (HIRA) in South Korea.  
23 HIRA is responsible for the examination of the claimed medical expenses data received from the  
24 National Health Insurance (NHI) and the appropriateness of medical care benefits.[30] NHI covers  
25 almost 98% (about 50 million) of the Korean population.[31] HIRA claims data include  
26 comprehensive information related to medical services, such as treatment, medicines, procedures and  
27 diagnostics of inpatients and outpatients.[30] In the HIRA database, all personally identifiable  
28 information was removed from the data sets and anonymized codes representing each patient were  
29 included for privacy protection. This study was approved by the institutional review board of Jeju  
30 National University Hospital with informed consent waived. (IRB No. JEJUNUH 2017-01-013)  
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### 44 *Inclusion criteria and exposures*

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46 We included adult patients older than 18 years. Only the first prescribed study medication was  
47 included in the analysis if the patient was prescribed more than one antibiotic during study period.  
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### 53 *Exclusion criteria*

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56 We excluded the patients who were hospitalized within 30 days before the index date which was  
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4 defined as the first prescription date of the study medication. We also excluded the patients prescribed  
5 any antibiotics from 30 days before the index date, prescribed medication associated with QT interval  
6 prolongation or increased risk for developing torsades de pointes from 30 days before the index date  
7 to 30 days after the index date, and who were already diagnosed serious ventricular arrhythmia before  
8 the index date.  
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### 13 14 15 16 17 *Outcome definition*

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20 The outcome of serious ventricular arrhythmia included ventricular tachycardia, fibrillation, flutter,  
21 and cardiac arrest. The International Classification of Diseases, Tenth Revision [ICD-10] codes (I472,  
22 I490.x, I460, I461, and I469) were used to identify the patients with serious ventricular arrhythmia.  
23 Only the main diagnostic codes were used. The first diagnosis was included when the patients had  
24 diagnosis codes of serious ventricular arrhythmia more than once. Because it is generally  
25 recommended to prescribe fluoroquinolone and cefixime for 7~14 days, we used observation periods  
26 of 1~7 days and 8~14 days after the index date to evaluate the adverse effect of the medications. This  
27 reflects that the acute side effect of the drug develops during the actual administration period. Follow-  
28 up started on the index date and ended on the date of serious arrhythmia, or 14 days after start of  
29 treatment, whichever came first.  
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### 43 *Covariates*

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46 Covariates were defined by ICD-10 codes. (Supplementary Appendix) Included diseases were  
47 hypertension, diabetes mellitus, acute myocardial infarction, ischemic heart disease, cardiomyopathy,  
48 valve disorder, arrhythmia, congestive heart failure, congenital heart disease, cancer, cerebrovascular  
49 disease, renal disease, arterial disease, venous thromboembolism, dementia, rheumatic disease, peptic  
50 ulcer disease, and chronic lung disease. Indications of antibiotics were identified by primary diagnosis  
51 codes of index date. Diagnosis of infections included as covariates were upper respiratory infection,  
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4 pneumonia, other respiratory infection, gastrointestinal infection, urinary tract infection, genitourinary  
5 tract infection, and skin/wound infection.  
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### 10 11 *Statistical analyses* 12

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14 The number of serious ventricular arrhythmia was identified and the incidence per 1,000,000 patients  
15 was calculated. Each group of patients prescribed ciprofloxacin, levofloxacin, ofloxacin, and  
16 moxifloxacin was compared with the group prescribed cefixime to assess the risk of ventricular  
17 arrhythmia. Using logistic regression with inverse probability treatment weighting (IPTW), we  
18 calculated the odds ratio (OR) and 95% confidence interval (CI) of serious ventricular arrhythmia  
19 compared to cefixime during days 1~7 and 8~14 after the index date.  
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26 We calculated propensity scores of being prescribed ciprofloxacin, levofloxacin, ofloxacin, and  
27 moxifloxacin compared to cefixime using logistic regression. Age, sex, the prescription month, all  
28 covariates related comorbidities, and indications of antibiotics were included in the propensity models.  
29 Then, inverse probability treatment weights are calculated with propensity scores to adjust for  
30 baseline differences and control for confounding by indication.[32] IPTW weighs the inverse of the  
31 estimated propensity score for treated patients and the inverse of one minus the estimated propensity  
32 score for control patients.[33] Propensity score matching has the disadvantage of including only a  
33 subset of subjects and controls in the analysis, but IPTW can be used without reducing samples. We  
34 evaluated the balance of baseline covariates between groups with standardized differences before and  
35 after IPTW. The standardized difference <0.1 indicate that covariates are well balanced between  
36 treatment and control patients.[34]  
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49 As subgroup analysis we divided patients by age, sex, and history of cardiovascular disease. Acute  
50 myocardial infarction, ischemic heart disease, cardiomyopathy, valve disorder, arrhythmia, congestive  
51 heart failure, and congenital heart disease were included in cardiovascular disease. We defined  
52 cardiovascular disease using the same ICD-10 code as that used to define baseline comorbidities. The  
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propensity score of each subgroup and drug type was calculated and the odds ratios were calculated, respectively. Statistical analyses were performed using R version 3.1.1 ([www.R-project.org](http://www.R-project.org)).

## Results

### *Characteristics of the study population*

We extracted 5,401,527 outpatients who were prescribed oral fluoroquinolones and cefixime from 01 January 2015 to 31 December 2015. After excluding 512,637 patients, 4,888,890 patients were included in the analysis. (Figure 1) The study population consisted of 1,466,133 users of ciprofloxacin, 1,141,961 users of levofloxacin, 1,830,786 users of ofloxacin, 47,080 users of moxifloxacin and 402,930 users of cefixime.

The baseline characteristics of study population are presented in Table 1. Compared with cefixime users, moxifloxacin users were older and had more comorbidities. Users of ciprofloxacin, levofloxacin, and ofloxacin had similar baseline comorbidities with users of cefixime, except that chronic lung disease was less prevalent in ciprofloxacin and ofloxacin users, and cancer was less prevalent in ofloxacin users.

### *Development of serious ventricular arrhythmia*

The incidence of serious ventricular arrhythmia and weighted ORs during days 1~7 after initiation of the prescription are presented in Table 2. ORs of serious ventricular arrhythmia compared to cefixime were 0.72 (95% CI, 0.49-1.06), 0.92 (0.66-1.29), 0.41 (0.27-0.61), 1.87 (1.15-3.11) for ciprofloxacin, levofloxacin, ofloxacin, and moxifloxacin, respectively. Overall, ciprofloxacin, levofloxacin and ofloxacin had no increased risk, whereas moxifloxacin had 1.87-fold increased risk of serious ventricular arrhythmia.

The incidence of serious ventricular arrhythmia and weighted OR during the 8~14 days after prescription are presented in table 3. ORs of serious ventricular arrhythmia compared to cefixime

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4 were 0.44 (95% CI, 0.29-0.65), 1.08 (95% CI, 0.70-1.69), 0.58 (95% CI, 0.36-0.92), 1.78 (95% CI,  
5 0.86-3.88) for ciprofloxacin, levofloxacin, ofloxacin, and moxifloxacin, respectively. Overall, all of  
6 four fluoroquinolones had no increased risk of serious ventricular arrhythmia.  
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### 10 11 12 13 *Subgroup analyses*

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16 Table 4 shows weighted ORs of serious ventricular arrhythmia 1~7 days after prescription of  
17 ciprofloxacin, levofloxacin, ofloxacin, and moxifloxacin compared to cefixime according to the  
18 history of cardiovascular disease, age, and gender. The risk of serious ventricular arrhythmia in  
19 ciprofloxacin, levofloxacin, and ofloxacin users did not differ significantly from that in cefixime users.  
20 Moxifloxacin users with a history of cardiovascular disease and those who were older had increased  
21 risk of serious ventricular arrhythmia compared to cefixime.  
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### 31 **Discussion**

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34 The general population data reveal that ciprofloxacin, levofloxacin, and ofloxacin use were not  
35 associated with increased risk of serious ventricular arrhythmia. Moxifloxacin use showed increased  
36 risk of serious ventricular arrhythmia. Moxifloxacin use was associated with a 1.87-fold increased risk  
37 of serious ventricular arrhythmia compared to cefixime during the first week after the drug was  
38 initiated. Especially, the risk of ventricular arrhythmia was high in moxifloxacin users who were older  
39 or who had cardiovascular disease.  
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47 In study of veterans in the United States,[21] levofloxacin use was associated with a 3.13-fold  
48 increased risk of cardiac arrhythmias compared to amoxicillin. But, levofloxacin use also showed  
49 increased risk of all-cause death, indicating that the baseline condition was more severe in the  
50 levofloxacin group compared to amoxicillin and that the study results were confounded. A recent  
51 cohort study in Denmark and Sweden[23] did not find an association of fluoroquinolone use and  
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4 serious arrhythmia in the general population. But, since 82% of the prescribed fluoroquinolones were  
5 ciprofloxacin, it cannot be ruled out that other fluoroquinolones could increase the risk. In a US study  
6 of a Tennessee Medicaid cohort,[35] patients who took ciprofloxacin and levofloxacin did not show  
7 increased risk of cardiovascular death compared to patients who took amoxicillin during a 10-day  
8 treatment course. A cohort study from Taiwan[22] that studied the risks of cardiac arrhythmia among  
9 patients using moxifloxacin, levofloxacin, and ciprofloxacin reported that moxifloxacin use was  
10 associated 3.30-fold increased risk for ventricular arrhythmia compared to amoxicillin-clavulanate,  
11 with no risk associated with levofloxacin and ciprofloxacin use. These data combined with our study  
12 reinforce the view that ciprofloxacin and levofloxacin are not associated with ventricular arrhythmia,  
13 while moxifloxacin seems to be associated with an increased risk. There is no published study about  
14 the risk of ofloxacin. Presently, ofloxacin use was not associated with serious ventricular arrhythmia.

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16 Medications can cause QT interval prolongation, which can lead to fatal ventricular arrhythmias,  
17 such as torsades de pointes.[27,28] Torsades de pointes is a polymorphic ventricular tachycardia,  
18 which can lead to ventricular fibrillation or sudden cardiac death. Drug-induced QT interval  
19 prolongation occurs by inhibition of cardiac voltage-gated potassium channels encoded by human  
20 ether-a-go-go-related gene (HERG).[36] Blockade of rapid component of delayed rectifier potassium  
21 current ( $I_{Kr}$ ) through HERG channel delays cardiac repolarization, represented by QT interval  
22 prolongation.

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24 Among medications considered to be associated with QT interval prolongation, fluoroquinolones  
25 and macrolides are the most commonly prescribed drugs in the clinical practices.[24] However, QT  
26 interval prolongation of fluoroquinolones appears to be different depending on the type. A prospective  
27 trial suggested that recommended doses of ciprofloxacin and levofloxacin have little effect on QT  
28 intervals, while moxifloxacin induces the greatest QT interval prolongation.[10] After 7 days of  
29 moxifloxacin use, the QTc interval was prolonged by 6 ms (millisecond) relative to baseline. On  
30 supratherapeutic dose of fluoroquinolones, all three fluoroquinolones increased QT interval compared  
31 to placebo, with moxifloxacin having the greatest effect on the interval.[11] Mean of increased QT

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4 interval for the 24-hour period after treatment were 2.3 ms to 4.9 ms, 3.5 ms to 4.9 ms, and 16.3 ms to  
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6 17.8 ms for ciprofloxacin 1500mg, levofloxacin 1000mg, and moxifloxacin 800mg, respectively.  
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8 There has not been published study about the effect of ofloxacin on QT interval. However, ofloxacin,  
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10 ciprofloxacin and levofloxacin were significantly less potent inhibitor of the HERG channel than  
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12 sparfloxacin, grepafloxacin, and moxifloxacin.[37] Ofloxacin was the least potent inhibitors of the  
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14 HERG channel. In contrast, sparfloxacin and grepafloxacin, which is the most potent HERG channel  
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16 inhibitors, were withdrawn from the market due to QT interval prolongation. Overall, standard doses  
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18 of ciprofloxacin, levofloxacin, and ofloxacin have low effect on increased QT interval, whereas  
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20 moxifloxacin has the highest effect on increased QT interval.  
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23 There are some case reports of torsades de pointes after fluoroquinolone use.[15–19] Most of the  
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25 cases were developed in patients with concomitant use of other medications associated QT interval  
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27 prolongation or with multiple risk factors of drug-induced arrhythmia. The risk factors of drug-  
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29 induced arrhythmia are baseline QT interval prolongation, rapid intravenous infusion of drug, digitalis  
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31 therapy, bradycardia, organic heart disease, and electrolyte imbalance.[36] Our study excluded  
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33 patients prescribed drug-associated QT interval prolongation and we just examined oral  
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35 fluoroquinolone.  
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38 This study has several limitations. First, we cannot rule out the effect of selection bias. We tried to  
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40 adjust the underlying characteristics and indications of antibiotics of both fluoroquinolone and  
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42 cefixime groups using IPTW to correct for this selection bias. However, it is possible that the ICD-10  
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44 codes to define covariates used in the propensity score were not appropriate. For example, the range  
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46 of chronic lung disease that we have defined is so wide that 40 to 70 percent of each antibiotic group  
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48 has chronic lung disease. This inadequately reflects the impact of chronic lung disease on actual  
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50 antibiotic prescriptions. Second, there may be an effect of residual confounding. This study did not  
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52 reflect baseline health information such as laboratory data or ECG because we used health claims data.  
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54 However, we tried to reduce residual confounding by excluding patients who were recently admitted,  
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56 or prescribed antibiotics, and those who were prescribed medications related to QT interval  
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4 prolongation. Third, the ICD-10 code to define the outcome serious ventricular arrhythmia was not  
5 directly validated in the Korean population. In one study, however, ICD-9 427.x predicted a  
6 ventricular arrhythmia with a positive predictive value of 78 to 100 percent.[38] ICD-9 code 427.x  
7 corresponds to the ICD-10 code used in our study. Fourth, because death data were not linked in  
8 HIRA data, number of deaths that occurred in the follow up period was not confirmed.  
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### 17 **Conclusion**

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20 In this population-based study, ciprofloxacin, levofloxacin, and ofloxacin were not associated with  
21 serious ventricular arrhythmia. Moxifloxacin was associated with a 1.87-fold increased risk of serious  
22 ventricular arrhythmia compared to cefixime. Additional studies are needed in other populations to  
23 ensure that these findings are valid.  
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### 34 **Contributors**

35  
36  
37 Y.C contributed to the design of the study, cleaned and analyzed the data, interpreted the data, and  
38 drafted and revised the paper.  
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41 H.P contributed to the design of the study, interpreted the data, and critically revised the paper.  
42  
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None

## Competing interests

All authors: There are no competing interests.

## Data sharing

HIRA data are third-party data not owned by the authors. Raw data can be accessed with permission from Health Insurance Review and Assessment Service (HIRA) in Korea.

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## Tables and Figure Legends

Table 1. Baseline characteristics of patients using study medications

Table 2. Risk of serious ventricular arrhythmia associated with oral fluoroquinolones compared to cefixime during the days 1~7 after the index date

Table 3. Risk of serious ventricular arrhythmia associated with oral fluoroquinolones compared to cefixime during the days 8~14 after the index date

Table 4. Subgroup analysis of the risk of serious ventricular arrhythmia associated with study oral fluoroquinolones compared to cefixime during the days 1 to 7 after the index date

Figure 1. Study flow diagram

Table 1. Baseline characteristics of patients using study medications

	Cefixime	Ciprofloxacin	Levofloxacin	Ofloxacin	Moxifloxacin
Subjects, No.	402930	1466133	1141961	1830786	47080
Age, mean $\pm$ SD	49.3 $\pm$ 17.7	48.5 $\pm$ 17.3	50.4 $\pm$ 16.7	50.3 $\pm$ 16.9	58.4 $\pm$ 17.4
Female sex, No. (%)	238329 (59.1)	951813 (64.9)	643076 (56.3)	1120119 (61.2)	23586 (50.1)
<i>Comorbidities, No. (%)</i>					
Hypertension	121529 (30.2)	410360 (28.0)	346918 (30.4)	540934 (29.5)	21690 (46.1)
Diabetes mellitus	97779 (24.3)	321483 (21.9)	268447 (23.5)	382877 (20.9)	17977 (38.2)
Acute myocardial infarction	6536 (1.6)	17451 (1.2)	15209 (1.3)	11731 (1.0)	1292 (2.7)
Ischemic heart disease	45810 (11.4)	137303 (9.4)	122740 (10.7)	161602 (8.8)	9408 (20)
Cardiomyopathy	1450 (0.4)	3668 (0.3)	3443 (0.3)	3924 (0.2)	438 (0.9)
Valve disorder	1826 (0.5)	4971 (0.3)	4643 (0.4)	6219 (0.3)	513 (1.1)
Arrhythmia	14387 (3.6)	45727 (3.1)	38751 (3.4)	53536 (2.9)	2761 (5.9)
Congestive heart failure	21753 (5.4)	59507 (4.1)	55276 (4.8)	68471 (3.7)	5724 (12.2)
Congenital heart disease	550 (0.1)	1599 (0.1)	1430 (0.1)	1894 (0.1)	110 (0.2)
Cancer	43336 (10.8)	128612 (8.8)	118618 (10.4)	122116 (6.7)	10285 (21.8)
Cerebrovascular disease	42741 (10.6)	127394 (8.7)	113241 (9.9)	155453 (8.5)	8389 (17.8)
Renal disease	27440 (6.8)	93946 (6.4)	73935 (6.5)	83202 (4.5)	5657 (12)
Arterial disease	58202 (14.4)	201275 (13.7)	173004 (15.1)	268362 (14.7)	9298 (19.7)
Venous thromboembolism	5613 (1.4)	15375 (1.0)	14016 (1.2)	16571 (0.9)	1704 (3.6)
Dementia	17245 (4.3)	48445 (3.3)	41097 (3.6)	46626 (2.5)	4046 (8.6)
Rheumatic disease	29610 (7.3)	97980 (6.7)	77971 (6.8)	112629 (6.2)	4453 (9.5)
Peptic ulcer disease	148247 (36.8)	527527(36.0)	418871 (36.7)	636452 (34.8)	21304 (45.3)
Chronic lung disease	215194 (53.4)	633215 (43.2)	586894 (51.4)	810357 (44.3)	36096 (76.7)
<i>Indications of Antibiotics, No. (%)</i>					
Upper respiration infection	41000 (10.2)	34919 (2.4)	71542 (6.3)	200376 (10.9)	2024 (4.3)
Pneumonia	17362 (4.3)	13792 (0.9)	54016 (4.7)	10048 (0.5)	10567 (22.4)
Other respiratory infection	31943 (7.9)	49097 (3.3)	118629 (10.4)	266793 (14.6)	2898 (6.2)
Gastrointestinal infection	10997 (2.7)	258359 (17.6)	26806 (2.3)	116001 (6.3)	142 (0.3)
Urinary tract infection	24497 (6.1)	477439 (32.6)	255878 (22.4)	204458 (11.2)	396 (0.8)
Genitourinary infection	10357 (2.6)	103874 (7.1)	104759 (9.2)	75822 (4.1)	806 (1.7)
Skin/Wound infection	15212 (3.8)	13240 (0.9)	20509 (1.8)	47573 (2.6)	589 (1.3)

Table 2. Risk of serious ventricular arrhythmia associated with oral fluoroquinolones compared to cefixime during the days 1~7 after the index date

	Cefixime	Ciprofloxacin	Levofloxacin	Ofloxacin	Moxifloxacin
Number of serious ventricular arrhythmia	18	31	48	26	7
Incidence per 1000000 subjects	44.7	21.1	42.0	14.2	148.7
Odds ratio (95% CI) (IPTW)	1	0.72 (0.49-1.06)	0.92 (0.66-1.29)	0.41 (0.27-0.61)	1.87 (1.15-3.11)

CI=confidence interval; IPTW =inverse probability of treatment weighting

Table 3. Risk of serious ventricular arrhythmia associated with oral fluoroquinolones compared to cefixime during the days 8~14 after the index date

	Cefixime	Ciprofloxacin	Levofloxacin	Ofloxacin	Moxifloxacin
Number of serious ventricular arrhythmia	8	24	29	21	4
Incidence per 1000000 subjects	19.9	16.4	25.4	11.5	85.0
Odds ratio (95% CI) (IPTW)	1	0.44 (0.29-0.65)	1.08 (0.70-1.69)	0.58 (0.36-0.92)	1.78 (0.86-3.88)

CI=confidence interval; IPTW =inverse probability of treatment weighting

Table 4. Subgroup analysis of the risk of serious ventricular arrhythmia associated with study oral fluoroquinolones compared to cefixime during the days 1 to 7 after the index date

	Cefixime	Ciprofloxacin	Levofloxacin	Ofloxacin	Moxifloxacin
<i>History of cardiovascular disease</i>					
Odds ratio (95% CI) (IPTW)	1	0.61 (0.34-1.08)	0.96 (0.58-1.57)	0.47 (0.24-0.85)	2.36 (1.17-5.12)
<i>Without cardiovascular disease</i>					
Odds ratio (95% CI) (IPTW)	1	0.79 (0.47-1.33)	0.86 (0.54-1.34)	0.36 (0.21-0.60)	1.63 (0.84-3.29)
<i>Age ≥65</i>					
Odds ratio (95% CI) (IPTW)	1	0.78 (0.48-1.24)	1.06 (0.71-1.60)	0.36 (0.22-0.57)	2.04 (1.16-3.73)
<i>Age &lt;65</i>					
Odds ratio (95% CI) (IPTW)	1	0.64 (0.32-1.25)	0.96 (0.51-1.81)	0.84 (0.38-1.85)	1.59 (0.60-4.58)
<i>Male</i>					
Odds ratio (95% CI) (IPTW)	1	0.61 (0.36-0.99)	0.82 (0.53-1.25)	0.53 (0.29-0.96)	1.91 (1.00-3.80)
<i>Female</i>					
Odds ratio (95% CI) (IPTW)	1	0.62 (0.35-1.07)	0.89 (0.54-1.46)	0.33 (0.19-0.56)	1.79 (0.87-3.92)

