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

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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 torsedes 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

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

Data Source and Ethics

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

Inclusion criteria and exposures

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.

Exclusion criteria

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.

Outcome definition

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. Only the main diagnostic codes were used. The first diagnosis was included when the patients had diagnosis codes of serious ventricular arrhythmia more than once. 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. This reflects that the acute side effect of the drug develops during the actual administration period. 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.

Covariates

Covariates were defined by ICD-10 codes. (Supplementary Appendix) Included diseases were hypertension, diabetes mellitus, acute myocardial infarction, ischemic heart disease, cardiomyopathy, valve disorder, arrhythmia, congestive heart failure, congenital heart disease, cancer, cerebrovascular disease, renal disease, arterial disease, venous thromboembolism, dementia, rheumatic disease, peptic ulcer disease, and chronic lung disease. Indications of antibiotics were identified by primary diagnosis codes of index date. Diagnosis of infections included as covariates were upper respiratory infection,

pneumonia, other respiratory infection, gastrointestinal infection, urinary tract infection, genitourinary tract infection, and skin/wound infection.

Statistical analyses

The number of serious ventricular arrhythmia was identified and the incidence per 1,000,000 patients was calculated. Each group of patients prescribed ciprofloxacin, levofloxacin, ofloxacin, and moxifloxacin was compared with the group prescribed cefixime to assess the risk of ventricular arrhythmia. Using logistic regression with inverse probability treatment weighting (IPTW), we calculated the odds ratio (OR) and 95% confidence interval (CI) of serious ventricular arrhythmia compared to cefixime during days 1~7 and 8~14 after the index date.

We calculated propensity scores of being prescribed ciprofloxacin, levofloxacin, ofloxacin, and moxifloxacin compared to cefixime using logistic regression. Age, sex, the prescription month, all covariates related comorbidities, and indications of antibiotics were included in the propensity models. Then, inverse probability treatment weights are calculated with propensity scores to adjust for baseline differences and control for confounding by indication.[32] IPTW weighs the inverse of the estimated propensity score for treated patients and the inverse of one minus the estimated propensity score for control patients.[33] Propensity score matching has the disadvantage of including only a subset of subjects and controls in the analysis, but IPTW can be used without reducing samples. We evaluated the balance of baseline covariates between groups with standardized differences before and after IPTW. The standardized difference <0.1 indicate that covariates are well balanced between treatment and control patients.[34]

As subgroup analysis we divided patients by age, sex, and history of cardiovascular disease. Acute myocardial infarction, ischemic heart disease, cardiomyopathy, valve disorder, arrhythmia, congestive heart failure, and congenital heart disease were included in cardiovascular disease. We defined cardiovascular disease using the same ICD-10 code as that used to define baseline comorbidities. The

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).

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

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, 0.86-3.88) for ciprofloxacin, levofloxacin, ofloxacin, and moxifloxacin, respectively. Overall, all of four fluoroquinolones had no increased risk of serious ventricular arrhythmia.

Subgroup analyses

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

Discussion

The general population data reveal that ciprofloxacin, levofloxacin, and ofloxacin use were not associated with increased risk of serious ventricular arrhythmia. Moxifloxacin use showed increased risk of serious ventricular arrhythmia. 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.

In study of veterans in the United States,[21] levofloxacin use was associated with a 3.13-fold increased risk of cardiac arrhythmias compared to amoxicillin. But, levofloxacin use also showed increased risk of all-cause death, indicating that the baseline condition was more severe in the levofloxacin group compared to amoxicillin and that the study results were confounded. A recent cohort study in Denmark and Sweden[23] did not find an association of fluoroquinolone use and

serious arrhythmia in the general population. But, since 82% of the prescribed fluoroquinolones were ciprofloxacin, it cannot be ruled out that other fluoroquinolones could increase the risk. In a US study of a Tennessee Medicaid cohort,[35] patients who took ciprofloxacin and levofloxacin did not show increased risk of cardiovascular death compared to patients who took amoxicillin during a 10-day treatment course. A cohort study from Taiwan[22] that studied the risks of cardiac arrhythmia among patients using moxifloxacin, levofloxacin, and ciprofloxacin reported that moxifloxacin use was associated 3.30-fold increased risk for ventricular arrhythmia compared to amoxicillin-clavulanate, with no risk associated with levofloxacin and ciprofloxacin use. These data combined with our study reinforce the view that ciprofloxacin and levofloxacin are not associated with ventricular arrhythmia, while moxifloxacin seems to be associated with an increased risk. There is no published study about the risk of ofloxacin. Presently, ofloxacin use was not associated with serious ventricular arrhythmia.