CI=confidence interval; IPTW =inverse probability of treatment weighting

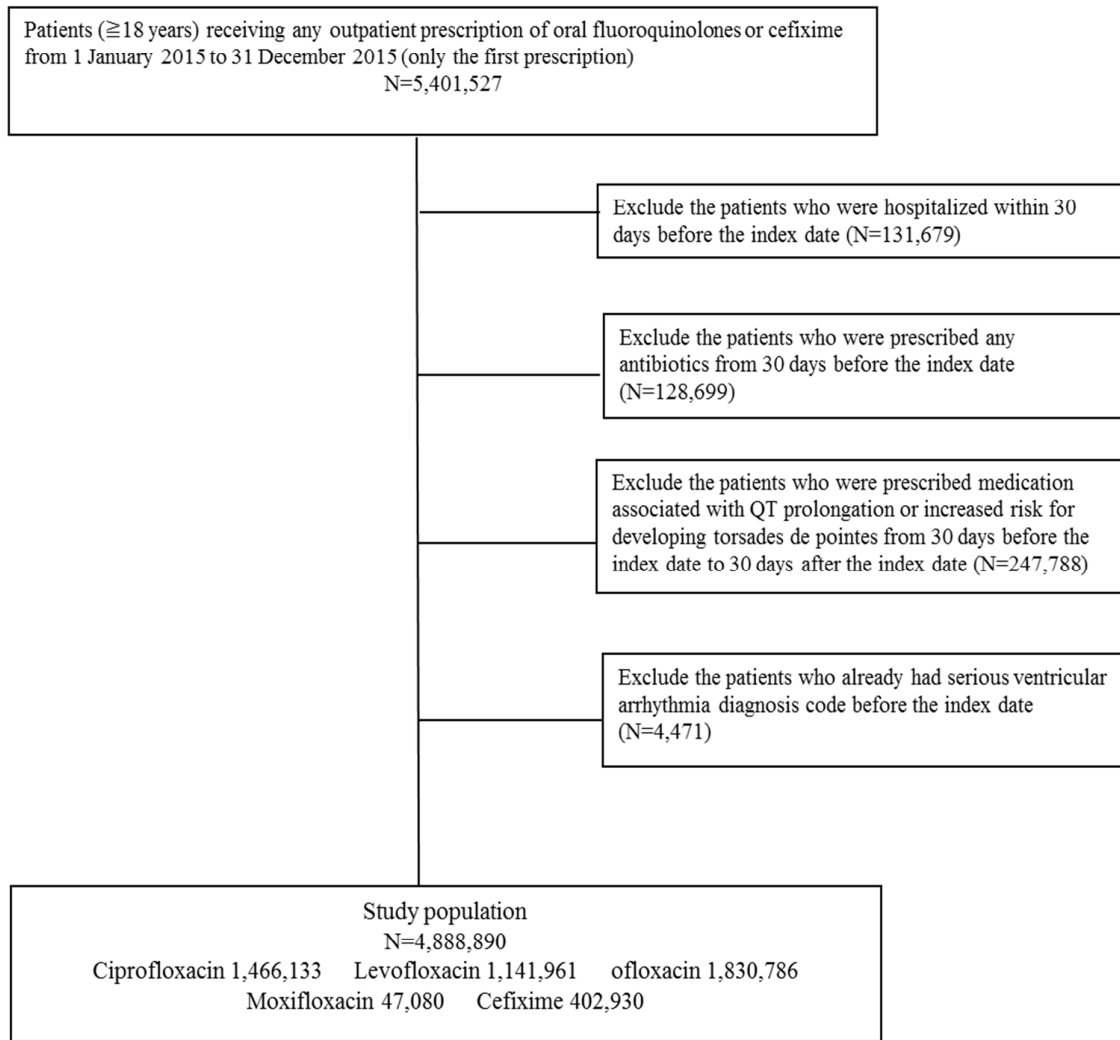


Figure 1. Study flow diagram

**Supplementary appendix**

Table S1. ICD-10 codes of covariates

Table S2. Korea Drug Codes for medications used in the exclusion criteria that is associated with QT prolongation or increased risk of developing torsades de pointes

Table S3. Korea Drug Codes for fluoroquinolones

Table S4. Baseline characteristics of patients using cefixime or ciprofloxacin and standardized difference before and after IPTW

Table S5. Baseline characteristics of patients using cefixime or levofloxacin and standardized difference before and after IPTW

Table S6. Baseline characteristics of patients using cefixime or ofloxacin and standardized difference before and after IPTW

Table S7. Baseline characteristics of patients using cefixime or moxifloxacin and standardized difference before and after IPTW

Table S1. ICD-10 codes of covariates

<i>Comorbidities</i>	
Hypertension	I10-I13.x, I15.x
Diabetes mellitus	E10.x-E14.x
Acute myocardial infarction	I21.x, I22.x, I23.x
Ischemic heart disease	I20.x, I24.x, I25.x
Cardiomyopathy	I42.x, I43.x
Valve disorder	I34.x-37.x
Arrhythmia	I44.x, I45.x, I47.0, I47.1, I47.9, I49.1-9
Congestive heart failure	I11.0, I13.0, I13.2, I50.x, J81.x
Congenital heart disease	Q20.x-26.x
Cancer	C00.x-C99.x
Cerebrovascular disease	G45.x, G46.x, I60.x-I69.x
Renal disease	N00.x-N08.x, N17.x-19.x, N25.x, Z49.x, Z94.0, Z99.2
Arterial disease	I70.x-I79.x
Venous thromboembolism	I26.x, I80.x
Dementia	F00.x-F03.x, G30.x
Rheumatic disease (connective tissue disease)	M05.x, M06.x, M32.x-M34.x
Peptic ulcer disease	K25.x-K28.x
Chronic lung disease	J40.x-47.x, J60.x-70.x
<i>Indications of Antibiotics</i>	
Upper respiratory infection	J01.x-J06.x
Pneumonia	J13.x-J18.x
Other respiratory infection	J20.x-J22.x
Gastrointestinal infection	A00.x-A09.x
Urinary tract infection	N10.x-N12.x, N30.x, N39.0, N41.x
Genitourinary infection	N34.x, N45.x, N70.x-77.x
Skin/Wound infection	L00.x-L08.x

ICD-10= International Classification of Diseases, Tenth Revision



Table S2. Korea Drug Codes for medications used in the exclusion criteria that is associated with QT prolongation or increased risk of developing torsades de pointes

Medications	Korea Drug Codes
Amiodarone	107401ATB
Sotalol	230401ATB, 230402ATB
Quinidine	222001ATB, 222002ATB
Digoxin	144801ATB
Flecainide	159302ATB
Propafenone	219501ATB, 219502ATB
Erythromycin	153501ACH, 153801ATB, 154001ACH
Clarithromycin	134901ATB, 134904ATB
Telithromycin	455901ATB
Chloroquine	171602ATB, 171701ATB, 171702ATB, 171703ATB, 171704ATB,
Ketoconazole	179601ATB,
Itraconazole	179101ACH, 179104ATB
Voriconazole	456501ATB
Sunitinib	487701ACH, 487702ACH, 487703ACH
Domperidone	148402ATB, 148501ATB
Dolasetron	414602ATB
Ondansetron	204601ATB, 204601ATD, 204603ATB
Granisetron	167301ATB, 167301ATD
Sumatriptan	233802ATB, 233803ATB
Zolmitriptan	415601ATB
Naratriptan	415501ATB
Chlorpromazine	131901ATB, 131905ATB, 131908ATB
Haloperidol	167903ATB, 167904ATB, 167905ATB, 167906ATB, 167908ATB,
Pimozide	212401ATB, 212402ATB
Clozapine	137501ATB, 137502ATB
Quetiapine	378601ATB, 378602ATB, 378603ATB, 378604ATB, 378605ATR, 378606ATR, 378607ATR, 378608ATR, 378609ATR,
Risperidone	224201ATB, 224201ATD, 224202ATB, 224203ATB, 224204ATB, 224207ATB,
Imipramine	173701ATB,
Paroxetine	209301ATB, 209302ATB, 209304ATR, 209305ATR, 209306ATR,
Sertraline	227001ATB, 227002ATB
Venlafaxine	247502ATR, 247504ATR
Fluoxetine	161501ACH, 161502ACH, 161502ATD, 161504ACR
Fluvoxamine	162501ATB, 162502ATB

Table S3. Korea Drug Codes for fluoroquinolones

Medications	Korea Drug Codes
Ciprofloxacin	134101ATB, 134103ATB, 134105ATB, 134105ATR, 134108ATR, 134109ATB
Levofloxacin	183201ATB, 183202ATB, 183203ATB
Ofloxacin	203901ATB, 203904ATB
Moxifloxacin	380301ATB
Cefixime	126301ACH

Table S4. Baseline characteristics of patients using cefixime or ciprofloxacin and standardized difference before and after IPTW

	Cefixime	Ciprofloxacin	Standardized difference	
			Before IPTW	After IPTW
Prescriptions, No.	402930	1466133		
Age, mean $\pm$ SD	49.3 $\pm$ 17.7	48.5 $\pm$ 17.3	0.041	0.046
Female sex, No. (%)	238329 (59.1)	951813 (64.9)	0.119	0.042
<i>Comorbidities, No. (%)</i>				
Hypertension	121529 (30.2)	410360 (28.0)	0.048	0.044
Diabetes mellitus	97779 (24.3)	321483 (21.9)	0.056	0.042
Acute myocardial infarction	6536 (1.6)	17451 (1.2)	0.037	0.008
Ischemic heart disease	45810 (11.4)	137303 (9.4)	0.066	0.019
Cardiomyopathy	1450 (0.4)	3668 (0.3)	0.020	0.003
Valve disorder	1826 (0.5)	4971 (0.3)	0.018	0.005
Arrhythmia	14387 (3.6)	45727 (3.1)	0.025	0.008
Congestive heart failure	21753 (5.4)	59507 (4.1)	0.063	0.019
Congenital heart disease	550 (0.1)	1599 (0.1)	0.008	0.002
Cancer	43336 (10.8)	128612 (8.8)	0.067	0.015
Cerebrovascular disease	42741 (10.6)	127394 (8.7)	0.065	0.030
Renal disease	27440 (6.8)	93946 (6.4)	0.016	0.027
Arterial disease	58202 (14.4)	201275 (13.7)	0.021	0.021
Venous thromboembolism	5613 (1.4)	15375 (1.0)	0.031	0.005
Dementia	17245 (4.3)	48445 (3.3)	0.051	0.037
Rheumatic disease	29610 (7.3)	97980 (6.7)	0.026	0.009
Peptic ulcer disease	148247 (36.8)	527527(36.0)	0.017	0.038
Chronic lung disease	215194 (53.4)	633215 (43.2)	0.206	0.026
<i>Indications of Antibiotics, No. (%)</i>				
Upper respiratory infection	41000 (10.2)	34919 (2.4)	0.326	0.002
Pneumonia	17362 (4.3)	13792 (0.9)	0.212	0.002
Other respiratory infection	31943 (7.9)	49097 (3.3)	0.200	0.003
Gastrointestinal infection	10997 (2.7)	258359 (17.6)	0.508	0.001
Urinary tract infection	24497 (6.1)	477439 (32.6)	0.712	0.014
Genitourinary infection	10357 (2.6)	103874 (7.1)	0.212	0.003
Skin/Wound infection	15212 (3.8)	13240 (0.9)	0.191	0.002
<i>Month, No (%)</i>				
1	51082 (12.7)	198022 (13.5)	0.122	0.028
2	41252 (10.2)	139390 (9.5)		
3	43687 (10.8)	136164 (9.3)		
4	39505 (9.8)	123691 (8.4)		
5	32150 (8.0)	107959 (7.4)		
6	28567 (7.1)	110219 (7.5)		
7	25587 (6.4)	121446 (8.3)		
8	26722 (6.6)	118711 (8.1)		
9	27912 (6.9)	104986 (7.2)		
10	29177 (7.2)	97368 (6.6)		
11	26293 (6.5)	97704 (6.7)		
12	30966 (7.7)	110473 (7.5)		

Table S5. Baseline characteristics of patients using cefixime or levofloxacin and standardized difference before and after IPTW

	Cefixime	Levofloxacin	Standardized difference	
			Before IPTW	After IPTW
Prescriptions, No.	402930	1141961		
Age, mean $\pm$ SD	49.3 $\pm$ 17.7	50.4 $\pm$ 16.7	0.068	0.042
Female sex, No. (%)	238329 (59.1)	643076 (56.3)	0.057	0.064
<i>Comorbidities, No. (%)</i>				
Hypertension	121529 (30.2)	346918 (30.4)	0.005	0.026
Diabetes mellitus	97779 (24.3)	268447 (23.5)	0.018	0.024
Acute myocardial infarction	6536 (1.6)	15209 (1.3)	0.024	0.005
Ischemic heart disease	45810 (11.4)	122740 (10.7)	0.020	0.014
Cardiomyopathy	1450 (0.4)	3443 (0.3)	0.010	0.001
Valve disorder	1826 (0.5)	4643 (0.4)	0.007	0.003
Arrhythmia	14387 (3.6)	38751 (3.4)	0.010	0.007
Congestive heart failure	21753 (5.4)	55276 (4.8)	0.025	0.013
Congenital heart disease	550 (0.1)	1430 (0.1)	0.003	<0.001
Cancer	43336 (10.8)	118618 (10.4)	0.012	0.011
Cerebrovascular disease	42741 (10.6)	113241 (9.9)	0.023	0.021
Renal disease	27440 (6.8)	73935 (6.5)	0.013	0.016
Arterial disease	58202 (14.4)	173004 (15.1)	0.020	0.015
Venous thromboembolism	5613 (1.4)	14016 (1.2)	0.015	0.004
Dementia	17245 (4.3)	41097 (3.6)	0.035	0.022
Rheumatic disease	29610 (7.3)	77971 (6.8)	0.020	0.006
Peptic ulcer disease	148247 (36.8)	418871 (36.7)	0.002	0.027
Chronic lung disease	215194 (53.4)	586894 (51.4)	0.040	0.019
<i>Indications of Antibiotics, No. (%)</i>				
Upper respiratory infection	41000 (10.2)	71542 (6.3)	0.143	0.002
Pneumonia	17362 (4.3)	54016 (4.7)	0.020	0.007
Other respiratory infection	31943 (7.9)	118629 (10.4)	0.085	0.001
Gastrointestinal infection	10997 (2.7)	26806 (2.3)	0.024	<0.001
Urinary tract infection	24497 (6.1)	255878 (22.4)	0.480	0.003
Genitourinary infection	10357 (2.6)	104759 (9.2)	0.284	0.012
Skin/Wound infection	15212 (3.8)	20509 (1.8)	0.121	0.001
<i>Month, No (%)</i>				
1	51082 (12.7)	186297 (16.3)	0.161	0.020
2	41252 (10.2)	128738 (11.3)		
3	43687 (10.8)	128601 (11.3)		
4	39505 (9.8)	113718 (10.0)		
5	32150 (8.0)	89592 (7.8)		
6	28567 (7.1)	83536 (7.3)		
7	25587 (6.4)	76140 (6.7)		
8	26722 (6.6)	74130 (6.5)		
9	27912 (6.9)	72417 (6.3)		
10	29177 (7.2)	72734 (6.4)		
11	26293 (6.5)	55296 (4.8)		
12	30966 (7.7)	60762 (5.3)		

Table S6. Baseline characteristics of patients using cefixime or ofloxacin and standardized difference before and after IPTW

	Cefixime	Ofloxacin	Standardized difference	
			Before IPTW	After IPTW
Prescriptions, No.	402930	1830786		
Age, mean $\pm$ SD	49.3 $\pm$ 17.7	50.3 $\pm$ 16.9	0.061	0.009
Female sex, No. (%)	238329 (59.1)	1120119 (61.2)	0.042	0.006
<i>Comorbidities, No. (%)</i>				
Hypertension	121529 (30.2)	540934 (29.5)	0.013	0.005
Diabetes mellitus	97779 (24.3)	382877 (20.9)	0.080	0.001
Acute myocardial infarction	6536 (1.6)	11731 (1.0)	0.058	0.001
Ischemic heart disease	45810 (11.4)	161602 (8.8)	0.084	0.004
Cardiomyopathy	1450 (0.4)	3924 (0.2)	0.027	<0.001
Valve disorder	1826 (0.5)	6219 (0.3)	0.018	0.001
Arrhythmia	14387 (3.6)	53536 (2.9)	0.036	0.001
Congestive heart failure	21753 (5.4)	68471 (3.7)	0.079	0.003
Congenital heart disease	550 (0.1)	1894 (0.1)	0.010	<0.001
Cancer	43336 (10.8)	122116 (6.7)	0.145	0.008
Cerebrovascular disease	42741 (10.6)	155453 (8.5)	0.072	0.001
Renal disease	27440 (6.8)	83202 (4.5)	0.098	0.005
Arterial disease	58202 (14.4)	268362 (14.7)	0.006	0.003
Venous thromboembolism	5613 (1.4)	16571 (0.9)	0.046	0.004
Dementia	17245 (4.3)	46626 (2.5)	0.096	0.005
Rheumatic disease	29610 (7.3)	112629 (6.2)	0.048	0.001
Peptic ulcer disease	148247 (36.8)	636452 (34.8)	0.042	0.004
Chronic lung disease	215194 (53.4)	810357 (44.3)	0.184	0.004
<i>Indications of Antibiotics, No. (%)</i>				
Upper respiratory infection	41000 (10.2)	200376 (10.9)	0.025	0.006
Pneumonia	17362 (4.3)	10048 (0.5)	0.246	0.001
Other respiratory infection	31943 (7.9)	266793 (14.6)	0.211	0.005
Gastrointestinal infection	10997 (2.7)	116001 (6.3)	0.174	0.002
Urinary tract infection	24497 (6.1)	204458 (11.2)	0.182	0.006
Genitourinary infection	10357 (2.6)	75822 (4.1)	0.087	0.004
Skin/Wound infection	15212 (3.8)	47573 (2.6)	0.067	0.004
<i>Month, No (%)</i>				
1	51082 (12.7)	255833 (14.0)	0.058	0.009
2	41252 (10.2)	200347 (10.9)		
3	43687 (10.8)	207332 (11.3)		
4	39505 (9.8)	177080 (9.7)		
5	32150 (8.0)	141413 (7.7)		
6	28567 (7.1)	127462 (7.0)		
7	25587 (6.4)	117053 (6.4)		
8	26722 (6.6)	115864 (6.3)		
9	27912 (6.9)	117031 (6.4)		
10	29177 (7.2)	124597 (6.8)		
11	26293 (6.5)	116492 (6.4)		
12	30966 (7.7)	130282 (7.1)		

Table S7. Baseline characteristics of patients using cefixime or moxifloxacin and standardized difference before and after IPTW

	Cefixime	Moxifloxacin	Standardized difference	
			Before IPTW	After IPTW
Prescriptions, No.	402930	47080		
Age, mean $\pm$ SD	49.3 $\pm$ 17.7	58.4 $\pm$ 17.4	0.521	0.007
Female sex, No. (%)	238329 (59.1)	23586 (50.1)	0.183	0.024
<i>Comorbidities, No. (%)</i>				
Hypertension	121529 (30.2)	21690 (46.1)	0.332	0.031
Diabetes mellitus	97779 (24.3)	17977 (38.2)	0.304	0.027
Acute myocardial infarction	6536 (1.6)	1292 (2.7)	0.077	0.011
Ischemic heart disease	45810 (11.4)	9408 (20)	0.239	0.024
Cardiomyopathy	1450 (0.4)	438 (0.9)	0.071	0.005
Valve disorder	1826 (0.5)	513 (1.1)	0.073	0.002
Arrhythmia	14387 (3.6)	2761 (5.9)	0.108	0.012
Congestive heart failure	21753 (5.4)	5724 (12.2)	0.241	0.013
Congenital heart disease	550 (0.1)	110 (0.2)	0.023	0.004
Cancer	43336 (10.8)	10285 (21.8)	0.304	0.010
Cerebrovascular disease	42741 (10.6)	8389 (17.8)	0.208	0.018
Renal disease	27440 (6.8)	5657 (12)	0.179	0.025
Arterial disease	58202 (14.4)	9298 (19.7)	0.141	0.019
Venous thromboembolism	5613 (1.4)	1704 (3.6)	0.143	0.002
Dementia	17245 (4.3)	4046 (8.6)	0.176	0.023
Rheumatic disease	29610 (7.3)	4453 (9.5)	0.076	0.012
Peptic ulcer disease	148247 (36.8)	21304 (45.3)	0.173	0.024
Chronic lung disease	215194 (53.4)	36096 (76.7)	0.503	0.003
<i>Indications of Antibiotics, No. (%)</i>				
Upper respiratory infection	41000 (10.2)	2024 (4.3)	0.228	0.019
Pneumonia	17362 (4.3)	10567 (22.4)	0.553	0.018
Other respiratory infection	31943 (7.9)	2898 (6.2)	0.069	0.017
Gastrointestinal infection	10997 (2.7)	142 (0.3)	0.200	<0.001
Urinary tract infection	24497 (6.1)	396 (0.8)	0.290	0.015
Genitourinary infection	10357 (2.6)	806 (1.7)	0.059	0.060
Skin/Wound infection	15212 (3.8)	589 (1.3)	0.162	0.040
<i>Month, No (%)</i>				
1	51082 (12.7)	8179 (17.4)	0.201	0.046
2	41252 (10.2)	5913 (12.6)		
3	43687 (10.8)	5674 (12.1)		
4	39505 (9.8)	4736 (10.1)		
5	32150 (8.0)	3549 (7.5)		
6	28567 (7.1)	3132 (6.7)		
7	25587 (6.4)	2486 (5.3)		
8	26722 (6.6)	2323 (4.9)		
9	27912 (6.9)	2383 (5.1)		
10	29177 (7.2)	2791 (5.9)		
11	26293 (6.5)	2412 (5.1)		
12	30966 (7.7)	3502 (7.4)		

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1	Oral fluoroquinolone type and risk of serious ventricular arrhythmia: population-based study
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2	
<b>Introduction</b>				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4	Previous studies have reported the risk of arrhythmia by type of fluoroquinolone, but the results differed for each study.
Objectives	3	State specific objectives, including any prespecified hypotheses	4	To provide clarity to this issue, we exploited a large general population database in Korea to examine whether oral ciprofloxacin, levofloxacin, ofloxacin, and moxifloxacin increase the risk of ventricular arrhythmia compared to cefixime.
<b>Methods</b>				
Study design	4	Present key elements of study design early in the paper	4,5	The population-based cohort study
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	2, 4,5	Design: Population-based cohort study using administrative claims data on a national scale in Korea Setting: Korean nationwide study from January to

				December 2015
Participants	6	<p>(a) <i>Cohort study</i>—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up</p> <p><i>Case-control study</i>—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls</p> <p><i>Cross-sectional study</i>—Give the eligibility criteria, and the sources and methods of selection of participants</p>	5, 6,	<p>Inclusion criteria and exposures</p> <p>We included adult patients older than 18 years. Only the first prescribed study medication was included in the analysis if the patient was prescribed more than one antibiotic during study period.</p> <p>Follow-up started on the index date and ended on the date of serious arrhythmia, or 14 days after start of treatment, whichever came first.</p>
		<p>(b) <i>Cohort study</i>—For matched studies, give matching criteria and number of exposed and unexposed</p> <p><i>Case-control study</i>—For matched studies, give matching criteria and the number of controls per case</p>		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6	<p>Outcome definition</p> <p>The outcome of serious ventricular arrhythmia included ventricular tachycardia, fibrillation, flutter, and cardiac arrest. The International Classification of Diseases, Tenth Revision [ICD-10] codes (I472, I490.x, I460, I461, and I469) were used to identify the patients with serious ventricular arrhythmia.</p>
Data sources/ measurement	8*	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	5,6,7	
Bias	9	Describe any efforts to address potential sources of bias	7	To reduce potential confounding by indication, oral cefixime was used as a control.

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							Then, inverse probability treatment weights are calculated with propensity scores to adjust for baseline differences and control for confounding by indication.
Study size	10	Explain how the study size was arrived at			5		The population-based cohort study involved patients who had been prescribed oral fluoroquinolones (ciprofloxacin, levofloxacin, ofloxacin, moxifloxacin) or cefixime in the outpatient department from 01 January 2015 to 31 December 2015.

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Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7,8	
		(b) Describe any methods used to examine subgroups and interactions	7,8	
		(c) Explain how missing data were addressed		No missing data
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	6	Follow-up started on the index date and ended on the date of serious arrhythmia, or 14 days after start of treatment, whichever came first.
		(e) Describe any sensitivity analyses		No sensitivity analysis
<b>Results</b>				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8	We extracted 5,401,527 outpatients who were prescribed oral fluoroquinolones and cefixime from 01 January 2015 to 31 December 2015. After excluding 512,637 patients, 4,888,890 patients were included in the analysis. (Figure 1) The study population consisted of 1,466,133 users of ciprofloxacin, 1,141,961 users of levofloxacin, 1,830,786 users of ofloxacin, 47,080 users of moxifloxacin and 402,930 users of cefixime.
		(b) Give reasons for non-participation at each stage	20 5, 6	Figure 1 We excluded the patients who were hospitalized within 30 days before the index date which was defined as the first prescription date of the study medication. We also excluded the patients prescribed any antibiotics from 30 days before the index date, prescribed medication associated with QT interval prolongation or increased risk for

				developing torsades de pointes from 30 days before the index date to 30 days after the index date, and who were already diagnosed serious ventricular arrhythmia before the index date.
			20	Figure 1
		(c) Consider use of a flow diagram	20	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8	Characteristics of the study population
		(b) Indicate number of participants with missing data for each variable of interest		No missing data
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	6	Because it is generally recommended to prescribe fluoroquinolone and cefixime for 7~14 days, we used observation periods of 1~7 days and 8~14 days after the index date to evaluate the adverse effect of the medications.
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	18	Table 2, Table 3
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure		
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures		
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	18	Table 2, Table 3
		(b) Report category boundaries when continuous variables were categorized		
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		

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Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	19	Table 4
<b>Discussion</b>				
Key results	18	Summarise key results with reference to study objectives	9	The general population data reveal an increased risk of serious ventricular arrhythmia with moxifloxacin use. Moxifloxacin use was associated with a 1.87-fold increased risk of serious ventricular arrhythmia compared to cefixime during the first week after the drug was initiated. Especially, the risk of ventricular arrhythmia was high in moxifloxacin users who were older or who had cardiovascular disease. Ciprofloxacin, levofloxacin, and ofloxacin use were not associated with increased risk of serious ventricular arrhythmia.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11, 12	This study has several limitations. First, we cannot rule out the effect of selection bias. We tried to adjust the underlying characteristics and indications of antibiotics of both fluoroquinolone and cefixime groups using IPTW to correct for this selection bias. However, it is possible that the ICD-10 codes to define covariates used in the propensity score were not appropriate. For example, the range of chronic lung disease that we have defined is so wide that 40 to 70 percent of each antibiotic group has chronic lung disease. This inadequately reflects the impact of

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chronic lung disease on actual antibiotic prescriptions. Second, there may be an effect of residual confounding. This study did not reflect baseline health information such as laboratory data or ECG because we used health claims data. However, we tried to reduce residual confounding by excluding patients who were recently admitted, or prescribed antibiotics, and those who were prescribed medications related to QT interval prolongation. Third, the ICD-10 code to define the outcome serious ventricular arrhythmia was not directly validated in the Korean population. In one study, however, ICD-9 427.x predicted a ventricular arrhythmia with a positive predictive value of 78 to 100 percent.[38] ICD-9 code 427.x corresponds to the ICD-10 code used in our study. Fourth, because death data were not linked in HIRA data, number of deaths that occurred in the follow up period was not confirmed.

Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
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In this population-based study, moxifloxacin was associated with a 1.87-fold increased risk of serious ventricular arrhythmia compared to cefixime. Ciprofloxacin, levofloxacin, and ofloxacin were not associated with serious ventricular arrhythmia.

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Generalisability	21	Discuss the generalisability (external validity) of the study results	12	Additional studies are needed in other populations to ensure that these findings are valid.
<b>Other information</b>				
Funding	22	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	12	This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

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# BMJ Open

## Association of oral ciprofloxacin, levofloxacin, ofloxacin, and moxifloxacin with the risk of serious ventricular arrhythmia: a nationwide cohort study in Korea

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Secondary Subject Heading:	Cardiovascular medicine, Epidemiology, Infectious diseases, Pharmacology and therapeutics
Keywords:	fluoroquinolone, ventricular arrhythmia, torsades de pointes, population-based study

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3 **Association of oral ciprofloxacin, levofloxacin, ofloxacin, and moxifloxacin with the risk of**  
4 **serious ventricular arrhythmia: a nationwide cohort study in Korea**  
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11 Yongil Cho<sup>1</sup>, Hyun Soo Park<sup>2</sup>  
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52 **Keywords:** fluoroquinolone; ventricular arrhythmia; torsades de pointes; population-based study  
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55 **Word count:** 3453 (Abstract: 282, Text: 3171)  
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## Abstract

**Objective:** To evaluate whether oral ciprofloxacin, levofloxacin, ofloxacin, and moxifloxacin increase the risk of ventricular arrhythmia in Korea's general population.

**Design:** Population-based cohort study using administrative claims data on a national scale in Korea.

**Setting:** All primary, secondary, and tertiary care settings from 01 January 2015 to 31 December 2015.

**Participants:** Patients who were prescribed the relevant study medications at outpatient visits.

**Primary outcome measures:** Each patient group that was prescribed ciprofloxacin, levofloxacin, ofloxacin, or moxifloxacin was compared with the group that was prescribed cefixime to assess the risk of serious ventricular arrhythmia (ventricular tachycardia, fibrillation, flutter and cardiac arrest). Using logistic regression analysis with inverse probability of treatment weighting using the propensity score, odds ratios and 95% confidence intervals for serious ventricular arrhythmia were calculated for days 1-7 and 8-14 after the patients commenced antibiotic use.

**Results:** During the study period, 4,888,890 patients were prescribed the study medications. They included 1,466,133 ciprofloxacin users, 1,141,961 levofloxacin users, 1,830,786 ofloxacin users, 47,080 moxifloxacin users, and 402,930 cefixime users. Between 1-7 days after index date, there was no evidence of increased serious ventricular arrhythmia related to the prescription of ciprofloxacin (odds ratio, 0.72; 95% confidence interval, 0.49-1.06) and levofloxacin (odds ratio, 0.92; 95% confidence interval, 0.66-1.29). Ofloxacin had a 59% reduced risk of serious ventricular arrhythmia compared with cefixime during 1-7 days after prescription. Whereas the odds ratio of serious ventricular arrhythmia after the prescription of moxifloxacin was 1.87 (95% confidence interval, 1.15-3.11) compared with cefixime during 1-7 days after prescription.

**Conclusions:** During 1-7 days after prescription, ciprofloxacin and levofloxacin were not associated with increased risk and ofloxacin showed reduced risk of serious ventricular arrhythmia. Moxifloxacin increased the risk of serious ventricular arrhythmia.



**Strengths and limitations of this study**

- This was a nationwide population-based study that included 4,888,890 patients who were prescribed oral fluoroquinolone or cefixime.
- This is the largest study to date evaluating the association between oral fluoroquinolone use and serious ventricular arrhythmia.
- This study adjusted the underlying characteristics and indications of the antibiotics for both the fluoroquinolone and cefixime groups using propensity score weighting.
- This study reflected no baseline health information, such as laboratory or ECG data, because we used health claims data.
- The number of deaths that occurred during the follow-up period could not be investigated.

## Introduction

Fluoroquinolones are a broad-spectrum antibiotics prescribed for many infectious diseases. Common adverse effects of fluoroquinolones include gastrointestinal symptoms, such as diarrhoea and nausea, and central nervous system side effects, such as headaches and dizziness.[1] These side effects are mild, and fluoroquinolone use is mostly safe; however, rare but serious adverse effects have been reported, including tendon rupture, retinal detachment, aortic aneurysm, and aortic dissection.[2–8]

Fluoroquinolones also have cardiac side effects. Several studies have reported QT interval increases after fluoroquinolone use,[9–14] which can lead to ventricular arrhythmia. Cases of torsades de pointes occurrence associated with fluoroquinolone use have also been reported.[15–19] Several population-based studies also reported that fluoroquinolones increased the risk of ventricular arrhythmia or sudden cardiac death.[20–22] Despite these reports, the association of fluoroquinolones with arrhythmia remains contentious. A recent observational study in Denmark and Sweden reported that oral fluoroquinolone treatment was not associated with the risk of serious arrhythmia.[23] This study compared 909,656 fluoroquinolone users with 909,656 penicillin V users, providing strong statistical power. However, the most frequently prescribed fluoroquinolone was ciprofloxacin; thus, the risk of arrhythmia by antibiotic type was undetermined. Previous studies have reported the risk of arrhythmia by fluoroquinolone type, but their results differed.

To clarify this issue, we utilized a large general population database in Korea to examine whether oral ciprofloxacin, levofloxacin, ofloxacin, or moxifloxacin increased the risk of ventricular arrhythmia compared with the risk associated with cefixime. We selected cefixime (an antibiotic with no pro-arrhythmic effect) as a comparison medication because fluoroquinolones and cefixime have overlapping indications.

## Methods

### *Study design*

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3 This population-based cohort study included patients who had been prescribed oral  
4 fluoroquinolones (ciprofloxacin, levofloxacin, ofloxacin, or moxifloxacin) or cefixime in the  
5 outpatient department from 01 January 2015 to 31 December 2015. To reduce potential confounding  
6 by indication, oral cefixime was used as a control. Both fluoroquinolones and cefixime are frequently  
7 prescribed for respiratory diseases and urinary tract infections in Korea. Other studies used  $\beta$ -lactam  
8 antibiotics, such as amoxicillin, amoxicillin-clavulanate, and penicillin V, as controls.[21–23]  
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10 However, in Korea,  $\beta$ -lactam antibiotics are not commonly used in UTI treatment; thus, cefixime was  
11 used in this study as a comparator. Cefixime is a medication with no pro-arrhythmic effects and is not  
12 in the list of drug-induced QT prolongation or torsades de pointes.[24–29]  
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#### 24 *Data source and ethics*

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27 We analysed claims data from the Health Insurance and Review Assessment (HIRA) in South  
28 Korea. HIRA examines the medical expense claims data received from the National Health Insurance  
29 (NHI) and the appropriateness of medical care benefits.[30] NHI covers almost 98% of the Korean  
30 population (approximately 50 million).[31] HIRA claims data include comprehensive information on  
31 inpatient and outpatient medical services, such as treatment, medicines, procedures and diagnoses.[30]  
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33 In the HIRA database, all personally identifiable information was removed from the data sets, and  
34 anonymized codes representing each patient were included for to protect privacy protection. This  
35 study was approved by the institutional review board of Jeju National University Hospital with  
36 informed consent waived. (IRB No. JEJUNUH 2017-01-013)  
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#### 48 *Inclusion criteria and exposures*

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51 We included adult patients over 18 years old. Only the first prescribed study medication was  
52 included in the analysis if the patient was prescribed more than one antibiotic during the study period.  
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54 Patients who were prescribed the relevant study medications outpatient visits in all primary, secondary,  
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3 and tertiary care settings were included.  
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### 8 *Exclusion criteria* 9

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11 We excluded patients who were hospitalized within 30 days of the index date, which was defined as  
12 the date on which the study medication was prescribed. We also excluded patients who were  
13 prescribed antibiotics within 30 days prior to the index date, who were prescribed medication  
14 associated with QT interval prolongation or who had an increased risk for developing torsades de  
15 pointes from 30 days before to 30 days after the index date, or who were already diagnosed with  
16 serious ventricular arrhythmia before the index date.  
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### 26 *Outcome definition* 27

28 The outcomes of serious ventricular arrhythmia included ventricular tachycardia, fibrillation, flutter,  
29 and cardiac arrest. The International Classification of Diseases, Tenth Revision [ICD-10] codes (I472,  
30 I490.x, I460, I461, and I469) were used to identify the patients with serious ventricular arrhythmias.  
31 Only the main diagnostic codes were used. Because diagnostic codes are sometimes used in patients  
32 with existing arrhythmias, only the first diagnosis was used when patients had more than one  
33 diagnostic code for serious ventricular arrhythmia to focus on incidence outcomes. Because  
34 fluoroquinolone and cefixime are generally recommended to be prescribed for 7-14 days, we used  
35 observation periods of 1-7 days and 8-14 days after the index date to evaluate the adverse effects of  
36 these medications. These periods were chosen because acute side effects from the drug can develop  
37 during the administration period. Follow-up began on the index date and ended on the date of serious  
38 arrhythmia or 14 days after starting treatment, whichever came first.  
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### 54 *Covariates* 55 56 57 58 59 60

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3 Covariates were defined by ICD-10 codes (Supplementary Appendix 1). The diseases  
4 included were hypertension, diabetes mellitus, acute myocardial infarction, ischaemic heart disease,  
5 cardiomyopathy, valve disorder, arrhythmia, congestive heart failure, congenital heart disease, cancer,  
6 cerebrovascular disease, renal disease, arterial disease, venous thromboembolism, dementia,  
7 rheumatic disease, peptic ulcer disease, and chronic lung disease. Antibiotic indications were  
8 identified by primary diagnosis codes on the index date. Infection diagnoses included as covariates  
9 were upper respiratory, other respiratory, gastrointestinal, urinary tract, genitourinary tract, and  
10 skin/wound infections, as well as pneumonia.  
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### 21 *Statistical analyses*

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24 The number of serious ventricular arrhythmias was identified, and the incidence per 1,000,000  
25 patients was calculated. Each patient group prescribed ciprofloxacin, levofloxacin, ofloxacin, or  
26 moxifloxacin was compared with the group prescribed cefixime to assess the risk of ventricular  
27 arrhythmia. Using logistic regression with inverse probability treatment weighting (IPTW), we  
28 calculated the odds ratios (OR) and 95% confidence intervals (CIs) of serious ventricular arrhythmia  
29 compared with cefixime for days 1-7 and 8-14 after the index date.  
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37 We calculated the propensity scores of being prescribed ciprofloxacin, levofloxacin, ofloxacin, or  
38 moxifloxacin compared with cefixime using logistic regression. Age, sex, prescription month, all  
39 covariate-related comorbidities, and antibiotic indications were included in the propensity models.  
40 Inverse probability treatment weights were calculated with propensity scores to adjust for baseline  
41 differences and control for confounding by indication.[32] IPTW weights the inverse of the estimated  
42 propensity score for treated patients and the inverse of one minus the estimated propensity score for  
43 control patients.[33] Propensity score matching has the disadvantage of including only a subset of  
44 subjects and controls in the analysis, but IPTW can be used without reducing sample number. We  
45 evaluated the baseline covariate balance between groups with standardized differences before and  
46 after IPTW. A standardized difference <0.1 indicated that covariates were well balanced between  
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3 treatment and control patients.[34]  
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5 For the subgroup analyses, we divided patients by age, sex, and cardiovascular disease history.  
6 Acute myocardial infarction, ischaemic heart disease, cardiomyopathy, valve disorder, arrhythmia,  
7 congestive heart failure, and congenital heart disease were included as cardiovascular diseases. We  
8 defined cardiovascular disease using the same ICD-10 code as that used to define baseline  
9 comorbidities. The propensity score for each subgroup and drug type was calculated and the odds  
10 ratios were calculated, respectively. No data were missing in this study. Statistical analyses were  
11 performed using R, version 3.1.1 (www.R-project.org).  
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### 23 *Patient and public involvement*

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25 No patients were involved in setting the research question or the outcome measures, nor were they  
26 involved in developing plans for design or implementation of the study. No patients were asked to  
27 advise on interpretation or writing up of results. There are no plans to disseminate the results of the  
28 research to study participants or the relevant patient community.  
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## 37 **Results**

### 38 *Study population characteristics*

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40 We extracted 5,401,527 outpatients who were prescribed oral fluoroquinolones and cefixime from 01  
41 January 2015 to 31 December 2015. After excluding 512,637 patients who were (1) hospitalized  
42 within 30 days of the index date (n=131,679), (2) prescribed antibiotics from 30 days prior to the  
43 index date (n=128,699), (3) prescribed medication associated with QT interval prolongation or who  
44 had an increased risk for developing torsades de pointes from 30 days before to 30 days after the  
45 index date (n=247,788), or (4) diagnosed with serious ventricular arrhythmia before the index date  
46 (n=4,471), 4,888,890 patients were included in the analysis (Figure 1). The study population consisted  
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3 of 1,466,133 ciprofloxacin users, 1,141,961 levofloxacin users, 1,830,786 ofloxacin users, 47,080  
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5 moxifloxacin users, and 402,930 cefixime users.  
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7 The baseline characteristics of the study population are presented in Table 1. Compared with  
8 cefixime users, moxifloxacin users were older and had more comorbidities. Ciprofloxacin,  
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11 levofloxacin, and ofloxacin users had similar baseline comorbidities as cefixime users, except that  
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13 chronic lung disease was less prevalent among ciprofloxacin and ofloxacin users and cancer was less  
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15 prevalent among ofloxacin users.  
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### 17 18 19 20 *Development of serious ventricular arrhythmia*

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23 Serious ventricular arrhythmia incidence, weighted ORs and 95% CIs for days 1-7 after antibiotic  
24 initiation are presented in Table 2. ORs for serious ventricular arrhythmia compared with cefixime  
25 were 0.72 (95% CI, 0.49-1.06), 0.92 (95% CI, 0.66-1.29), 0.41 (95% CI, 0.27-0.61), and 1.87 (95%  
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27 CI, 1.15-3.11) for ciprofloxacin, levofloxacin, ofloxacin, and moxifloxacin, respectively.  
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29 Ciprofloxacin and levofloxacin were not associated with an increased risk, while moxifloxacin was  
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31 associated with a 1.87-fold increased risk of serious ventricular arrhythmia. Ofloxacin was associated  
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33 with a 59% reduced risk of serious ventricular arrhythmia compared with cefixime for 1-7 days after  
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35 the index date.  
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40 The serious ventricular arrhythmia incidence and weighted OR for the 8-14 days post-prescription  
41 are presented in Table 3. ORs for serious ventricular arrhythmia compared with cefixime were 0.44  
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43 (95% CI, 0.29-0.65), 1.08 (95% CI, 0.70-1.69), 0.58 (95% CI, 0.36-0.92), and 1.78 (95% CI, 0.86-  
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45 3.88) for ciprofloxacin, levofloxacin, ofloxacin, and moxifloxacin, respectively. Risk reductions of 66%  
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47 and 42% were found for ciprofloxacin and ofloxacin, respectively. No evidence of an increased risk  
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49 was found for levofloxacin. Moxifloxacin was associated with a 1.78-fold increased risk of serious  
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51 ventricular arrhythmia for 8-14 days after the index date; however, this increased risk was not  
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53 statistically significant.  
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### *Subgroup analyses*

Table 4 shows the weighted ORs for serious ventricular arrhythmia 1-7 days after prescribing ciprofloxacin, levofloxacin, ofloxacin, or moxifloxacin compared with cefixime according to history of cardiovascular disease, age, and gender. The risk of serious ventricular arrhythmia for ciprofloxacin, levofloxacin, and ofloxacin users was not increased compared with that for cefixime users. Moxifloxacin users with histories of cardiovascular disease (OR, 2.36; 95% CI, 1.17-5.12) and those over 65 years old (OR, 2.04; 95% CI, 1.16-3.73) had significantly increased risks of serious ventricular arrhythmia compared with cefixime users.