Medications can cause QT interval prolongation, 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 inhibition of cardiac voltage-gated potassium channels encoded by human ether-a-go-go-related gene (HERG).[36] Blockade of rapid component of delayed rectifier potassium current (I_{Kr}) through HERG channel delays cardiac repolarization, represented by QT interval prolongation.

Among medications considered to be associated with QT interval prolongation, fluoroquinolones and macrolides are the most commonly prescribed drugs in the clinical practices.[24] However, QT interval prolongation of fluoroquinolones appears to be different depending on the type. A prospective trial suggested that recommended doses of ciprofloxacin and levofloxacin 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 (millisecond) relative to baseline. On supratherapeutic dose of fluoroquinolones, all three fluoroquinolones increased QT interval compared to placebo, with moxifloxacin having the greatest effect on the interval.[11] Mean of increased QT

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 17.8 ms for ciprofloxacin 1500mg, levofloxacin 1000mg, and moxifloxacin 800mg, respectively. There has not been published study about the effect of ofloxacin on QT interval. However, ofloxacin, ciprofloxacin and levofloxacin were significantly less potent inhibitor of the HERG channel than sparfloxacin, grepafloxacin, and moxifloxacin.[37] Ofloxacin was the least potent inhibitors of the HERG channel. In contrast, sparfloxacin and grepafloxacin, which is the most potent HERG channel inhibitors, were withdrawn from the market due to QT interval prolongation. Overall, standard doses of ciprofloxacin, levofloxacin, and ofloxacin have low effect on increased QT interval, whereas moxifloxacin has the highest effect on increased QT interval.

There are some case reports of torsades de pointes after fluoroquinolone use.[15–19] Most of the cases were developed in patients with concomitant use of other medications associated QT interval prolongation or with multiple risk factors of drug-induced arrhythmia. The risk factors of drug-induced arrhythmia are baseline QT interval prolongation, rapid intravenous infusion of drug, digitalis therapy, bradycardia, organic heart disease, and electrolyte imbalance.[36] Our study excluded patients prescribed drug-associated QT interval prolongation and we just examined oral fluoroquinolone.

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 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.

Conclusion

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

Contributors

Y.C contributed to the design of the study, cleaned and analyzed the data, interpreted the data, and drafted and revised the paper.

H.P contributed to the design of the study, interpreted the data, and critically revised the paper.

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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.

References

1 Owens RC, Ambrose PG. Antimicrobial safety: focus on fluoroquinolones. *Clin Infect Dis* 2005;41 Suppl 2:S144-157. doi:10.1086/428055

2 Singh S, Nautiyal A. Aortic dissection and aortic aneurysms associated with fluoroquinolones: a systematic review and meta-analysis of observational studies. *Am J Med* Published Online First: 21 July 2017. doi:10.1016/j.amjmed.2017.06.029

3 Pasternak B, Svanström H, Melbye M, *et al.* Association between oral fluoroquinolone use and retinal detachment. *JAMA* 2013;310:2184–90. doi:10.1001/jama.2013.280500

4 Raguideau F, Lemaitre M, Dray-Spira R, *et al.* Association between oral fluoroquinolone use and retinal detachment. *JAMA Ophthalmol* 2016;134:415–21. doi:10.1001/jamaophthalmol.2015.6205

5 Kuo S-C, Chen Y-T, Lee Y-T, *et al.* Association between recent use of fluoroquinolones and rhegmatogenous retinal detachment: a population-based cohort study. *Clin Infect Dis* 2014;58:197–203. doi:10.1093/cid/cit708

6 Daneman N, Lu H, Redelmeier DA. Fluoroquinolones and collagen associated severe adverse events: a longitudinal cohort study. *BMJ Open* 2015;5:e010077. doi:10.1136/bmjopen-2015-010077

7 Wise BL, Peloquin C, Choi H, *et al.* Impact of age, sex, obesity, and steroid use on quinolone-associated tendon disorders. *Am J Med* 2012;125:1228.e23-1228.e28. doi:10.1016/j.amjmed.2012.05.027