## **Discussion**

### *Overall findings*

The general population data revealed that ciprofloxacin and levofloxacin were not associated with an increased risk for serious ventricular arrhythmia for 1-7 days after the prescription date and that ofloxacin was associated with a reduced risk of arrhythmia. Moxifloxacin use was associated with a 1.87-fold increased risk of serious ventricular arrhythmia compared with cefixime during the first week after initiating the drug. The risk of ventricular arrhythmia was especially high in moxifloxacin users who were older or had cardiovascular disease. For 8-14 days after the index date, moxifloxacin showed a 1.78-fold increased risk; however, the 95% CI was not statistically significant. All moxifloxacin subgroups showed a high risk, but this risk was statistically significant only in patients with cardiovascular disease and those over 65 years old. The 95% CIs were wide because the number of moxifloxacin users (n=47,080) included in the study was fewer than that for other drugs, and the number of serious ventricular arrhythmias was only 7 for days 1-7 after the index date and 4 for days 8-14. Further studies with more subjects are needed to confirm the risk of moxifloxacin.

### *Drug induced QT interval prolongation*



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3 Medications can prolong QT intervals, which can lead to fatal ventricular arrhythmias, such as  
4 torsades de pointes.[27,28] Torsades de pointes is a polymorphic ventricular tachycardia, which can  
5 lead to ventricular fibrillation or sudden cardiac death. Drug-induced QT interval prolongation occurs  
6 by inhibiting of cardiac voltage-gated potassium channels encoded by the human ether-a-go-go-  
7 related gene (hERG).[35] Blocking the rapid component of the delayed rectifier potassium current ( $I_{Kr}$ )  
8 through hERG channels delays cardiac repolarization, represented by prolonged QT intervals.  
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15 Among the medications considered to be associated with prolonged QT intervals, fluoroquinolones  
16 and macrolides are the most commonly prescribed drugs in clinical practice;[24] however, QT interval  
17 prolongation by fluoroquinolones appears to differ depending by type. A prospective trial suggested  
18 that recommended ciprofloxacin and levofloxacin doses have little effect on QT intervals, while  
19 moxifloxacin induces the greatest QT interval prolongation.[10] After 7 days of moxifloxacin use, the  
20 QTc interval was prolonged by 6 ms relative to baseline. Regarding supratherapeutic fluoroquinolone  
21 doses, all three fluoroquinolones increased QT intervals compared with placebo, with moxifloxacin  
22 most strongly affecting the interval.[11] The increased QT interval means for the 24-hour period after  
23 treatment were 2.3 ms to 4.9 ms, 3.5 ms to 4.9 ms, and 16.3 ms to 17.8 ms for 1500 mg ciprofloxacin,  
24 1000 mg levofloxacin, and 800 mg moxifloxacin, respectively.[11] No studies have been published on  
25 the effect of ofloxacin on QT intervals. However, ofloxacin, ciprofloxacin and levofloxacin were  
26 significantly less potent hERG channel inhibitors than sparfloxacin, grepafloxacin, or  
27 moxifloxacin.[36] Ofloxacin was the least potent hERG channel inhibitor. In contrast, sparfloxacin  
28 and grepafloxacin, the most potent hERG channel inhibitors, were withdrawn from the market due to  
29 QT interval prolongation. Overall, standard ciprofloxacin, levofloxacin, and ofloxacin doses have  
30 little effect on increased QT intervals, while moxifloxacin has the highest effect.  
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#### 50 *Comparison with other population-based studies*

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53 In a study on veterans in the United States,[21] levofloxacin use was associated with a 3.13-fold  
54 increased risk of cardiac arrhythmias and a 2.49-fold increased risk of all-cause death compared with  
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3 amoxicillin. The veteran population was older (mean age, 56.8 years) than our cohort (mean age,  
4 cefixime, 49.3 years; levofloxacin, 50.4 years), which likely explains the different results. A recent  
5 cohort study in Denmark and Sweden[23] found no association between fluoroquinolone use and  
6 serious arrhythmias in the general population; however, because 82% of the prescribed  
7 fluoroquinolones were ciprofloxacin, it remains possible that other fluoroquinolones could increase  
8 the risk. In a US study in a Tennessee Medicaid cohort,[37] patients who took ciprofloxacin and  
9 levofloxacin showed no increased risk for cardiovascular death compared with patients who took  
10 amoxicillin for a 10-day treatment course. A cohort study from Taiwan[22] on the risks of cardiac  
11 arrhythmia among patients using moxifloxacin, levofloxacin, and ciprofloxacin reported that  
12 moxifloxacin use was associated with a 3.30-fold increased risk for ventricular arrhythmia compared  
13 with amoxicillin-clavulanate, with no risk associated with levofloxacin or ciprofloxacin use. These  
14 data, combined with those from our study, reinforce the hypothesis that ciprofloxacin and levofloxacin  
15 are not associated with ventricular arrhythmia, while moxifloxacin appears to be associated with an  
16 increased risk. No studies have been published on ofloxacin risk. Currently, ofloxacin use is not  
17 associated with serious ventricular arrhythmia.

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33 In this study, ciprofloxacin and levofloxacin were not associated with increased ventricular  
34 arrhythmia risk, but whether these drugs induce torsades de pointes is unclear. Some case reports exist  
35 on torsades de pointes after fluoroquinolone use.[15–19] Most of these cases were patients with  
36 concomitant use of other medications associated with QT interval prolongation or with multiple risk  
37 factors associated with drug-induced arrhythmia. The risk factors for drug-induced arrhythmia are  
38 baseline QT interval prolongation, rapid intravenous drug infusion, digitalis therapy, bradycardia,  
39 organic heart disease, and electrolyte imbalances.[35] Our study excluded patients who were  
40 prescribed drugs associated with QT interval prolongation, and we could not confirm whether the risk  
41 of ventricular arrhythmia was increased by the concomitant fluoroquinolone use with drugs that  
42 increase the risk of torsades de pointes. We also could not assess whether intravenous use was  
43 associated with increased risk because this study was conducted only in oral fluoroquinolone users.  
44 Furthermore, no baseline ECG or electrolyte data were available. Further studies are needed to  
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3 determine whether fluoroquinolones increase the risk of arrhythmias in patients with these risk factors.  
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### 8 *Strengths and limitations* 9

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11 One of the strengths of this study is that it is the largest study to date evaluating the association  
12 between oral fluoroquinolone use and serious ventricular arrhythmia. This study was a nationwide  
13 population-based study including 4,888,890 patients who were prescribed oral fluoroquinolone or  
14 cefixime. In addition, the datasets had no missing values, thus minimizing the number of subjects.  
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18 Second, propensity score weighting was performed to adjust the underlying characteristics and  
19 antibiotic indications of both the fluoroquinolone and cefixime groups. In the propensity score  
20 matching, unmatched subjects occur and subject numbers decreased. In this study, all subjects can be  
21 included for comparison using IPTW.  
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28 This study also had several limitations. First, we cannot rule out the effect of selection bias.  
29 We attempted to adjust the underlying antibiotic characteristics and indications of the fluoroquinolone  
30 and cefixime groups using IPTW to correct for this selection bias. However, it is possible that the  
31 ICD-10 codes used to define covariates in the propensity score weighting were inappropriate. For  
32 example, the range of chronic lung diseases that we defined was wide, with 40 to 70% of the  
33 individuals in each antibiotic group having chronic lung disease. This wide range of diagnostic codes  
34 suggests that chronic respiratory illnesses that are unrelated to the antibiotic prescription may have  
35 been included. The propensity score obtained using these covariates may insufficiently reflect the  
36 actual antibiotic prescription. Second, there may be a residual confounding effect. This study did not  
37 reflect baseline health information, such as laboratory or ECG data, because we used health claims  
38 data. However, we tried to reduce residual confounding by excluding patients who were recently  
39 admitted, prescribed antibiotics, or prescribed medications that prolonged QT intervals. Third, the  
40 ICD-10 code defining the serious ventricular arrhythmia outcome was not directly validated in the  
41 Korean population. In one study, however, ICD-9 code 427.x predicted a ventricular arrhythmia with  
42 a positive predictive value of 78 to 100%.<sup>[38]</sup> ICD-9 code 427.x corresponds to the ICD-10 code used  
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3 in our study. Fourth, because death data were not linked to the HIRA data, the number of deaths that  
4 occurred during the follow-up period was unconfirmed. Finally, the drug dose was not investigated,  
5 and the effect of the drug dose was not analysed in this study. Further studies are needed to determine  
6 how the effects of fluoroquinolone on arrhythmias vary with drug dose.  
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## 10 11 12 13 **Conclusion**

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16 In this population-based study, ciprofloxacin and levofloxacin were not associated with serious  
17 ventricular arrhythmia, and ofloxacin reduced the risk of arrhythmia. Moxifloxacin was associated  
18 with a 1.87-fold increased risk of serious ventricular arrhythmia compared with cefixime for 1-7 days  
19 after being prescribed. Additional studies in other populations are required to ensure that these  
20 findings are valid for patients with risk factors excluded in this cohort.  
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## 29 **Contributors**

30  
31 Y.C. contributed to the study design; cleaned, analysed, and interpreted the data; and drafted and  
32 revised the manuscript.  
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35 H.P. contributed to the study design, interpreted the data, and critically revised the paper.  
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53 None  
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### Competing interests

All authors declare no competing interests.

### Data sharing

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**Tables legends**

Table 1. Baseline characteristics of patients using study medications

Table 2. Risk of serious ventricular arrhythmia associated with oral fluoroquinolones compared with cefixime 1-7 days after the index date

Table 3. Risk of serious ventricular arrhythmia associated with oral fluoroquinolones compared with cefixime for 8-14 days after the index date

Table 4. Subgroup analysis of the risk of serious ventricular arrhythmia associated with oral fluoroquinolones assessed in this study compared with cefixime for 1-7 days after the index date

Table 1. Baseline characteristics of patients using study medications

	Cefixime	Ciprofloxacin	Levofloxacin	Ofloxacin	Moxifloxacin
No. of subjects	402930	1466133	1141961	1830786	47080
Age, mean $\pm$ SD	49.3 $\pm$ 17.7	48.5 $\pm$ 17.3	50.4 $\pm$ 16.7	50.3 $\pm$ 16.9	58.4 $\pm$ 17.4
No. of females (%)	238329 (59.1)	951813 (64.9)	643076 (56.3)	1120119 (61.2)	23586 (50.1)
<i>No. of Comorbidities (%)</i>					
Hypertension	121529 (30.2)	410360 (28.0)	346918 (30.4)	540934 (29.5)	21690 (46.1)
Diabetes mellitus	97779 (24.3)	321483 (21.9)	268447 (23.5)	382877 (20.9)	17977 (38.2)
Acute myocardial infarction	6536 (1.6)	17451 (1.2)	15209 (1.3)	11731 (1.0)	1292 (2.7)
Ischaemic heart disease	45810 (11.4)	137303 (9.4)	122740 (10.7)	161602 (8.8)	9408 (20)
Cardiomyopathy	1450 (0.4)	3668 (0.3)	3443 (0.3)	3924 (0.2)	438 (0.9)
Valve disorder	1826 (0.5)	4971 (0.3)	4643 (0.4)	6219 (0.3)	513 (1.1)
Arrhythmia	14387 (3.6)	45727 (3.1)	38751 (3.4)	53536 (2.9)	2761 (5.9)
Congestive heart failure	21753 (5.4)	59507 (4.1)	55276 (4.8)	68471 (3.7)	5724 (12.2)
Congenital heart disease	550 (0.1)	1599 (0.1)	1430 (0.1)	1894 (0.1)	110 (0.2)
Cancer	43336 (10.8)	128612 (8.8)	118618 (10.4)	122116 (6.7)	10285 (21.8)
Cerebrovascular disease	42741 (10.6)	127394 (8.7)	113241 (9.9)	155453 (8.5)	8389 (17.8)
Renal disease	27440 (6.8)	93946 (6.4)	73935 (6.5)	83202 (4.5)	5657 (12)
Arterial disease	58202 (14.4)	201275 (13.7)	173004 (15.1)	268362 (14.7)	9298 (19.7)
Venous thromboembolism	5613 (1.4)	15375 (1.0)	14016 (1.2)	16571 (0.9)	1704 (3.6)
Dementia	17245 (4.3)	48445 (3.3)	41097 (3.6)	46626 (2.5)	4046 (8.6)
Rheumatic disease	29610 (7.3)	97980 (6.7)	77971 (6.8)	112629 (6.2)	4453 (9.5)
Peptic ulcer disease	148247 (36.8)	527527(36.0)	418871 (36.7)	636452 (34.8)	21304 (45.3)
Chronic lung disease	215194 (53.4)	633215 (43.2)	586894 (51.4)	810357 (44.3)	36096 (76.7)
<i>No. of Antibiotic Indications (%)</i>					
Upper respiration infection	41000 (10.2)	34919 (2.4)	71542 (6.3)	200376 (10.9)	2024 (4.3)
Pneumonia	17362 (4.3)	13792 (0.9)	54016 (4.7)	10048 (0.5)	10567 (22.4)
Other respiratory infection	31943 (7.9)	49097 (3.3)	118629 (10.4)	266793 (14.6)	2898 (6.2)
Gastrointestinal infection	10997 (2.7)	258359 (17.6)	26806 (2.3)	116001 (6.3)	142 (0.3)
Urinary tract infection	24497 (6.1)	477439 (32.6)	255878 (22.4)	204458 (11.2)	396 (0.8)
Genitourinary infection	10357 (2.6)	103874 (7.1)	104759 (9.2)	75822 (4.1)	806 (1.7)
Skin/Wound infection	15212 (3.8)	13240 (0.9)	20509 (1.8)	47573 (2.6)	589 (1.3)

Table 2. Risk of serious ventricular arrhythmia associated with oral fluoroquinolones compared with cefixime 1-7 days after the index date

	Cefixime	Ciprofloxacin	Levofloxacin	Ofloxacin	Moxifloxacin
Number of serious ventricular arrhythmia	18	31	48	26	7
Incidence per 1000000 subjects	44.7	21.1	42.0	14.2	148.7
Odds ratio (95% CI) (IPTW)	Reference	0.72 (0.49-1.06)	0.92 (0.66-1.29)	0.41 (0.27-0.61)	1.87 (1.15-3.11)

CI=confidence interval; IPTW =inverse probability of treatment weighting

Table 3. Risk of serious ventricular arrhythmia associated with oral fluoroquinolones compared with cefixime for 8-14 days after the index date

	Cefixime	Ciprofloxacin	Levofloxacin	Ofloxacin	Moxifloxacin
Number of serious ventricular arrhythmia	8	24	29	21	4
Incidence per 1000000 subjects	19.9	16.4	25.4	11.5	85.0
Odds ratio (95% CI) (IPTW)	Reference	0.44 (0.29-0.65)	1.08 (0.70-1.69)	0.58 (0.36-0.92)	1.78 (0.86-3.88)

CI=confidence interval; IPTW =inverse probability of treatment weighting

Table 4. Subgroup analysis of the risk of serious ventricular arrhythmia associated with oral fluoroquinolones assessed in this study compared with cefixime for 1-7 days after the index date

	Cefixime	Ciprofloxacin	Levofloxacin	Ofloxacin	Moxifloxacin
<i>History of cardiovascular disease</i>					
Odds ratio (95% CI) (IPTW)	Reference	0.61 (0.34-1.08)	0.96 (0.58-1.57)	0.47 (0.24-0.85)	2.36 (1.17-5.12)
<i>Without cardiovascular disease</i>					
Odds ratio (95% CI) (IPTW)	Reference	0.79 (0.47-1.33)	0.86 (0.54-1.34)	0.36 (0.21-0.60)	1.63 (0.84-3.29)
<i>Age ≥65</i>					
Odds ratio (95% CI) (IPTW)	Reference	0.78 (0.48-1.24)	1.06 (0.71-1.60)	0.36 (0.22-0.57)	2.04 (1.16-3.73)
<i>Age &lt;65</i>					
Odds ratio (95% CI) (IPTW)	Reference	0.64 (0.32-1.25)	0.96 (0.51-1.81)	0.84 (0.38-1.85)	1.59 (0.60-4.58)
<i>Male</i>					
Odds ratio (95% CI) (IPTW)	Reference	0.61 (0.36-0.99)	0.82 (0.53-1.25)	0.53 (0.29-0.96)	1.91 (1.00-3.80)
<i>Female</i>					
Odds ratio (95% CI) (IPTW)	Reference	0.62 (0.35-1.07)	0.89 (0.54-1.46)	0.33 (0.19-0.56)	1.79 (0.87-3.92)

CI=confidence interval; IPTW =inverse probability of treatment weighting

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**Figure Legends**

Figure 1. Study flow chart

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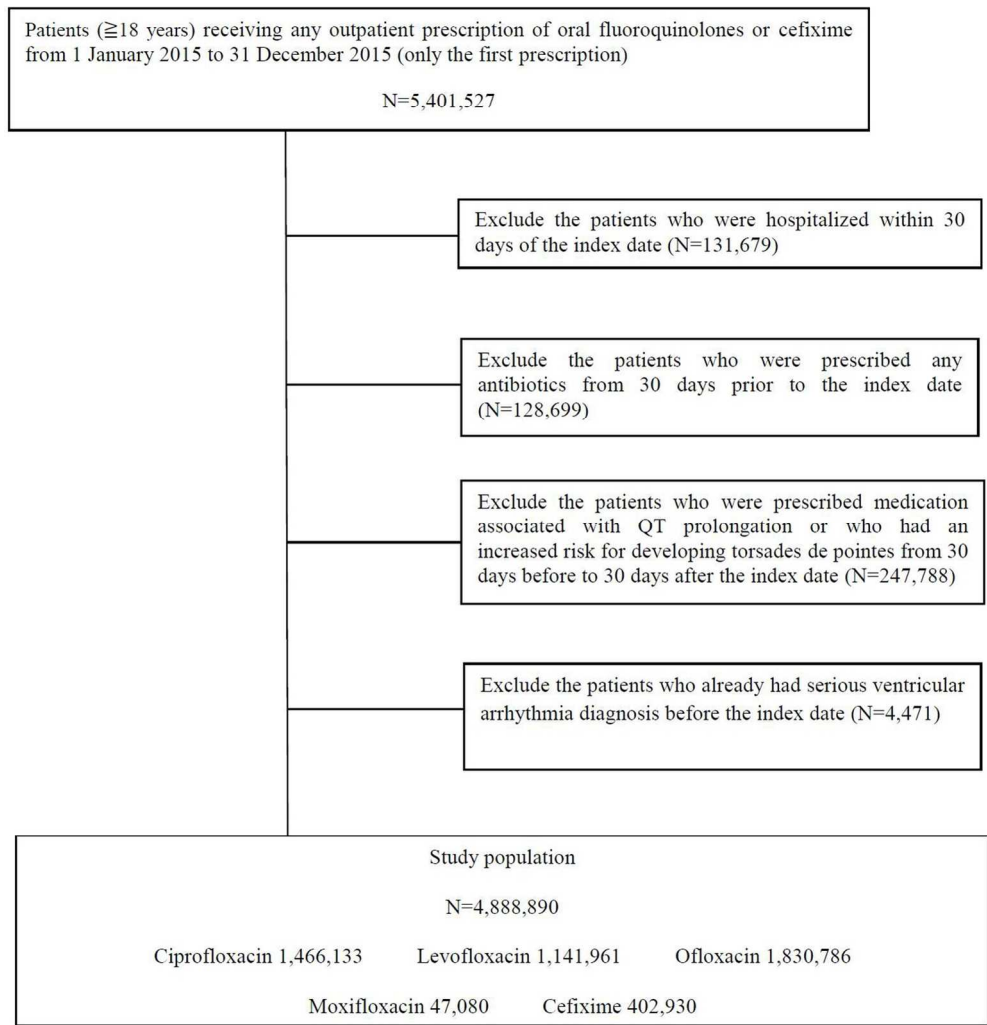


Figure 1. Study flow chart  
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**Supplementary appendix**

Table S1. ICD-10 covariate codes

Table S2. Korea Drug Codes for medications used in the exclusion criteria that are associated with prolonged QT intervals or an increased risk of developing torsades de pointes

Table S3. Korea Drug Codes for fluoroquinolones

Table S4. Baseline characteristics of patients using cefixime or ciprofloxacin and the standardized differences before and after IPTW

Table S5. Baseline characteristics of patients using cefixime or levofloxacin and the standardized differences before and after IPTW

Table S6. Baseline characteristics of patients using cefixime or ofloxacin and the standardized differences before and after IPTW

Table S7. Baseline characteristics of patients using cefixime or moxifloxacin and the standardized differences before and after IPTW

Table S1. ICD-10 covariate codes

<i>Comorbidities</i>	
Hypertension	I10-I13.x, I15.x
Diabetes mellitus	E10.x-E14.x
Acute myocardial infarction	I21.x, I22.x, I23.x
Ischaemic heart disease	I20.x, I24.x, I25.x
Cardiomyopathy	I42.x, I43.x
Valve disorder	I34.x-37.x
Arrhythmia	I44.x, I45.x, I47.0, I47.1, I47.9, I49.1-9
Congestive heart failure	I11.0, I13.0, I13.2, I50.x, J81.x
Congenital heart disease	Q20.x-26.x
Cancer	C00.x-C99.x
Cerebrovascular disease	G45.x, G46.x, I60.x-I69.x
Renal disease	N00.x-N08.x, N17.x-19.x, N25.x, Z49.x, Z94.0, Z99.2
Arterial disease	I70.x-I79.x
Venous thromboembolism	I26.x, I80.x
Dementia	F00.x-F03.x, G30.x
Rheumatic disease (connective tissue disease)	M05.x, M06.x, M32.x-M34.x
Peptic ulcer disease	K25.x-K28.x
Chronic lung disease	J40.x-47.x, J60.x-70.x
<i>Indications for antibiotics</i>	
Upper respiratory infection	J01.x-J06.x
Pneumonia	J13.x-J18.x
Other respiratory infection	J20.x-J22.x
Gastrointestinal infection	A00.x-A09.x
Urinary tract infection	N10.x-N12.x, N30.x, N39.0, N41.x
Genitourinary infection	N34.x, N45.x, N70.x-77.x
Skin/wound infection	L00.x-L08.x

ICD-10=International Classification of Diseases, Tenth Revision



Table S2. Korea Drug Codes for medications used in the exclusion criteria that are associated with prolonged QT intervals or an increased risk of developing torsades de pointes

Medications	Korea Drug Codes
Amiodarone	107401ATB
Sotalol	230401ATB, 230402ATB
Quinidine	222001ATB, 222002ATB
Digoxin	144801ATB
Flecainide	159302ATB
Propafenone	219501ATB, 219502ATB
Erythromycin	153501ACH, 153801ATB, 154001ACH
Clarithromycin	134901ATB, 134904ATB
Telithromycin	455901ATB
Chloroquine	171602ATB, 171701ATB, 171702ATB, 171703ATB, 171704ATB,
Ketoconazole	179601ATB,
Itraconazole	179101ACH, 179104ATB
Voriconazole	456501ATB
Sunitinib	487701ACH, 487702ACH, 487703ACH
Domperidone	148402ATB, 148501ATB
Dolasetron	414602ATB
Ondansetron	204601ATB, 204601ATD, 204603ATB
Granisetron	167301ATB, 167301ATD
Sumatriptan	233802ATB, 233803ATB
Zolmitriptan	415601ATB
Naratriptan	415501ATB
Chlorpromazine	131901ATB, 131905ATB, 131908ATB
Haloperidol	167903ATB, 167904ATB, 167905ATB, 167906ATB, 167908ATB,
Pimozide	212401ATB, 212402ATB
Clozapine	137501ATB, 137502ATB
Quetiapine	378601ATB, 378602ATB, 378603ATB, 378604ATB, 378605ATR, 378606ATR, 378607ATR, 378608ATR, 378609ATR,
Risperidone	224201ATB, 224201ATD, 224202ATB, 224203ATB, 224204ATB, 224207ATB,
Imipramine	173701ATB,
Paroxetine	209301ATB, 209302ATB, 209304ATR, 209305ATR, 209306ATR,
Sertraline	227001ATB, 227002ATB
Venlafaxine	247502ATR, 247504ATR
Fluoxetine	161501ACH, 161502ACH, 161502ATD, 161504ACR
Fluvoxamine	162501ATB, 162502ATB

Table S3. Korea Drug Codes for fluoroquinolones

Medications	Korea Drug Codes
Ciprofloxacin	134101ATB, 134103ATB, 134105ATB, 134105ATR, 134108ATR, 134109ATB
Levofloxacin	183201ATB, 183202ATB, 183203ATB
Ofloxacin	203901ATB, 203904ATB
Moxifloxacin	380301ATB
Cefixime	126301ACH

Table S4. Baseline characteristics of patients using cefixime or ciprofloxacin and the standardized difference before and after IPTW

	Cefixime	Ciprofloxacin	Standardized difference	
			Before IPTW	After IPTW
No. of subjects	402930	1466133		
Age, mean $\pm$ SD	49.3 $\pm$ 17.7	48.5 $\pm$ 17.3	0.041	0.046
No. of females (%)	238329 (59.1)	951813 (64.9)	0.119	0.042
<i>No. of Comorbidities (%)</i>				
Hypertension	121529 (30.2)	410360 (28.0)	0.048	0.044
Diabetes mellitus	97779 (24.3)	321483 (21.9)	0.056	0.042
Acute myocardial infarction	6536 (1.6)	17451 (1.2)	0.037	0.008
Ischaemic heart disease	45810 (11.4)	137303 (9.4)	0.066	0.019
Cardiomyopathy	1450 (0.4)	3668 (0.3)	0.020	0.003
Valve disorder	1826 (0.5)	4971 (0.3)	0.018	0.005
Arrhythmia	14387 (3.6)	45727 (3.1)	0.025	0.008
Congestive heart failure	21753 (5.4)	59507 (4.1)	0.063	0.019
Congenital heart disease	550 (0.1)	1599 (0.1)	0.008	0.002
Cancer	43336 (10.8)	128612 (8.8)	0.067	0.015
Cerebrovascular disease	42741 (10.6)	127394 (8.7)	0.065	0.030
Renal disease	27440 (6.8)	93946 (6.4)	0.016	0.027
Arterial disease	58202 (14.4)	201275 (13.7)	0.021	0.021
Venous thromboembolism	5613 (1.4)	15375 (1.0)	0.031	0.005
Dementia	17245 (4.3)	48445 (3.3)	0.051	0.037
Rheumatic disease	29610 (7.3)	97980 (6.7)	0.026	0.009
Peptic ulcer disease	148247 (36.8)	527527(36.0)	0.017	0.038
Chronic lung disease	215194 (53.4)	633215 (43.2)	0.206	0.026
<i>No. of Antibiotic Indications (%)</i>				
Upper respiratory infection	41000 (10.2)	34919 (2.4)	0.326	0.002
Pneumonia	17362 (4.3)	13792 (0.9)	0.212	0.002
Other respiratory infection	31943 (7.9)	49097 (3.3)	0.200	0.003
Gastrointestinal infection	10997 (2.7)	258359 (17.6)	0.508	0.001
Urinary tract infection	24497 (6.1)	477439 (32.6)	0.712	0.014
Genitourinary infection	10357 (2.6)	103874 (7.1)	0.212	0.003
Skin/Wound infection	15212 (3.8)	13240 (0.9)	0.191	0.002
<i>Month, No (%)</i>				
1	51082 (12.7)	198022 (13.5)	0.122	0.028
2	41252 (10.2)	139390 (9.5)		
3	43687 (10.8)	136164 (9.3)		
4	39505 (9.8)	123691 (8.4)		
5	32150 (8.0)	107959 (7.4)		
6	28567 (7.1)	110219 (7.5)		
7	25587 (6.4)	121446 (8.3)		
8	26722 (6.6)	118711 (8.1)		
9	27912 (6.9)	104986 (7.2)		
10	29177 (7.2)	97368 (6.6)		
11	26293 (6.5)	97704 (6.7)		
12	30966 (7.7)	110473 (7.5)		

Table S5. Baseline characteristics of patients using cefixime or levofloxacin and the standardized difference before and after IPTW

	Cefixime	Levofloxacin	Standardized difference	
			Before IPTW	After IPTW
No. of subjects	402930	1141961		
Age, mean $\pm$ SD	49.3 $\pm$ 17.7	50.4 $\pm$ 16.7	0.068	0.042
No. of females (%)	238329 (59.1)	643076 (56.3)	0.057	0.064
<i>No. of Comorbidities (%)</i>				
Hypertension	121529 (30.2)	346918 (30.4)	0.005	0.026
Diabetes mellitus	97779 (24.3)	268447 (23.5)	0.018	0.024
Acute myocardial infarction	6536 (1.6)	15209 (1.3)	0.024	0.005
Ischaemic heart disease	45810 (11.4)	122740 (10.7)	0.020	0.014
Cardiomyopathy	1450 (0.4)	3443 (0.3)	0.010	0.001
Valve disorder	1826 (0.5)	4643 (0.4)	0.007	0.003
Arrhythmia	14387 (3.6)	38751 (3.4)	0.010	0.007
Congestive heart failure	21753 (5.4)	55276 (4.8)	0.025	0.013
Congenital heart disease	550 (0.1)	1430 (0.1)	0.003	<0.001
Cancer	43336 (10.8)	118618 (10.4)	0.012	0.011
Cerebrovascular disease	42741 (10.6)	113241 (9.9)	0.023	0.021
Renal disease	27440 (6.8)	73935 (6.5)	0.013	0.016
Arterial disease	58202 (14.4)	173004 (15.1)	0.020	0.015
Venous thromboembolism	5613 (1.4)	14016 (1.2)	0.015	0.004
Dementia	17245 (4.3)	41097 (3.6)	0.035	0.022
Rheumatic disease	29610 (7.3)	77971 (6.8)	0.020	0.006
Peptic ulcer disease	148247 (36.8)	418871 (36.7)	0.002	0.027
Chronic lung disease	215194 (53.4)	586894 (51.4)	0.040	0.019
<i>No. of Antibiotic Indications (%)</i>				
Upper respiratory infection	41000 (10.2)	71542 (6.3)	0.143	0.002
Pneumonia	17362 (4.3)	54016 (4.7)	0.020	0.007
Other respiratory infection	31943 (7.9)	118629 (10.4)	0.085	0.001
Gastrointestinal infection	10997 (2.7)	26806 (2.3)	0.024	<0.001
Urinary tract infection	24497 (6.1)	255878 (22.4)	0.480	0.003
Genitourinary infection	10357 (2.6)	104759 (9.2)	0.284	0.012
Skin/Wound infection	15212 (3.8)	20509 (1.8)	0.121	0.001
<i>Month, No (%)</i>				
1	51082 (12.7)	186297 (16.3)	0.161	0.020
2	41252 (10.2)	128738 (11.3)		
3	43687 (10.8)	128601 (11.3)		
4	39505 (9.8)	113718 (10.0)		
5	32150 (8.0)	89592 (7.8)		
6	28567 (7.1)	83536 (7.3)		
7	25587 (6.4)	76140 (6.7)		
8	26722 (6.6)	74130 (6.5)		
9	27912 (6.9)	72417 (6.3)		
10	29177 (7.2)	72734 (6.4)		
11	26293 (6.5)	55296 (4.8)		
12	30966 (7.7)	60762 (5.3)		

Table S6. Baseline characteristics of patients using cefixime or ofloxacin and the standardized difference before and after IPTW

	Cefixime	Ofloxacin	Standardized difference	
			Before IPTW	After IPTW
No. of subjects	402930	1830786		
Age, mean $\pm$ SD	49.3 $\pm$ 17.7	50.3 $\pm$ 16.9	0.061	0.009
No. of females (%)	238329 (59.1)	1120119 (61.2)	0.042	0.006
<i>No. of Comorbidities (%)</i>				
Hypertension	121529 (30.2)	540934 (29.5)	0.013	0.005
Diabetes mellitus	97779 (24.3)	382877 (20.9)	0.080	0.001
Acute myocardial infarction	6536 (1.6)	11731 (1.0)	0.058	0.001
Ischaemic heart disease	45810 (11.4)	161602 (8.8)	0.084	0.004
Cardiomyopathy	1450 (0.4)	3924 (0.2)	0.027	<0.001
Valve disorder	1826 (0.5)	6219 (0.3)	0.018	0.001
Arrhythmia	14387 (3.6)	53536 (2.9)	0.036	0.001
Congestive heart failure	21753 (5.4)	68471 (3.7)	0.079	0.003
Congenital heart disease	550 (0.1)	1894 (0.1)	0.010	<0.001
Cancer	43336 (10.8)	122116 (6.7)	0.145	0.008
Cerebrovascular disease	42741 (10.6)	155453 (8.5)	0.072	0.001
Renal disease	27440 (6.8)	83202 (4.5)	0.098	0.005
Arterial disease	58202 (14.4)	268362 (14.7)	0.006	0.003
Venous thromboembolism	5613 (1.4)	16571 (0.9)	0.046	0.004
Dementia	17245 (4.3)	46626 (2.5)	0.096	0.005
Rheumatic disease	29610 (7.3)	112629 (6.2)	0.048	0.001
Peptic ulcer disease	148247 (36.8)	636452 (34.8)	0.042	0.004
Chronic lung disease	215194 (53.4)	810357 (44.3)	0.184	0.004
<i>No. of Antibiotic Indications (%)</i>				
Upper respiratory infection	41000 (10.2)	200376 (10.9)	0.025	0.006
Pneumonia	17362 (4.3)	10048 (0.5)	0.246	0.001
Other respiratory infection	31943 (7.9)	266793 (14.6)	0.211	0.005
Gastrointestinal infection	10997 (2.7)	116001 (6.3)	0.174	0.002
Urinary tract infection	24497 (6.1)	204458 (11.2)	0.182	0.006
Genitourinary infection	10357 (2.6)	75822 (4.1)	0.087	0.004
Skin/Wound infection	15212 (3.8)	47573 (2.6)	0.067	0.004
<i>Month, No (%)</i>				
1	51082 (12.7)	255833 (14.0)	0.058	0.009
2	41252 (10.2)	200347 (10.9)		
3	43687 (10.8)	207332 (11.3)		
4	39505 (9.8)	177080 (9.7)		
5	32150 (8.0)	141413 (7.7)		
6	28567 (7.1)	127462 (7.0)		
7	25587 (6.4)	117053 (6.4)		
8	26722 (6.6)	115864 (6.3)		
9	27912 (6.9)	117031 (6.4)		
10	29177 (7.2)	124597 (6.8)		
11	26293 (6.5)	116492 (6.4)		
12	30966 (7.7)	130282 (7.1)		

Table S7. Baseline characteristics of patients using cefixime or moxifloxacin and the standardized difference before and after IPTW

	Cefixime	Moxifloxacin	Standardized difference	
			Before IPTW	After IPTW
No. of subjects	402930	47080		
Age, mean $\pm$ SD	49.3 $\pm$ 17.7	58.4 $\pm$ 17.4	0.521	0.007
No. of females (%)	238329 (59.1)	23586 (50.1)	0.183	0.024
<i>No. of Comorbidities (%)</i>				
Hypertension	121529 (30.2)	21690 (46.1)	0.332	0.031
Diabetes mellitus	97779 (24.3)	17977 (38.2)	0.304	0.027
Acute myocardial infarction	6536 (1.6)	1292 (2.7)	0.077	0.011
Ischaemic heart disease	45810 (11.4)	9408 (20)	0.239	0.024
Cardiomyopathy	1450 (0.4)	438 (0.9)	0.071	0.005
Valve disorder	1826 (0.5)	513 (1.1)	0.073	0.002
Arrhythmia	14387 (3.6)	2761 (5.9)	0.108	0.012
Congestive heart failure	21753 (5.4)	5724 (12.2)	0.241	0.013
Congenital heart disease	550 (0.1)	110 (0.2)	0.023	0.004
Cancer	43336 (10.8)	10285 (21.8)	0.304	0.010
Cerebrovascular disease	42741 (10.6)	8389 (17.8)	0.208	0.018
Renal disease	27440 (6.8)	5657 (12)	0.179	0.025
Arterial disease	58202 (14.4)	9298 (19.7)	0.141	0.019
Venous thromboembolism	5613 (1.4)	1704 (3.6)	0.143	0.002
Dementia	17245 (4.3)	4046 (8.6)	0.176	0.023
Rheumatic disease	29610 (7.3)	4453 (9.5)	0.076	0.012
Peptic ulcer disease	148247 (36.8)	21304 (45.3)	0.173	0.024
Chronic lung disease	215194 (53.4)	36096 (76.7)	0.503	0.003
<i>No. of Antibiotic Indications (%)</i>				
Upper respiratory infection	41000 (10.2)	2024 (4.3)	0.228	0.019
Pneumonia	17362 (4.3)	10567 (22.4)	0.553	0.018
Other respiratory infection	31943 (7.9)	2898 (6.2)	0.069	0.017
Gastrointestinal infection	10997 (2.7)	142 (0.3)	0.200	<0.001
Urinary tract infection	24497 (6.1)	396 (0.8)	0.290	0.015
Genitourinary infection	10357 (2.6)	806 (1.7)	0.059	0.060
Skin/Wound infection	15212 (3.8)	589 (1.3)	0.162	0.040
<i>Month, No (%)</i>				
1	51082 (12.7)	8179 (17.4)	0.201	0.046
2	41252 (10.2)	5913 (12.6)		
3	43687 (10.8)	5674 (12.1)		
4	39505 (9.8)	4736 (10.1)		
5	32150 (8.0)	3549 (7.5)		
6	28567 (7.1)	3132 (6.7)		
7	25587 (6.4)	2486 (5.3)		
8	26722 (6.6)	2323 (4.9)		
9	27912 (6.9)	2383 (5.1)		
10	29177 (7.2)	2791 (5.9)		
11	26293 (6.5)	2412 (5.1)		
12	30966 (7.7)	3502 (7.4)		

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1	Association of oral ciprofloxacin, levofloxacin, ofloxacin, and moxifloxacin with the risk of serious ventricular arrhythmia: a nationwide cohort study in Korea
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2	
<b>Introduction</b>				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4	Previous studies have reported the risk of arrhythmia by fluoroquinolone type, but their results differed.
Objectives	3	State specific objectives, including any prespecified hypotheses	4	To clarify this issue, we utilized a large general population database in Korea to examine whether oral ciprofloxacin, levofloxacin, ofloxacin, or moxifloxacin increased the risk of ventricular arrhythmia compared with the risk associated with cefixime
<b>Methods</b>				
Study design	4	Present key elements of study design early in the paper	5	The population-based cohort study
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	2, 4,5	Design: Population-based cohort study using administrative claims data on a national scale in Korea.

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				Setting: All primary, secondary, and tertiary care settings from 01 January 2015 to 31 December 2015.
Participants	6	<p>(a) <i>Cohort study</i>—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up</p> <p><i>Case-control study</i>—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls</p> <p><i>Cross-sectional study</i>—Give the eligibility criteria, and the sources and methods of selection of participants</p>	5, 6,	<p>Inclusion criteria and exposures</p> <p>We included adult patients over 18 years old. Only the first prescribed study medication was included in the analysis if the patient was prescribed more than one antibiotic during the study period. Patients who were prescribed the relevant study medications outpatient visits in all primary, secondary, and tertiary care settings were included.</p> <p>Follow-up began on the index date and ended on the date of serious arrhythmia or 14 days after starting treatment, whichever came first.</p>
		<p>(b) <i>Cohort study</i>—For matched studies, give matching criteria and number of exposed and unexposed</p> <p><i>Case-control study</i>—For matched studies, give matching criteria and the number of controls per case</p>		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6	<p>Outcome definition</p> <p>The outcomes of serious ventricular arrhythmia included ventricular tachycardia, fibrillation, flutter, and cardiac arrest. The International Classification of Diseases, Tenth Revision [ICD-10] codes (I472, I490.x, I460, I461, and</p>

				I469) were used to identify the patients with serious ventricular arrhythmias.
Data sources/ measurement	8*	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	5,6,7,8	
Bias	9	Describe any efforts to address potential sources of bias	5, 7	To reduce potential confounding by indication, oral cefixime was used as a control. Inverse probability treatment weights were calculated with propensity scores to adjust for baseline differences and control for confounding by indication.
Study size	10	Explain how the study size was arrived at	5	This population-based cohort study included patients who had been prescribed oral fluoroquinolones (ciprofloxacin, levofloxacin, ofloxacin, or moxifloxacin) or cefixime in the outpatient department from 01 January 2015 to 31 December 2015.