8 Lee C-C, Lee M-TG, Chen Y-S, *et al.* Risk of aortic dissection and aortic aneurysm in patients taking oral fluoroquinolone. *JAMA Intern Med* 2015;175:1839–47. doi:10.1001/jamainternmed.2015.5389

9 Démolis JL, Kubitza D, Tennezé L, *et al.* Effect of a single oral dose of moxifloxacin (400 mg and 800 mg) on ventricular repolarization in healthy subjects. *Clin Pharmacol Ther* 2000;68:658–66. doi:10.1067/mcp.2000.111482

10 Tsikouris JP, Peeters MJ, Cox CD, *et al.* Effects of three fluoroquinolones on QT analysis after standard treatment courses. *Ann Noninvasive Electrocardiol* 2006;11:52–6. doi:10.1111/j.1542-474X.2006.00082.x

11 Noel GJ, Natarajan J, Chien S, *et al.* Effects of three fluoroquinolones on QT interval in healthy adults after single doses. *Clin Pharmacol Ther* 2003;73:292–303.

12 Noel GJ, Goodman DB, Chien S, *et al.* Measuring the effects of supratherapeutic doses of levofloxacin on healthy volunteers using four methods of QT correction and periodic and continuous ECG recordings. *J Clin Pharmacol* 2004;44:464–473.

13 Haq S, Khaja M, Holt JJ, *et al.* The effects of intravenous levofloxacin on the QT interval and QT dispersion. *Int J Angiol* 2006;15:16–19.

14 Bloomfield DM, Kost JT, Ghosh K, *et al.* The effect of moxifloxacin on QTc and implications for the design of thorough QT studies. *Clin Pharmacol Ther* 2008;84:475–80.

15 Daya SK, Gowda RM, Khan IA. Ciprofloxacin- and hypocalcemia-induced torsade de pointes triggered by hemodialysis. *Am J Ther* 2004;11:77–9.

16 Ibrahim M, Omar B. Ciprofloxacin-induced torsade de pointes. *Am J Emerg Med* 2012;30:252.e5-9. doi:10.1016/j.ajem.2010.09.039

17 Nair MK, Patel K, Starer PJ. Ciprofloxacin-induced torsades de pointes in a methadone-dependent patient. *Addict Abingdon Engl* 2008;103:2062–4. doi:10.1111/j.1360-0443.2008.02390.x

18 Gandhi PJ, Menezes PA, Vu HT, *et al.* Fluconazole- and levofloxacin-induced torsades de pointes in an intensive care unit patient. *Am J Health Syst Pharm* 2003;60:2479–83.

19 Dale KM, Lertsburapa K, Kluger J, *et al.* Moxifloxacin and torsade de pointes. *Ann Pharmacother* 2007;41:336–40. doi:10.1345/aph.1H474

20 Zambon A, Polo Friz H, Contiero P, *et al.* Effect of macrolide and fluoroquinolone antibacterials on the risk of ventricular arrhythmia and cardiac arrest: an observational study in Italy using case-control, case-crossover and case-time-control designs. *Drug Saf* 2009;32:159–67.

21 Rao GA, Mann JR, Shoaibi A, *et al.* Azithromycin and levofloxacin use and increased risk of cardiac arrhythmia and death. *Ann Fam Med* 2014;12:121–127.

22 Chou H-W, Wang J-L, Chang C-H, *et al.* Risks of cardiac arrhythmia and mortality among patients using new-generation macrolides, fluoroquinolones, and β-lactam/β-lactamase inhibitors: a Taiwanese nationwide study. *Clin Infect Dis* 2015;60:566–77. doi:10.1093/cid/ciu914

23 Inghammar M, Svanström H, Melbye M, *et al.* Oral fluoroquinolone use and serious arrhythmia: bi-national cohort study. *BMJ* 2016;352:i843.

24 Abo-Salem E, Fowler JC, Attari M, *et al.* Antibiotic-induced cardiac arrhythmias. *Cardiovasc Ther* 2014;32:19–25. doi:10.1111/1755-5922.12054

25 Owens RC, Nolin TD. Antimicrobial-associated QT interval prolongation: pointes of interest. *Clin Infect Dis* 2006;43:1603–11. doi:10.1086/508873

26 Li EC, Esterly JS, Pohl S, *et al.* Drug-induced QT-interval prolongation: considerations for clinicians. *Pharmacotherapy* 2010;30:684–701. doi:10.1592/phco.30.7.684