Continued on next page



Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7,8	
		(b) Describe any methods used to examine subgroups and interactions	7,8	
		(c) Explain how missing data were addressed	8	No data were missing in this study.
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	6	Follow-up began on the index date and ended on the date of serious arrhythmia or 14 days after starting treatment, whichever came first.
		(e) Describe any sensitivity analyses		No sensitivity analysis
<b>Results</b>				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8	4,888,890 patients were included in the analysis (Figure 1). The study population consisted of 1,466,133 ciprofloxacin users, 1,141,961 levofloxacin users, 1,830,786 ofloxacin users, 47,080 moxifloxacin users, and 402,930 cefixime users.
		(b) Give reasons for non-participation at each stage	8	We extracted 5,401,527 outpatients who were prescribed oral fluoroquinolones and cefixime from 01 January 2015 to 31 December 2015. After excluding 512,637 patients who were (1) hospitalized within 30 days of the index date (n=131,679), (2) prescribed antibiotics from 30 days prior to the index date (n=128,699), (3) prescribed medication associated with QT interval prolongation or who had an increased risk for developing torsades de pointes from 30 days before to 30 days after the index date (n=247,788), or (4)

			20	diagnosed with serious ventricular arrhythmia before the index date (n=4,471), Figure 1
		(c) Consider use of a flow diagram	20	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8	Study population characteristics
		(b) Indicate number of participants with missing data for each variable of interest	Table 1	No missing data
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	6	Because fluoroquinolone and cefixime are generally recommended to be prescribed for 7-14 days, we used observation periods of 1-7 days and 8-14 days after the index date to evaluate the adverse effects of these medications. These periods were chosen because acute side effects from the drug can develop during the administration period.
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	21	Table 2, Table 3
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure		
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures		
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	21	Table 2, Table 3
		(b) Report category boundaries when continuous variables were categorized		
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		

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Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	22	Table 4
<b>Discussion</b>				
Key results	18	Summarise key results with reference to study objectives	10	Overall findings The general population data revealed that ciprofloxacin and levofloxacin were not associated with an increased risk for serious ventricular arrhythmia for 1-7 days after the prescription date and that ofloxacin was associated with a reduced risk of arrhythmia. Moxifloxacin use was associated with a 1.87-fold increased risk of serious ventricular arrhythmia compared with cefixime during the first week after initiating the drug. The risk of ventricular arrhythmia was especially high in moxifloxacin users who were older or had cardiovascular disease. For 8-14 days after the index date, moxifloxacin showed a 1.78-fold increased risk; however, the 95% CI was not statistically significant. All moxifloxacin subgroups showed a high risk, but this risk was statistically significant only in patients with cardiovascular disease and those over 65 years old. The 95% CIs were wide because the number of moxifloxacin users (n=47,080) included in the study was fewer than that for other drugs, and the number of serious ventricular arrhythmias was only 7

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				for days 1-7 after the index date and 4 for days 8-14. Further studies with more subjects are needed to confirm the risk of moxifloxacin.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13	This study also had several limitations. First, we cannot rule out the effect of selection bias. We attempted to adjust the underlying antibiotic characteristics and indications of the fluoroquinolone and cefixime groups using IPTW to correct for this selection bias. However, it is possible that the ICD-10 codes used to define covariates in the propensity score weighting were inappropriate. For example, the range of chronic lung diseases that we defined was wide, with 40 to 70% of the individuals in each antibiotic group having chronic lung disease. This wide range of diagnostic codes suggests that chronic respiratory illnesses that are unrelated to the antibiotic prescription may have been included. The propensity score obtained using these covariates may insufficiently reflect the actual antibiotic prescription. Second, there may be a residual confounding effect. This study did not reflect baseline health information, such as laboratory or ECG data, because we used health claims data. However, we tried to reduce residual confounding by

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excluding patients who were recently admitted, prescribed antibiotics, or prescribed medications that prolonged QT intervals. Third, the ICD-10 code defining the serious ventricular arrhythmia outcome was not directly validated in the Korean population. In one study, however, ICD-9 code 427.x predicted a ventricular arrhythmia with a positive predictive value of 78 to 100%.<sup>[38]</sup> ICD-9 code 427.x corresponds to the ICD-10 code used in our study. Fourth, because death data were not linked to the HIRA data, the number of deaths that occurred during the follow-up period was unconfirmed. Finally, the drug dose was not investigated, and the effect of the drug dose was not analysed in this study. Further studies are needed to determine how the effects of fluoroquinolone on arrhythmias vary with drug dose.

Interpretation 20 Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence 13

All moxifloxacin subgroups showed a high risk, but this risk was statistically significant only in patients with cardiovascular disease and those over 65 years old. The 95% CIs were wide because the number of moxifloxacin users (n=47,080) included in the study was fewer than that for other drugs, and the number of serious ventricular arrhythmias was only 7

				for days 1-7 after the index date and 4 for days 8-14. Further studies with more subjects are needed to confirm the risk of moxifloxacin.
Generalisability	21	Discuss the generalisability (external validity) of the study results	14	Additional studies in other populations are required to ensure that these findings are valid for patients with risk factors excluded in this cohort.
<b>Other information</b>				
Funding	22	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	14	This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

# BMJ Open

## Association of oral ciprofloxacin, levofloxacin, ofloxacin, and moxifloxacin with the risk of serious ventricular arrhythmia: a nationwide cohort study in Korea

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Secondary Subject Heading:	Cardiovascular medicine, Epidemiology, Infectious diseases, Pharmacology and therapeutics
Keywords:	fluoroquinolone, ventricular arrhythmia, torsades de pointes, population-based study

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4 **serious ventricular arrhythmia: a nationwide cohort study in Korea**  
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52 **Keywords:** fluoroquinolone; ventricular arrhythmia; torsades de pointes; population-based study  
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55 **Word count:** 3536(Abstract: 282, Text: 3254)  
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## Abstract

**Objective:** To evaluate whether oral ciprofloxacin, levofloxacin, ofloxacin, and moxifloxacin increase the risk of ventricular arrhythmia in Korea's general population.

**Design:** Population-based cohort study using administrative claims data on a national scale in Korea.

**Setting:** All primary, secondary, and tertiary care settings from 01 January 2015 to 31 December 2015.

**Participants:** Patients who were prescribed the relevant study medications at outpatient visits.

**Primary outcome measures:** Each patient group that was prescribed ciprofloxacin, levofloxacin, ofloxacin, or moxifloxacin was compared with the group that was prescribed cefixime to assess the risk of serious ventricular arrhythmia (ventricular tachycardia, fibrillation, flutter and cardiac arrest). Using logistic regression analysis with inverse probability of treatment weighting using the propensity score, odds ratios and 95% confidence intervals for serious ventricular arrhythmia were calculated for days 1-7 and 8-14 after the patients commenced antibiotic use.

**Results:** During the study period, 4,888,890 patients were prescribed the study medications. They included 1,466,133 ciprofloxacin users, 1,141,961 levofloxacin users, 1,830,786 ofloxacin users, 47,080 moxifloxacin users, and 402,930 cefixime users. Between 1-7 days after index date, there was no evidence of increased serious ventricular arrhythmia related to the prescription of ciprofloxacin (odds ratio, 0.72; 95% confidence interval, 0.49-1.06) and levofloxacin (odds ratio, 0.92; 95% confidence interval, 0.66-1.29). Ofloxacin had a 59% reduced risk of serious ventricular arrhythmia compared with cefixime during 1-7 days after prescription. Whereas the odds ratio of serious ventricular arrhythmia after the prescription of moxifloxacin was 1.87 (95% confidence interval, 1.15-3.11) compared with cefixime during 1-7 days after prescription.

**Conclusions:** During 1-7 days after prescription, ciprofloxacin and levofloxacin were not associated with increased risk and ofloxacin showed reduced risk of serious ventricular arrhythmia. Moxifloxacin increased the risk of serious ventricular arrhythmia.

**Strengths and limitations of this study**

- This was a nationwide population-based study that included 4,888,890 patients who were prescribed oral fluoroquinolone or cefixime.
- This is the largest study to date evaluating the association between oral fluoroquinolone use and serious ventricular arrhythmia.
- This study adjusted the underlying characteristics and indications of the antibiotics for both the fluoroquinolone and cefixime groups using propensity score weighting.
- This study reflected no baseline health information, such as laboratory or ECG data, because we used health claims data.
- The number of deaths that occurred during the follow-up period could not be investigated.

## Introduction

Fluoroquinolones are a broad-spectrum antibiotics prescribed for many infectious diseases. Common adverse effects of fluoroquinolones include gastrointestinal symptoms, such as diarrhoea and nausea, and central nervous system side effects, such as headaches and dizziness.[1] These side effects are mild, and fluoroquinolone use is mostly safe; however, rare but serious adverse effects have been reported, including tendon rupture, retinal detachment, aortic aneurysm, and aortic dissection.[2–8]

Fluoroquinolones also have cardiac side effects. Several studies have reported QT interval increases after fluoroquinolone use,[9–14] which can lead to ventricular arrhythmia. Cases of torsades de pointes occurrence associated with fluoroquinolone use have also been reported.[15–19] Several population-based studies also reported that fluoroquinolones increased the risk of ventricular arrhythmia or sudden cardiac death.[20–22] Despite these reports, the association of fluoroquinolones with arrhythmia remains contentious. A recent observational study in Denmark and Sweden reported that oral fluoroquinolone treatment was not associated with the risk of serious arrhythmia.[23] This study compared 909,656 fluoroquinolone users with 909,656 penicillin V users, providing strong statistical power. However, the most frequently prescribed fluoroquinolone was ciprofloxacin; thus, the risk of arrhythmia by antibiotic type was undetermined. Previous studies have reported the risk of arrhythmia by fluoroquinolone type, but their results differed.

To clarify this issue, we utilized a large general population database in Korea to examine whether oral ciprofloxacin, levofloxacin, ofloxacin, or moxifloxacin increased the risk of ventricular arrhythmia compared with the risk associated with cefixime. We selected cefixime (an antibiotic with no pro-arrhythmic effect) as a comparison medication because fluoroquinolones and cefixime have overlapping indications.

## Methods

### *Study design*

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3 This population-based cohort study included patients who had been prescribed oral  
4 fluoroquinolones (ciprofloxacin, levofloxacin, ofloxacin, or moxifloxacin) or cefixime in the  
5 outpatient department from 01 January 2015 to 31 December 2015 (see online supplementary table 1).  
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7 To reduce potential confounding by indication, oral cefixime was used as a control. Both  
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9 fluoroquinolones and cefixime are frequently prescribed for respiratory diseases and urinary tract  
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11 infections in Korea. Other studies used  $\beta$ -lactam antibiotics, such as amoxicillin, amoxicillin-  
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13 clavulanate, and penicillin V, as controls.[21–23] However, in Korea,  $\beta$ -lactam antibiotics are not  
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15 commonly used in UTI treatment; thus, cefixime was used in this study as a comparator. Cefixime is a  
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17 medication with no pro-arrhythmic effects and is not in the list of drug-induced QT prolongation or  
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19 torsades de pointes.[24–29]  
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#### 26 *Data source and ethics*

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29 We analysed claims data from the Health Insurance and Review Assessment (HIRA) in South  
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31 Korea. HIRA examines the medical expense claims data received from the National Health Insurance  
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33 (NHI) and the appropriateness of medical care benefits.[30] NHI covers almost 98% of the Korean  
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35 population (approximately 50 million).[31] HIRA claims data include comprehensive information on  
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37 inpatient and outpatient medical services, such as treatment, medicines, procedures and diagnoses.[30]  
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39 In the HIRA database, all personally identifiable information was removed from the data sets, and  
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41 anonymized codes representing each patient were included for to protect privacy protection. This  
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43 study was approved by the institutional review board of Jeju National University Hospital with  
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45 informed consent waived. (IRB No. JEJUNUH 2017-01-013)  
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#### 50 *Inclusion criteria and exposures*

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53 We included adult patients over 18 years old. Only the first prescribed study medication was  
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55 included in the analysis if the patient was prescribed more than one antibiotic during the study period.  
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3 Patients who were prescribed the relevant study medications outpatient visits in all primary, secondary,  
4 and tertiary care settings were included.  
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### 10 *Exclusion criteria*

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13 We excluded patients who were hospitalized within 30 days of the index date, which was defined as  
14 the date on which the study medication was prescribed. We also excluded patients who were  
15 prescribed antibiotics within 30 days prior to the index date, who were prescribed medication  
16 associated with QT interval prolongation or increased risk for developing torsades de pointes from 30  
17 days before to 30 days after the index date (see online supplementary table 2), or who were already  
18 diagnosed with serious ventricular arrhythmia before the index date.  
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### 28 *Outcome definition*

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30 The outcomes of serious ventricular arrhythmia included ventricular tachycardia, fibrillation, flutter,  
31 and cardiac arrest. The International Classification of Diseases, Tenth Revision [ICD-10] codes (I472,  
32 I490.x, I460, I461, and I469) were used to identify the patients with serious ventricular arrhythmias.  
33  
34 Only the main diagnostic codes were used. Because diagnostic codes are sometimes used in patients  
35 with existing arrhythmias, only the first diagnosis was used when patients had more than one  
36 diagnostic code for serious ventricular arrhythmia to focus on incidence outcomes. Because  
37 fluoroquinolone and cefixime are generally recommended to be prescribed for 7-14 days, we used  
38 observation periods of 1-7 days and 8-14 days after the index date to evaluate the adverse effects of  
39 these medications. These periods were chosen because acute side effects from the drug can develop  
40 during the administration period. Follow-up began on the index date and ended on the date of serious  
41 arrhythmia or 14 days after starting treatment, whichever came first.  
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### 56 *Covariates*

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3 Covariates were defined by ICD-10 codes (see online supplementary table 3). The diseases  
4 included were hypertension, diabetes mellitus, acute myocardial infarction, ischaemic heart disease,  
5 cardiomyopathy, valve disorder, arrhythmia, congestive heart failure, congenital heart disease, cancer,  
6 cerebrovascular disease, renal disease, arterial disease, venous thromboembolism, dementia,  
7 rheumatic disease, peptic ulcer disease, and chronic lung disease. Antibiotic indications were  
8 identified by primary diagnosis codes on the index date. Infection diagnoses included as covariates  
9 were upper respiratory, other respiratory, gastrointestinal, urinary tract, genitourinary tract, and  
10 skin/wound infections, as well as pneumonia.  
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### 21 *Statistical analyses*

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24 The number of serious ventricular arrhythmias was identified, and the incidence per 1,000,000  
25 patients was calculated. Each patient group prescribed ciprofloxacin, levofloxacin, ofloxacin, or  
26 moxifloxacin was compared with the group prescribed cefixime to assess the risk of ventricular  
27 arrhythmia. Using logistic regression with inverse probability treatment weighting (IPTW), we  
28 calculated the odds ratios (OR) and 95% confidence intervals (CIs) of serious ventricular arrhythmia  
29 compared with cefixime for days 1-7 and 8-14 after the index date.  
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37 We calculated the propensity scores of being prescribed ciprofloxacin, levofloxacin, ofloxacin, or  
38 moxifloxacin compared with cefixime using logistic regression. Age, sex, prescription month, all  
39 covariate-related comorbidities, and antibiotic indications were included in the propensity models.  
40 Inverse probability treatment weights were calculated with propensity scores to adjust for baseline  
41 differences and control for confounding by indication.[32] IPTW weights the inverse of the estimated  
42 propensity score for treated patients and the inverse of one minus the estimated propensity score for  
43 control patients.[33] Propensity score matching has the disadvantage of including only a subset of  
44 subjects and controls in the analysis, but IPTW can be used without reducing sample number. We  
45 evaluated the baseline covariate balance between groups with standardized differences before and  
46 after IPTW. A standardized difference <0.1 indicated that covariates were well balanced between  
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3 treatment and control patients.[34]  
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5 For the subgroup analyses, we divided patients by age, sex, and cardiovascular disease history.  
6 Acute myocardial infarction, ischaemic heart disease, cardiomyopathy, valve disorder, arrhythmia,  
7 congestive heart failure, and congenital heart disease were included as cardiovascular diseases. We  
8 defined cardiovascular disease using the same ICD-10 code as that used to define baseline  
9 comorbidities. The propensity score for each subgroup and drug type was calculated and the odds  
10 ratios were calculated, respectively. No data were missing in this study. Statistical analyses were  
11 performed using R, version 3.1.1 ([www.R-project.org](http://www.R-project.org)).  
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### 23 *Patient and public involvement*

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25 No patients were involved in setting the research question or the outcome measures, nor were they  
26 involved in developing plans for design or implementation of the study. No patients were asked to  
27 advise on interpretation or writing up of results. There are no plans to disseminate the results of the  
28 research to study participants or the relevant patient community.  
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## 37 **Results**

### 38 *Study population characteristics*

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40 We extracted 5,401,527 outpatients who were prescribed oral fluoroquinolones and cefixime from 01  
41 January 2015 to 31 December 2015. After excluding 512,637 patients who were (1) hospitalized  
42 within 30 days of the index date (n=131,679), (2) prescribed antibiotics from 30 days prior to the  
43 index date (n=128,699), (3) prescribed medication associated with QT interval prolongation or  
44 increased risk for developing torsades de pointes from 30 days before to 30 days after the index date  
45 (n=247,788), or (4) diagnosed with serious ventricular arrhythmia before the index date (n=4,471),  
46 4,888,890 patients were included in the analysis (Figure 1). The study population consisted of  
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3 1,466,133 ciprofloxacin users, 1,141,961 levofloxacin users, 1,830,786 ofloxacin users, 47,080  
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5 moxifloxacin users, and 402,930 cefixime users.

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7 The baseline characteristics of the study population before weighting are presented in Table 1.  
8  
9 Compared with cefixime users, moxifloxacin users were older and had more comorbidities.  
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11 Ciprofloxacin, levofloxacin, and ofloxacin users had similar baseline comorbidities as cefixime users,  
12  
13 except that chronic lung disease was less prevalent among ciprofloxacin and ofloxacin users and  
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15 cancer was less prevalent among ofloxacin users. After the study population had been weighting using  
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17 the IPTW, all baseline differences were less than 0.1 standardized differences (see online  
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19 supplementary table 4-7).  
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#### 22 23 24 *Development of serious ventricular arrhythmia*

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27 Serious ventricular arrhythmia incidence, weighted ORs and 95% CIs for days 1-7 after antibiotic  
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29 initiation are presented in Table 2. ORs for serious ventricular arrhythmia compared with cefixime  
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31 were 0.72 (95% CI, 0.49-1.06), 0.92 (95% CI, 0.66-1.29), 0.41 (95% CI, 0.27-0.61), and 1.87 (95%  
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33 CI, 1.15-3.11) for ciprofloxacin, levofloxacin, ofloxacin, and moxifloxacin, respectively.  
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35 Ciprofloxacin and levofloxacin were not associated with an increased risk, while moxifloxacin was  
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37 associated with a 1.87-fold increased risk of serious ventricular arrhythmia. Ofloxacin was associated  
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39 with a 59% reduced risk of serious ventricular arrhythmia compared with cefixime for 1-7 days after  
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41 the index date.  
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44 The serious ventricular arrhythmia incidence and weighted OR for the 8-14 days post-prescription  
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46 are presented in Table 3. ORs for serious ventricular arrhythmia compared with cefixime were 0.44  
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48 (95% CI, 0.29-0.65), 1.08 (95% CI, 0.70-1.69), 0.58 (95% CI, 0.36-0.92), and 1.78 (95% CI, 0.86-  
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50 3.88) for ciprofloxacin, levofloxacin, ofloxacin, and moxifloxacin, respectively. Risk reductions of 66%  
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52 and 42% were found for ciprofloxacin and ofloxacin, respectively. No evidence of an increased risk  
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54 was found for levofloxacin. Moxifloxacin was associated with a 1.78-fold increased risk of serious  
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56 ventricular arrhythmia for 8-14 days after the index date; however, this increased risk was not  
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3 statistically significant.  
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### 8 *Subgroup analyses* 9

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11 Table 4 shows the weighted ORs for serious ventricular arrhythmia 1-7 days after prescribing  
12 ciprofloxacin, levofloxacin, ofloxacin, or moxifloxacin compared with cefixime according to history  
13 of cardiovascular disease, age, and gender. The risk of serious ventricular arrhythmia for ciprofloxacin,  
14 levofloxacin, and ofloxacin users was not increased compared with that for cefixime users.  
15 Moxifloxacin users with histories of cardiovascular disease (OR, 2.36; 95% CI, 1.17-5.12) and those  
16 over 65 years old (OR, 2.04; 95% CI, 1.16-3.73) had significantly increased risks of serious  
17 ventricular arrhythmia compared with cefixime users.  
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## 28 **Discussion** 29

### 30 *Overall findings* 31 32 33

34 The general population data revealed that ciprofloxacin and levofloxacin were not associated with  
35 an increased risk for serious ventricular arrhythmia for 1-7 days after the prescription date and that  
36 ofloxacin was associated with a reduced risk of arrhythmia. Moxifloxacin use was associated with a  
37 1.87-fold increased risk of serious ventricular arrhythmia compared with cefixime during the first  
38 week after initiating the drug. The risk of ventricular arrhythmia was especially high in moxifloxacin  
39 users who were older or had cardiovascular disease. For 8-14 days after the index date, moxifloxacin  
40 showed a 1.78-fold increased risk; however, the 95% CI was not statistically significant. All  
41 moxifloxacin subgroups showed a high risk, but this risk was statistically significant only in patients  
42 with cardiovascular disease and those over 65 years old. The 95% CIs were wide because the number  
43 of moxifloxacin users (n=47,080) included in the study was fewer than that for other drugs, and the  
44 number of serious ventricular arrhythmias was only 7 for days 1-7 after the index date and 4 for days  
45 8-14. Further studies with more subjects are needed to confirm the risk of moxifloxacin.  
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### *Drug induced QT interval prolongation*

Medications can prolong QT intervals, which can lead to fatal ventricular arrhythmias, such as torsades de pointes.[27,28] Torsades de pointes is a polymorphic ventricular tachycardia, which can lead to ventricular fibrillation or sudden cardiac death. Drug-induced QT interval prolongation occurs by inhibiting of cardiac voltage-gated potassium channels encoded by the human ether-a-go-go-related gene (hERG).[35] Blocking the rapid component of the delayed rectifier potassium current ( $I_{Kr}$ ) through hERG channels delays cardiac repolarization, represented by prolonged QT intervals.

Among the medications considered to be associated with prolonged QT intervals, fluoroquinolones and macrolides are the most commonly prescribed drugs in clinical practice;[24] however, QT interval prolongation by fluoroquinolones appears to differ depending by type. A prospective trial suggested that recommended ciprofloxacin and levofloxacin doses have little effect on QT intervals, while moxifloxacin induces the greatest QT interval prolongation.[10] After 7 days of moxifloxacin use, the QTc interval was prolonged by 6 ms relative to baseline. Regarding supratherapeutic fluoroquinolone doses, all three fluoroquinolones increased QT intervals compared with placebo, with moxifloxacin most strongly affecting the interval.[11] The increased QT interval means for the 24-hour period after treatment were 2.3 ms to 4.9 ms, 3.5 ms to 4.9 ms, and 16.3 ms to 17.8 ms for 1500 mg ciprofloxacin, 1000 mg levofloxacin, and 800 mg moxifloxacin, respectively.[11] No studies have been published on the effect of ofloxacin on QT intervals. However, ofloxacin, ciprofloxacin and levofloxacin were significantly less potent hERG channel inhibitors than sparfloxacin, grepafloxacin, or moxifloxacin.[36] Ofloxacin was the least potent hERG channel inhibitor. In contrast, sparfloxacin and grepafloxacin, the most potent hERG channel inhibitors, were withdrawn from the market due to QT interval prolongation.

### *Comparison with other population-based studies*

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3 In a study on veterans in the United States,[21] levofloxacin use was associated with a 3.13-fold  
4 increased risk of cardiac arrhythmias and a 2.49-fold increased risk of all-cause death compared with  
5 amoxicillin. The veteran population was older (mean age, 56.8 years) than our cohort (mean age,  
6 cefixime, 49.3 years; levofloxacin, 50.4 years), which likely explains the different results. In another  
7 study in United States, 0.3, 5.4, and, 2.1 cases of torsades de pointes per 10 million prescriptions from  
8 1996 to 2001 for ciprofloxacin, levofloxacin, and ofloxacin, respectively.[37] A recent cohort study in  
9 Denmark and Sweden[23] found no association between fluoroquinolone use and serious arrhythmias  
10 in the general population; however, because 82% of the prescribed fluoroquinolones were  
11 ciprofloxacin, it remains possible that other fluoroquinolones could increase the risk. In a US study in  
12 a Tennessee Medicaid cohort,[38] patients who took ciprofloxacin and levofloxacin showed no  
13 increased risk for cardiovascular death compared with patients who took amoxicillin for a 10-day  
14 treatment course. A cohort study from Taiwan[22] on the risks of cardiac arrhythmia among patients  
15 using moxifloxacin, levofloxacin, and ciprofloxacin reported that moxifloxacin use was associated  
16 with a 3.30-fold increased risk for ventricular arrhythmia compared with amoxicillin-clavulanate, with  
17 no risk associated with levofloxacin or ciprofloxacin use.

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33 In this study, ciprofloxacin and levofloxacin were not associated with increased ventricular  
34 arrhythmia risk, however, some case reports exist on QT interval prolongation and torsades de pointes  
35 after fluoroquinolone use.[15–19] Most of these cases were patients with concomitant use of other  
36 medications associated with QT interval prolongation or with multiple risk factors associated with  
37 drug-induced arrhythmia. The risk factors for drug-induced arrhythmia are baseline QT interval  
38 prolongation, rapid intravenous drug infusion, digitalis therapy, bradycardia, organic heart disease,  
39 and electrolyte imbalances.[35] Our study excluded patients who were prescribed drugs associated  
40 with QT interval prolongation, and we could not confirm whether the risk of ventricular arrhythmia  
41 was increased by the concomitant fluoroquinolone use with drugs that increase the risk of torsades de  
42 pointes. We also could not assess whether intravenous use was associated with increased risk because  
43 this study was conducted only in oral fluoroquinolone users. Furthermore, no baseline ECG or  
44 electrolyte data were available. Further studies are needed to determine whether fluoroquinolones  
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3 increase the risk of arrhythmias in patients with these risk factors.  
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5 In this study, ofloxacin users had a reduced risk of serious ventricular arrhythmia. However, it is not  
6 possible to conclude that ofloxacin has an anti-arrhythmic effect. In fact, cases of torsades de pointes  
7 had been reported to occur after taking ofloxacin.[37,39] A study with US FDA Adverse Event  
8 Reporting System data reported a reduced risk of torsades de pointes, but the adjusted odds ratio was  
9 not statistically significant (OR, 0.67; 95% CI, 0.03-4.38).[39] In addition, reason for the reduced risk  
10 of arrhythmia in ofloxacin users cannot be clearly explained. Additional clinical and population-based  
11 studies are needed.  
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### 23 *Strengths and limitations*

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25 One of the strengths of this study is that it is the largest study to date evaluating the association  
26 between oral fluoroquinolone use and serious ventricular arrhythmia. This study was a nationwide  
27 population-based study including 4,888,890 patients who were prescribed oral fluoroquinolone or  
28 cefixime. In addition, the datasets had no missing values, thus minimizing the number of subjects.  
29  
30 Second, propensity score weighting was performed to adjust the underlying characteristics and  
31 antibiotic indications of both the fluoroquinolone and cefixime groups. In the propensity score  
32 matching, unmatched subjects occur and subject numbers decreased. In this study, all subjects can be  
33 included for comparison using IPTW.  
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42 This study also had several limitations. First, we cannot rule out the effect of selection bias. We  
43 attempted to adjust the underlying antibiotic characteristics and indications of the fluoroquinolone and  
44 cefixime groups using IPTW to correct for this selection bias. However, it is possible that the ICD-10  
45 codes used to define covariates in the propensity score weighting were inappropriate. For example,  
46 the range of chronic lung diseases that we defined was wide, with 40 to 70% of the individuals in each  
47 antibiotic group having chronic lung disease. This wide range of diagnostic codes suggests that  
48 chronic respiratory illnesses that are unrelated to the antibiotic prescription may have been included.  
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50 The propensity score obtained using these covariates may insufficiently reflect the actual antibiotic  
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3 prescription. Second, there may be a residual confounding effect. This study did not reflect baseline  
4 health information, such as laboratory or ECG data, because we used health claims data. However, we  
5 tried to reduce residual confounding by excluding patients who were recently admitted, prescribed  
6 antibiotics, or prescribed medications that prolonged QT intervals. Third, the ICD-10 code defining  
7 the serious ventricular arrhythmia outcome was not directly validated in the Korean population. In one  
8 study, however, ICD-9 code 427.x predicted a ventricular arrhythmia with a positive predictive value  
9 of 78 to 100%.[40] ICD-9 code 427.x corresponds to the ICD-10 code used in our study. Fourth,  
10 because death data were not linked to the HIRA data, the number of deaths that occurred during the  
11 follow-up period was unconfirmed. Finally, the drug dose was not investigated, and the effect of the  
12 drug dose was not analysed in this study. Further studies are needed to determine how the effects of  
13 fluoroquinolone on arrhythmias vary with drug dose.  
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## 28 **Conclusion**

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31 In this population-based study, ciprofloxacin and levofloxacin were not associated with serious  
32 ventricular arrhythmia, and ofloxacin reduced the risk of arrhythmia. Moxifloxacin was associated  
33 with a 1.87-fold increased risk of serious ventricular arrhythmia compared with cefixime for 1-7 days  
34 after being prescribed. Additional studies in other populations are required to ensure that these  
35 findings are valid for patients with risk factors excluded in this cohort.  
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## 44 **Contributors**

45  
46 Y.C. contributed to the study design; cleaned, analysed, and interpreted the data; and drafted and  
47 revised the manuscript.  
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50 H.P. contributed to the study design, interpreted the data, and critically revised the paper.  
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12  
13 None  
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### 16 **Competing interests**

17  
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19 All authors declare no competing interests.  
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### 26 **Data sharing**

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28 HIRA data are third-party data not owned by the authors. Raw data can be accessed with  
29 permission from the Health Insurance Review and Assessment Service (HIRA) in Korea.  
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8 Table 1. Baseline characteristics of patients using study medications  
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12 cefixime 1-7 days after the index date  
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16 Table 3. Risk of serious ventricular arrhythmia associated with oral fluoroquinolones compared with  
17 cefixime for 8-14 days after the index date  
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21 Table 4. Subgroup analysis of the risk of serious ventricular arrhythmia associated with oral  
22 fluoroquinolones assessed in this study compared with cefixime for 1-7 days after the index date  
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Table 1. Baseline characteristics of patients using study medications

	Cefixime	Ciprofloxacin	Levofloxacin	Ofloxacin	Moxifloxacin
No. of subjects	402930	1466133	1141961	1830786	47080
Age, mean $\pm$ SD	49.3 $\pm$ 17.7	48.5 $\pm$ 17.3	50.4 $\pm$ 16.7	50.3 $\pm$ 16.9	58.4 $\pm$ 17.4
No. of females (%)	238329 (59.1)	951813 (64.9)	643076 (56.3)	1120119 (61.2)	23586 (50.1)
<i>No. of Comorbidities (%)</i>					
Hypertension	121529 (30.2)	410360 (28.0)	346918 (30.4)	540934 (29.5)	21690 (46.1)
Diabetes mellitus	97779 (24.3)	321483 (21.9)	268447 (23.5)	382877 (20.9)	17977 (38.2)
Acute myocardial infarction	6536 (1.6)	17451 (1.2)	15209 (1.3)	11731 (1.0)	1292 (2.7)
Ischaemic heart disease	45810 (11.4)	137303 (9.4)	122740 (10.7)	161602 (8.8)	9408 (20)
Cardiomyopathy	1450 (0.4)	3668 (0.3)	3443 (0.3)	3924 (0.2)	438 (0.9)
Valve disorder	1826 (0.5)	4971 (0.3)	4643 (0.4)	6219 (0.3)	513 (1.1)
Arrhythmia	14387 (3.6)	45727 (3.1)	38751 (3.4)	53536 (2.9)	2761 (5.9)
Congestive heart failure	21753 (5.4)	59507 (4.1)	55276 (4.8)	68471 (3.7)	5724 (12.2)
Congenital heart disease	550 (0.1)	1599 (0.1)	1430 (0.1)	1894 (0.1)	110 (0.2)
Cancer	43336 (10.8)	128612 (8.8)	118618 (10.4)	122116 (6.7)	10285 (21.8)
Cerebrovascular disease	42741 (10.6)	127394 (8.7)	113241 (9.9)	155453 (8.5)	8389 (17.8)
Renal disease	27440 (6.8)	93946 (6.4)	73935 (6.5)	83202 (4.5)	5657 (12)
Arterial disease	58202 (14.4)	201275 (13.7)	173004 (15.1)	268362 (14.7)	9298 (19.7)
Venous thromboembolism	5613 (1.4)	15375 (1.0)	14016 (1.2)	16571 (0.9)	1704 (3.6)
Dementia	17245 (4.3)	48445 (3.3)	41097 (3.6)	46626 (2.5)	4046 (8.6)
Rheumatic disease	29610 (7.3)	97980 (6.7)	77971 (6.8)	112629 (6.2)	4453 (9.5)
Peptic ulcer disease	148247 (36.8)	527527(36.0)	418871 (36.7)	636452 (34.8)	21304 (45.3)
Chronic lung disease	215194 (53.4)	633215 (43.2)	586894 (51.4)	810357 (44.3)	36096 (76.7)
<i>No. of Antibiotic Indications (%)</i>					
Upper respiration infection	41000 (10.2)	34919 (2.4)	71542 (6.3)	200376 (10.9)	2024 (4.3)
Pneumonia	17362 (4.3)	13792 (0.9)	54016 (4.7)	10048 (0.5)	10567 (22.4)
Other respiratory infection	31943 (7.9)	49097 (3.3)	118629 (10.4)	266793 (14.6)	2898 (6.2)
Gastrointestinal infection	10997 (2.7)	258359 (17.6)	26806 (2.3)	116001 (6.3)	142 (0.3)
Urinary tract infection	24497 (6.1)	477439 (32.6)	255878 (22.4)	204458 (11.2)	396 (0.8)
Genitourinary infection	10357 (2.6)	103874 (7.1)	104759 (9.2)	75822 (4.1)	806 (1.7)
Skin/Wound infection	15212 (3.8)	13240 (0.9)	20509 (1.8)	47573 (2.6)	589 (1.3)

Table 2. Risk of serious ventricular arrhythmia associated with oral fluoroquinolones compared with cefixime 1-7 days after the index date

	Cefixime	Ciprofloxacin	Levofloxacin	Ofloxacin	Moxifloxacin
Number of serious ventricular arrhythmia	18	31	48	26	7
Incidence per 1000000 subjects	44.7	21.1	42.0	14.2	148.7
Odds ratio (95% CI) (IPTW)	Reference	0.72 (0.49-1.06)	0.92 (0.66-1.29)	0.41 (0.27-0.61)	1.87 (1.15-3.11)

CI=confidence interval; IPTW =inverse probability of treatment weighting

Table 3. Risk of serious ventricular arrhythmia associated with oral fluoroquinolones compared with cefixime for 8-14 days after the index date

	Cefixime	Ciprofloxacin	Levofloxacin	Ofloxacin	Moxifloxacin
Number of serious ventricular arrhythmia	8	24	29	21	4
Incidence per 1000000 subjects	19.9	16.4	25.4	11.5	85.0
Odds ratio (95% CI) (IPTW)	Reference	0.44 (0.29-0.65)	1.08 (0.70-1.69)	0.58 (0.36-0.92)	1.78 (0.86-3.88)

CI=confidence interval; IPTW =inverse probability of treatment weighting

Table 4. Subgroup analysis of the risk of serious ventricular arrhythmia associated with oral fluoroquinolones assessed in this study compared with cefixime for 1-7 days after the index date

	Cefixime	Ciprofloxacin	Levofloxacin	Ofloxacin	Moxifloxacin
<i>History of cardiovascular disease</i>					
Odds ratio (95% CI) (IPTW)	Reference	0.61 (0.34-1.08)	0.96 (0.58-1.57)	0.47 (0.24-0.85)	2.36 (1.17-5.12)
<i>Without cardiovascular disease</i>					
Odds ratio (95% CI) (IPTW)	Reference	0.79 (0.47-1.33)	0.86 (0.54-1.34)	0.36 (0.21-0.60)	1.63 (0.84-3.29)
<i>Age ≥65</i>					
Odds ratio (95% CI) (IPTW)	Reference	0.78 (0.48-1.24)	1.06 (0.71-1.60)	0.36 (0.22-0.57)	2.04 (1.16-3.73)
<i>Age &lt;65</i>					
Odds ratio (95% CI) (IPTW)	Reference	0.64 (0.32-1.25)	0.96 (0.51-1.81)	0.84 (0.38-1.85)	1.59 (0.60-4.58)
<i>Male</i>					
Odds ratio (95% CI) (IPTW)	Reference	0.61 (0.36-0.99)	0.82 (0.53-1.25)	0.53 (0.29-0.96)	1.91 (1.00-3.80)
<i>Female</i>					
Odds ratio (95% CI) (IPTW)	Reference	0.62 (0.35-1.07)	0.89 (0.54-1.46)	0.33 (0.19-0.56)	1.79 (0.87-3.92)

CI=confidence interval; IPTW =inverse probability of treatment weighting

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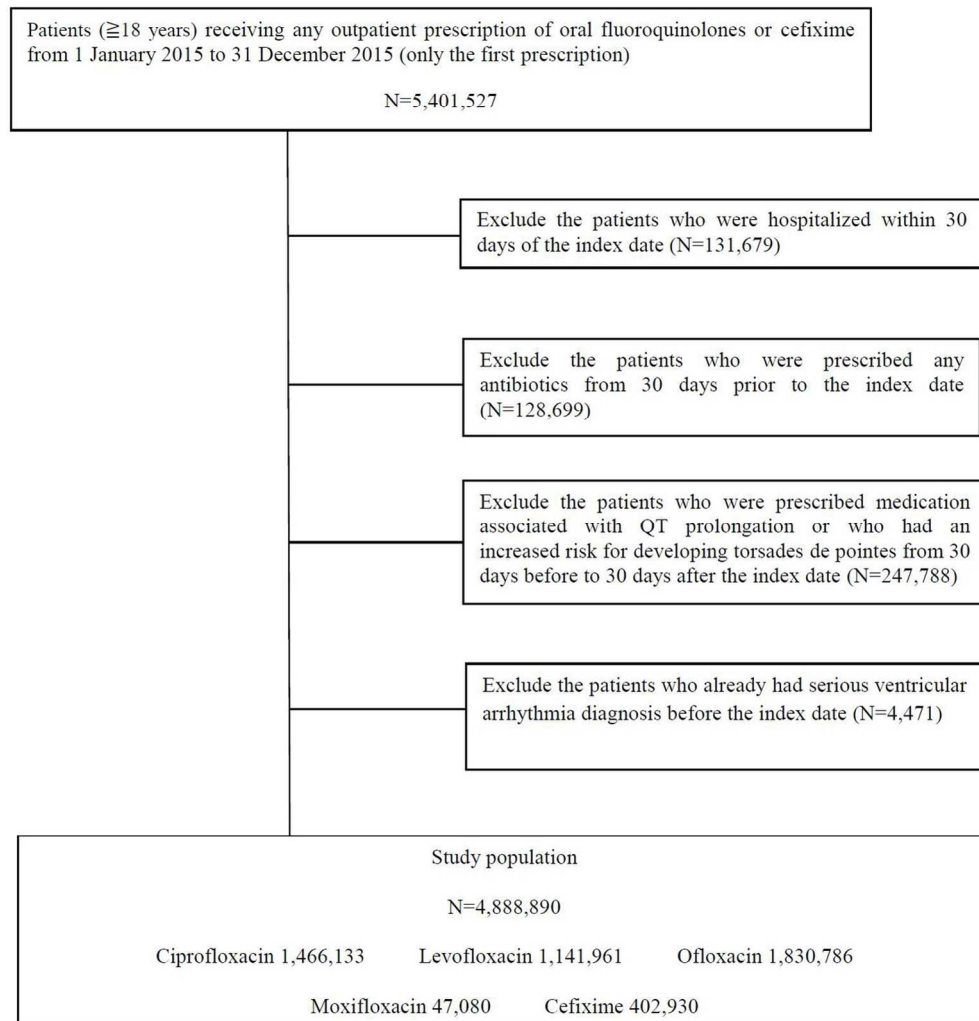


Figure 1. Study flow chart  
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**Supplementary appendix**

Table S1. Korea Drug Codes for oral fluoroquinolones and cefixime

Table S2. Korea Drug Codes for medications used in the exclusion criteria that are associated with prolonged QT intervals or an increased risk of developing torsades de pointes

Table S3. ICD-10 covariate codes

Table S4. Baseline characteristics of patients using cefixime or ciprofloxacin and the standardized differences before and after IPTW

Table S5. Baseline characteristics of patients using cefixime or levofloxacin and the standardized differences before and after IPTW

Table S6. Baseline characteristics of patients using cefixime or ofloxacin and the standardized differences before and after IPTW

Table S7. Baseline characteristics of patients using cefixime or moxifloxacin and the standardized differences before and after IPTW

Table S1. Korea Drug Codes for oral fluoroquinolones and cefixime

Medications	Korea Drug Codes
Ciprofloxacin	134101ATB,134103ATB, 134105ATB, 134105ATR, 134108ATR, 134109ATB
Levofloxacin	183201ATB, 183202ATB, 183203ATB
Ofloxacin	203901ATB, 203904ATB
Moxifloxacin	380301ATB
Cefixime	126301ACH

Table S2. Korea Drug Codes for medications used in the exclusion criteria that are associated with prolonged QT intervals or an increased risk of developing torsades de pointes

Medications	Korea Drug Codes
Amiodarone	107401ATB
Sotalol	230401ATB, 230402ATB
Quinidine	222001ATB, 222002ATB
Digoxin	144801ATB
Flecainide	159302ATB
Propafenone	219501ATB, 219502ATB
Erythromycin	153501ACH, 153801ATB, 154001ACH
Clarithromycin	134901ATB, 134904ATB
Telithromycin	455901ATB
Chloroquine	171602ATB, 171701ATB, 171702ATB, 171703ATB, 171704ATB,
Ketoconazole	179601ATB,
Itraconazole	179101ACH, 179104ATB
Voriconazole	456501ATB
Sunitinib	487701ACH, 487702ACH, 487703ACH
Domperidone	148402ATB, 148501ATB
Dolasetron	414602ATB
Ondansetron	204601ATB, 204601ATD, 204603ATB
Granisetron	167301ATB, 167301ATD
Sumatriptan	233802ATB, 233803ATB
Zolmitriptan	415601ATB
Naratriptan	415501ATB
Chlorpromazine	131901ATB, 131905ATB, 131908ATB
Haloperidol	167903ATB, 167904ATB, 167905ATB, 167906ATB, 167908ATB,
Pimozide	212401ATB, 212402ATB
Clozapine	137501ATB, 137502ATB
Quetiapine	378601ATB, 378602ATB, 378603ATB, 378604ATB, 378605ATR, 378606ATR, 378607ATR, 378608ATR, 378609ATR,
Risperidone	224201ATB, 224201ATD, 224202ATB, 224203ATB, 224204ATB, 224207ATB,
Imipramine	173701ATB,
Paroxetine	209301ATB, 209302ATB, 209304ATR, 209305ATR, 209306ATR,
Sertraline	227001ATB, 227002ATB
Venlafaxine	247502ATR, 247504ATR
Fluoxetine	161501ACH, 161502ACH, 161502ATD, 161504ACR
Fluvoxamine	162501ATB, 162502ATB

Table S3. ICD-10 covariate codes

<i>Comorbidities</i>	
Hypertension	I10-I13.x, I15.x
Diabetes mellitus	E10.x-E14.x
Acute myocardial infarction	I21.x, I22.x, I23.x
Ischaemic heart disease	I20.x, I24.x, I25.x
Cardiomyopathy	I42.x, I43.x
Valve disorder	I34.x-37.x
Arrhythmia	I44.x, I45.x, I47.0, I47.1, I47.9, I49.1-9
Congestive heart failure	I11.0, I13.0, I13.2, I50.x, J81.x
Congenital heart disease	Q20.x-26.x
Cancer	C00.x-C99.x
Cerebrovascular disease	G45.x, G46.x, I60.x-I69.x
Renal disease	N00.x-N08.x, N17.x-19.x, N25.x, Z49.x, Z94.0, Z99.2
Arterial disease	I70.x-I79.x
Venous thromboembolism	I26.x, I80.x
Dementia	F00.x-F03.x, G30.x
Rheumatic disease (connective tissue disease)	M05.x, M06.x, M32.x-M34.x
Peptic ulcer disease	K25.x-K28.x
Chronic lung disease	J40.x-47.x, J60.x-70.x
<i>Indications for antibiotics</i>	
Upper respiratory infection	J01.x-J06.x
Pneumonia	J13.x-J18.x
Other respiratory infection	J20.x-J22.x
Gastrointestinal infection	A00.x-A09.x
Urinary tract infection	N10.x-N12.x, N30.x, N39.0, N41.x
Genitourinary infection	N34.x, N45.x, N70.x-77.x
Skin/wound infection	L00.x-L08.x