27 Yap YG, Camm AJ. Drug induced QT prolongation and torsades de pointes. *Heart Br Card Soc* 2003;89:1363–72.

28 Cubeddu LX. Iatrogenic QT Abnormalities and Fatal Arrhythmias: Mechanisms and Clinical Significance. *Curr Cardiol Rev* 2009;5:166–76. doi:10.2174/157340309788970397

29 Isbister GK. Risk assessment of drug-induced QT prolongation. *Aust Prescr* 2015;38:20–4.

30 Kim JA, Yoon S, Kim LY, *et al.* Towards Actualizing the Value Potential of Korea Health Insurance Review and Assessment (HIRA) Data as a Resource for Health Research: Strengths, Limitations, Applications, and Strategies for Optimal Use of HIRA Data. *J Korean Med Sci* 2017;32:718–28. doi:10.3346/jkms.2017.32.5.718

31 Song SO, Jung CH, Song YD, *et al.* Background and data configuration process of a nationwide population-based study using the korean national health insurance system. *Diabetes Metab J* 2014;38:395–403. doi:10.4093/dmj.2014.38.5.395

32 Mansournia MA, Altman DG. Inverse probability weighting. *BMJ* 2016;352:i189.

33 Brookhart MA, Wyss R, Layton JB, *et al.* Propensity score methods for confounding control in nonexperimental research. *Circ Cardiovasc Qual Outcomes* 2013;6:604–11. doi:10.1161/CIRCOUTCOMES.113.000359

34 Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med* 2009;28:3083–107. doi:10.1002/sim.3697

35 Ray WA, Murray KT, Hall K, *et al.* Azithromycin and the risk of cardiovascular death. *N Engl J Med* 2012;366:1881–90. doi:10.1056/NEJMoa1003833

36 Roden DM. Drug-induced prolongation of the QT interval. *N Engl J Med* 2004;350:1013–22. doi:10.1056/NEJMra032426

37 Kang J, Wang L, Chen XL, *et al.* Interactions of a series of fluoroquinolone antibacterial drugs with the human cardiac K+ channel HERG. *Mol Pharmacol* 2001;59:122–6.

38 Tamariz L, Harkins T, Nair V. A systematic review of validated methods for identifying ventricular arrhythmias using administrative and claims data. *Pharmacoepidemiol Drug Saf* 2012;21 Suppl 1:148–53. doi:10.1002/pds.2340

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 ±SD	49.3 ±17.7	48.5 ±17.3	50.4 ±16.7	50.3 ±16.9	58.4 ±17.4
Female sex, No. (%)	238329 (59.1)	951813 (64.9)	643076 (56.3)	1120119 (61.2)	23586 (50.1)
Comorbidities, No. (%)					
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)
Indications of Antibiotics, No. (%)					
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
History of cardiovascular disease					
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)
Without cardiovascular disease					
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)
Age >=65					
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)
Age <65					
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)
Male					
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)
Female					
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