ICD-10=International Classification of Diseases, Tenth Revision

Table S4. Baseline characteristics of patients using cefixime or ciprofloxacin and the standardized difference before and after IPTW

	Cefixime	Ciprofloxacin	Standardized difference	
			Before IPTW	After IPTW
No. of subjects	402930	1466133		
Age, mean $\pm$ SD	49.3 $\pm$ 17.7	48.5 $\pm$ 17.3	0.041	0.046
No. of females (%)	238329 (59.1)	951813 (64.9)	0.119	0.042
<i>No. of Comorbidities (%)</i>				
Hypertension	121529 (30.2)	410360 (28.0)	0.048	0.044
Diabetes mellitus	97779 (24.3)	321483 (21.9)	0.056	0.042
Acute myocardial infarction	6536 (1.6)	17451 (1.2)	0.037	0.008
Ischaemic heart disease	45810 (11.4)	137303 (9.4)	0.066	0.019
Cardiomyopathy	1450 (0.4)	3668 (0.3)	0.020	0.003
Valve disorder	1826 (0.5)	4971 (0.3)	0.018	0.005
Arrhythmia	14387 (3.6)	45727 (3.1)	0.025	0.008
Congestive heart failure	21753 (5.4)	59507 (4.1)	0.063	0.019
Congenital heart disease	550 (0.1)	1599 (0.1)	0.008	0.002
Cancer	43336 (10.8)	128612 (8.8)	0.067	0.015
Cerebrovascular disease	42741 (10.6)	127394 (8.7)	0.065	0.030
Renal disease	27440 (6.8)	93946 (6.4)	0.016	0.027
Arterial disease	58202 (14.4)	201275 (13.7)	0.021	0.021
Venous thromboembolism	5613 (1.4)	15375 (1.0)	0.031	0.005
Dementia	17245 (4.3)	48445 (3.3)	0.051	0.037
Rheumatic disease	29610 (7.3)	97980 (6.7)	0.026	0.009
Peptic ulcer disease	148247 (36.8)	527527(36.0)	0.017	0.038
Chronic lung disease	215194 (53.4)	633215 (43.2)	0.206	0.026
<i>No. of Antibiotic Indications (%)</i>				
Upper respiratory infection	41000 (10.2)	34919 (2.4)	0.326	0.002
Pneumonia	17362 (4.3)	13792 (0.9)	0.212	0.002
Other respiratory infection	31943 (7.9)	49097 (3.3)	0.200	0.003
Gastrointestinal infection	10997 (2.7)	258359 (17.6)	0.508	0.001
Urinary tract infection	24497 (6.1)	477439 (32.6)	0.712	0.014
Genitourinary infection	10357 (2.6)	103874 (7.1)	0.212	0.003
Skin/Wound infection	15212 (3.8)	13240 (0.9)	0.191	0.002
<i>Month, No (%)</i>				
1	51082 (12.7)	198022 (13.5)	0.122	0.028
2	41252 (10.2)	139390 (9.5)		
3	43687 (10.8)	136164 (9.3)		
4	39505 (9.8)	123691 (8.4)		
5	32150 (8.0)	107959 (7.4)		
6	28567 (7.1)	110219 (7.5)		
7	25587 (6.4)	121446 (8.3)		
8	26722 (6.6)	118711 (8.1)		
9	27912 (6.9)	104986 (7.2)		
10	29177 (7.2)	97368 (6.6)		
11	26293 (6.5)	97704 (6.7)		
12	30966 (7.7)	110473 (7.5)		

Table S5. Baseline characteristics of patients using cefixime or levofloxacin and the standardized difference before and after IPTW

	Cefixime	Levofloxacin	Standardized difference	
			Before IPTW	After IPTW
No. of subjects	402930	1141961		
Age, mean $\pm$ SD	49.3 $\pm$ 17.7	50.4 $\pm$ 16.7	0.068	0.042
No. of females (%)	238329 (59.1)	643076 (56.3)	0.057	0.064
<i>No. of Comorbidities (%)</i>				
Hypertension	121529 (30.2)	346918 (30.4)	0.005	0.026
Diabetes mellitus	97779 (24.3)	268447 (23.5)	0.018	0.024
Acute myocardial infarction	6536 (1.6)	15209 (1.3)	0.024	0.005
Ischaemic heart disease	45810 (11.4)	122740 (10.7)	0.020	0.014
Cardiomyopathy	1450 (0.4)	3443 (0.3)	0.010	0.001
Valve disorder	1826 (0.5)	4643 (0.4)	0.007	0.003
Arrhythmia	14387 (3.6)	38751 (3.4)	0.010	0.007
Congestive heart failure	21753 (5.4)	55276 (4.8)	0.025	0.013
Congenital heart disease	550 (0.1)	1430 (0.1)	0.003	<0.001
Cancer	43336 (10.8)	118618 (10.4)	0.012	0.011
Cerebrovascular disease	42741 (10.6)	113241 (9.9)	0.023	0.021
Renal disease	27440 (6.8)	73935 (6.5)	0.013	0.016
Arterial disease	58202 (14.4)	173004 (15.1)	0.020	0.015
Venous thromboembolism	5613 (1.4)	14016 (1.2)	0.015	0.004
Dementia	17245 (4.3)	41097 (3.6)	0.035	0.022
Rheumatic disease	29610 (7.3)	77971 (6.8)	0.020	0.006
Peptic ulcer disease	148247 (36.8)	418871 (36.7)	0.002	0.027
Chronic lung disease	215194 (53.4)	586894 (51.4)	0.040	0.019
<i>No. of Antibiotic Indications (%)</i>				
Upper respiratory infection	41000 (10.2)	71542 (6.3)	0.143	0.002
Pneumonia	17362 (4.3)	54016 (4.7)	0.020	0.007
Other respiratory infection	31943 (7.9)	118629 (10.4)	0.085	0.001
Gastrointestinal infection	10997 (2.7)	26806 (2.3)	0.024	<0.001
Urinary tract infection	24497 (6.1)	255878 (22.4)	0.480	0.003
Genitourinary infection	10357 (2.6)	104759 (9.2)	0.284	0.012
Skin/Wound infection	15212 (3.8)	20509 (1.8)	0.121	0.001
<i>Month, No (%)</i>				
1	51082 (12.7)	186297 (16.3)	0.161	0.020
2	41252 (10.2)	128738 (11.3)		
3	43687 (10.8)	128601 (11.3)		
4	39505 (9.8)	113718 (10.0)		
5	32150 (8.0)	89592 (7.8)		
6	28567 (7.1)	83536 (7.3)		
7	25587 (6.4)	76140 (6.7)		
8	26722 (6.6)	74130 (6.5)		
9	27912 (6.9)	72417 (6.3)		
10	29177 (7.2)	72734 (6.4)		
11	26293 (6.5)	55296 (4.8)		
12	30966 (7.7)	60762 (5.3)		

Table S6. Baseline characteristics of patients using cefixime or ofloxacin and the standardized difference before and after IPTW

	Cefixime	Ofloxacin	Standardized difference	
			Before IPTW	After IPTW
No. of subjects	402930	1830786		
Age, mean $\pm$ SD	49.3 $\pm$ 17.7	50.3 $\pm$ 16.9	0.061	0.009
No. of females (%)	238329 (59.1)	1120119 (61.2)	0.042	0.006
<i>No. of Comorbidities (%)</i>				
Hypertension	121529 (30.2)	540934 (29.5)	0.013	0.005
Diabetes mellitus	97779 (24.3)	382877 (20.9)	0.080	0.001
Acute myocardial infarction	6536 (1.6)	11731 (1.0)	0.058	0.001
Ischaemic heart disease	45810 (11.4)	161602 (8.8)	0.084	0.004
Cardiomyopathy	1450 (0.4)	3924 (0.2)	0.027	<0.001
Valve disorder	1826 (0.5)	6219 (0.3)	0.018	0.001
Arrhythmia	14387 (3.6)	53536 (2.9)	0.036	0.001
Congestive heart failure	21753 (5.4)	68471 (3.7)	0.079	0.003
Congenital heart disease	550 (0.1)	1894 (0.1)	0.010	<0.001
Cancer	43336 (10.8)	122116 (6.7)	0.145	0.008
Cerebrovascular disease	42741 (10.6)	155453 (8.5)	0.072	0.001
Renal disease	27440 (6.8)	83202 (4.5)	0.098	0.005
Arterial disease	58202 (14.4)	268362 (14.7)	0.006	0.003
Venous thromboembolism	5613 (1.4)	16571 (0.9)	0.046	0.004
Dementia	17245 (4.3)	46626 (2.5)	0.096	0.005
Rheumatic disease	29610 (7.3)	112629 (6.2)	0.048	0.001
Peptic ulcer disease	148247 (36.8)	636452 (34.8)	0.042	0.004
Chronic lung disease	215194 (53.4)	810357 (44.3)	0.184	0.004
<i>No. of Antibiotic Indications (%)</i>				
Upper respiratory infection	41000 (10.2)	200376 (10.9)	0.025	0.006
Pneumonia	17362 (4.3)	10048 (0.5)	0.246	0.001
Other respiratory infection	31943 (7.9)	266793 (14.6)	0.211	0.005
Gastrointestinal infection	10997 (2.7)	116001 (6.3)	0.174	0.002
Urinary tract infection	24497 (6.1)	204458 (11.2)	0.182	0.006
Genitourinary infection	10357 (2.6)	75822 (4.1)	0.087	0.004
Skin/Wound infection	15212 (3.8)	47573 (2.6)	0.067	0.004
<i>Month, No (%)</i>				
1	51082 (12.7)	255833 (14.0)	0.058	0.009
2	41252 (10.2)	200347 (10.9)		
3	43687 (10.8)	207332 (11.3)		
4	39505 (9.8)	177080 (9.7)		
5	32150 (8.0)	141413 (7.7)		
6	28567 (7.1)	127462 (7.0)		
7	25587 (6.4)	117053 (6.4)		
8	26722 (6.6)	115864 (6.3)		
9	27912 (6.9)	117031 (6.4)		
10	29177 (7.2)	124597 (6.8)		
11	26293 (6.5)	116492 (6.4)		
12	30966 (7.7)	130282 (7.1)		

Table S7. Baseline characteristics of patients using cefixime or moxifloxacin and the standardized difference before and after IPTW

	Cefixime	Moxifloxacin	Standardized difference	
			Before IPTW	After IPTW
No. of subjects	402930	47080		
Age, mean $\pm$ SD	49.3 $\pm$ 17.7	58.4 $\pm$ 17.4	0.521	0.007
No. of females (%)	238329 (59.1)	23586 (50.1)	0.183	0.024
<i>No. of Comorbidities (%)</i>				
Hypertension	121529 (30.2)	21690 (46.1)	0.332	0.031
Diabetes mellitus	97779 (24.3)	17977 (38.2)	0.304	0.027
Acute myocardial infarction	6536 (1.6)	1292 (2.7)	0.077	0.011
Ischaemic heart disease	45810 (11.4)	9408 (20)	0.239	0.024
Cardiomyopathy	1450 (0.4)	438 (0.9)	0.071	0.005
Valve disorder	1826 (0.5)	513 (1.1)	0.073	0.002
Arrhythmia	14387 (3.6)	2761 (5.9)	0.108	0.012
Congestive heart failure	21753 (5.4)	5724 (12.2)	0.241	0.013
Congenital heart disease	550 (0.1)	110 (0.2)	0.023	0.004
Cancer	43336 (10.8)	10285 (21.8)	0.304	0.010
Cerebrovascular disease	42741 (10.6)	8389 (17.8)	0.208	0.018
Renal disease	27440 (6.8)	5657 (12)	0.179	0.025
Arterial disease	58202 (14.4)	9298 (19.7)	0.141	0.019
Venous thromboembolism	5613 (1.4)	1704 (3.6)	0.143	0.002
Dementia	17245 (4.3)	4046 (8.6)	0.176	0.023
Rheumatic disease	29610 (7.3)	4453 (9.5)	0.076	0.012
Peptic ulcer disease	148247 (36.8)	21304 (45.3)	0.173	0.024
Chronic lung disease	215194 (53.4)	36096 (76.7)	0.503	0.003
<i>No. of Antibiotic Indications (%)</i>				
Upper respiratory infection	41000 (10.2)	2024 (4.3)	0.228	0.019
Pneumonia	17362 (4.3)	10567 (22.4)	0.553	0.018
Other respiratory infection	31943 (7.9)	2898 (6.2)	0.069	0.017
Gastrointestinal infection	10997 (2.7)	142 (0.3)	0.200	<0.001
Urinary tract infection	24497 (6.1)	396 (0.8)	0.290	0.015
Genitourinary infection	10357 (2.6)	806 (1.7)	0.059	0.060
Skin/Wound infection	15212 (3.8)	589 (1.3)	0.162	0.040
<i>Month, No (%)</i>				
1	51082 (12.7)	8179 (17.4)	0.201	0.046
2	41252 (10.2)	5913 (12.6)		
3	43687 (10.8)	5674 (12.1)		
4	39505 (9.8)	4736 (10.1)		
5	32150 (8.0)	3549 (7.5)		
6	28567 (7.1)	3132 (6.7)		
7	25587 (6.4)	2486 (5.3)		
8	26722 (6.6)	2323 (4.9)		
9	27912 (6.9)	2383 (5.1)		
10	29177 (7.2)	2791 (5.9)		
11	26293 (6.5)	2412 (5.1)		
12	30966 (7.7)	3502 (7.4)		

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
<b>Title and abstract</b>	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1	Association of oral ciprofloxacin, levofloxacin, ofloxacin, and moxifloxacin with the risk of serious ventricular arrhythmia: a nationwide cohort study in Korea
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2	
<b>Introduction</b>				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4	Previous studies have reported the risk of arrhythmia by fluoroquinolone type, but their results differed.
Objectives	3	State specific objectives, including any prespecified hypotheses	4	To clarify this issue, we utilized a large general population database in Korea to examine whether oral ciprofloxacin, levofloxacin, ofloxacin, or moxifloxacin increased the risk of ventricular arrhythmia compared with the risk associated with cefixime
<b>Methods</b>				
Study design	4	Present key elements of study design early in the paper	5	The population-based cohort study
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	2, 4,5	Design: Population-based cohort study using administrative claims data on a national scale in Korea.



				Setting: All primary, secondary, and tertiary care settings from 01 January 2015 to 31 December 2015.
Participants	6	<p>(a) <i>Cohort study</i>—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up</p> <p><i>Case-control study</i>—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls</p> <p><i>Cross-sectional study</i>—Give the eligibility criteria, and the sources and methods of selection of participants</p>	5, 6,	<p>Inclusion criteria and exposures</p> <p>We included adult patients over 18 years old. Only the first prescribed study medication was included in the analysis if the patient was prescribed more than one antibiotic during the study period. Patients who were prescribed the relevant study medications outpatient visits in all primary, secondary, and tertiary care settings were included.</p> <p>Follow-up began on the index date and ended on the date of serious arrhythmia or 14 days after starting treatment, whichever came first.</p>
		<p>(b) <i>Cohort study</i>—For matched studies, give matching criteria and number of exposed and unexposed</p> <p><i>Case-control study</i>—For matched studies, give matching criteria and the number of controls per case</p>		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6	<p>Outcome definition</p> <p>The outcomes of serious ventricular arrhythmia included ventricular tachycardia, fibrillation, flutter, and cardiac arrest. The International Classification of Diseases, Tenth Revision [ICD-10] codes (I472, I490.x, I460, I461, and</p>

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				I469) were used to identify the patients with serious ventricular arrhythmias.
Data sources/ measurement	8*	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	5,6,7,8	
Bias	9	Describe any efforts to address potential sources of bias	5, 7	To reduce potential confounding by indication, oral cefixime was used as a control. Inverse probability treatment weights were calculated with propensity scores to adjust for baseline differences and control for confounding by indication.
Study size	10	Explain how the study size was arrived at	5	This population-based cohort study included patients who had been prescribed oral fluoroquinolones (ciprofloxacin, levofloxacin, ofloxacin, or moxifloxacin) or cefixime in the outpatient department from 01 January 2015 to 31 December 2015.

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Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7,8	
		(b) Describe any methods used to examine subgroups and interactions	7,8	
		(c) Explain how missing data were addressed	8	No data were missing in this study.
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	6	Follow-up began on the index date and ended on the date of serious arrhythmia or 14 days after starting treatment, whichever came first.
		(e) Describe any sensitivity analyses		No sensitivity analysis
<b>Results</b>				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8	4,888,890 patients were included in the analysis (Figure 1). The study population consisted of 1,466,133 ciprofloxacin users, 1,141,961 levofloxacin users, 1,830,786 ofloxacin users, 47,080 moxifloxacin users, and 402,930 cefixime users.
		(b) Give reasons for non-participation at each stage	8	We extracted 5,401,527 outpatients who were prescribed oral fluoroquinolones and cefixime from 01 January 2015 to 31 December 2015. After excluding 512,637 patients who were (1) hospitalized within 30 days of the index date (n=131,679), (2) prescribed antibiotics from 30 days prior to the index date (n=128,699), (3) prescribed medication associated with QT interval prolongation or who had an increased risk for developing torsades de pointes from 30 days before to 30 days after the index date (n=247,788), or (4)

			20	diagnosed with serious ventricular arrhythmia before the index date (n=4,471), Figure 1
		(c) Consider use of a flow diagram	20	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8	Study population characteristics
		(b) Indicate number of participants with missing data for each variable of interest	Table 1	No missing data
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	6	Because fluoroquinolone and cefixime are generally recommended to be prescribed for 7-14 days, we used observation periods of 1-7 days and 8-14 days after the index date to evaluate the adverse effects of these medications. These periods were chosen because acute side effects from the drug can develop during the administration period.
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	21	Table 2, Table 3
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure		
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures		
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	21	Table 2, Table 3
		(b) Report category boundaries when continuous variables were categorized		
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		

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Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	22	Table 4
<b>Discussion</b>				
Key results	18	Summarise key results with reference to study objectives	10	Overall findings The general population data revealed that ciprofloxacin and levofloxacin were not associated with an increased risk for serious ventricular arrhythmia for 1-7 days after the prescription date and that ofloxacin was associated with a reduced risk of arrhythmia. Moxifloxacin use was associated with a 1.87-fold increased risk of serious ventricular arrhythmia compared with cefixime during the first week after initiating the drug. The risk of ventricular arrhythmia was especially high in moxifloxacin users who were older or had cardiovascular disease. For 8-14 days after the index date, moxifloxacin showed a 1.78-fold increased risk; however, the 95% CI was not statistically significant. All moxifloxacin subgroups showed a high risk, but this risk was statistically significant only in patients with cardiovascular disease and those over 65 years old. The 95% CIs were wide because the number of moxifloxacin users (n=47,080) included in the study was fewer than that for other drugs, and the number of serious ventricular arrhythmias was only 7

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				for days 1-7 after the index date and 4 for days 8-14. Further studies with more subjects are needed to confirm the risk of moxifloxacin.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13	This study also had several limitations. First, we cannot rule out the effect of selection bias. We attempted to adjust the underlying antibiotic characteristics and indications of the fluoroquinolone and cefixime groups using IPTW to correct for this selection bias. However, it is possible that the ICD-10 codes used to define covariates in the propensity score weighting were inappropriate. For example, the range of chronic lung diseases that we defined was wide, with 40 to 70% of the individuals in each antibiotic group having chronic lung disease. This wide range of diagnostic codes suggests that chronic respiratory illnesses that are unrelated to the antibiotic prescription may have been included. The propensity score obtained using these covariates may insufficiently reflect the actual antibiotic prescription. Second, there may be a residual confounding effect. This study did not reflect baseline health information, such as laboratory or ECG data, because we used health claims data. However, we tried to reduce residual confounding by

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excluding patients who were recently admitted, prescribed antibiotics, or prescribed medications that prolonged QT intervals. Third, the ICD-10 code defining the serious ventricular arrhythmia outcome was not directly validated in the Korean population. In one study, however, ICD-9 code 427.x predicted a ventricular arrhythmia with a positive predictive value of 78 to 100%.<sup>[38]</sup> ICD-9 code 427.x corresponds to the ICD-10 code used in our study. Fourth, because death data were not linked to the HIRA data, the number of deaths that occurred during the follow-up period was unconfirmed. Finally, the drug dose was not investigated, and the effect of the drug dose was not analysed in this study. Further studies are needed to determine how the effects of fluoroquinolone on arrhythmias vary with drug dose.

30 Interpretation 20 Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of  
31 analyses, results from similar studies, and other relevant evidence

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32 All moxifloxacin subgroups showed a high risk, but this risk was statistically significant only in patients with cardiovascular disease and those over 65 years old. The 95% CIs were wide because the number of moxifloxacin users (n=47,080) included in the study was fewer than that for other drugs, and the number of serious ventricular arrhythmias was only 7

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				for days 1-7 after the index date and 4 for days 8-14. Further studies with more subjects are needed to confirm the risk of moxifloxacin.
Generalisability	21	Discuss the generalisability (external validity) of the study results	14	Additional studies in other populations are required to ensure that these findings are valid for patients with risk factors excluded in this cohort.
<b>Other information</b>				
Funding	22	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	14	This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).