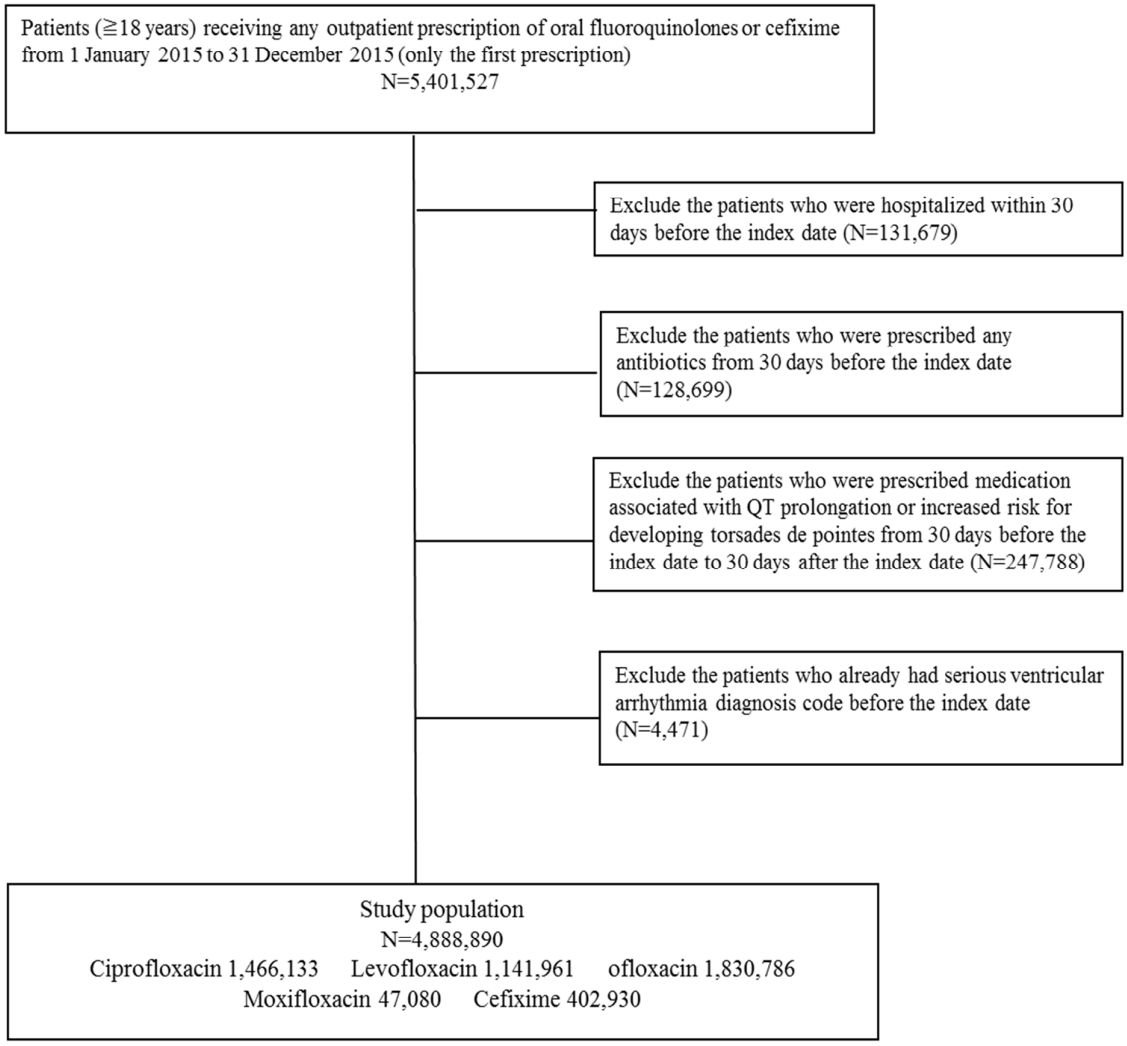

Figure 1. Study flow diagram

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

Comorbidities	
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
Indications of Antibiotics	
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

			Standardized difference	
	Cefixime	Ciprofloxacin	Before IPTW	After IPTW
Prescriptions, No.	402930	1466133		
Age, mean ±SD	49.3 ±17.7	48.5 ±17.3	0.041	0.046
Female sex, No. (%)	238329 (59.1)	951813 (64.9)	0.119	0.042
Comorbidities, No. (%)				
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
Indications of Antibiotics, No. (%)				
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
Month, No (%)				
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

			Standardized difference	
	Cefixime	Levofloxacin	Before IPTW	After IPTW
Prescriptions, No.	402930	1141961		
Age, mean ±SD	49.3 ±17.7	50.4 ±16.7	0.068	0.042
Female sex, No. (%)	238329 (59.1)	643076 (56.3)	0.057	0.064
Comorbidities, No. (%)				
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
Indications of Antibiotics, No. (%)				
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
Month, No (%)				
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

			Standardized difference	
	Cefixime	Ofloxacin	Before IPTW	After IPTW
Prescriptions, No.	402930	1830786		
Age, mean ±SD	49.3 ±17.7	50.3 ±16.9	0.061	0.009
Female sex, No. (%)	238329 (59.1)	1120119 (61.2)	0.042	0.006
Comorbidities, No. (%)				
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
Indications of Antibiotics, No. (%)				
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
Month, No (%)				
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

			Standardized difference	
	Cefixime	Moxifloxacin	Before IPTW	After IPTW
Prescriptions, No.	402930	47080		
Age, mean ±SD	49.3 ±17.7	58.4 ±17.4	0.521	0.007
Female sex, No. (%)	238329 (59.1)	23586 (50.1)	0.183	0.024
Comorbidities, No. (%)				
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
Indications of Antibiotics, No. (%)				
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
Month, No (%)				
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
Title and abstract	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	
Introduction				
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.
Methods				
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	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—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 *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5, 6,	Inclusion criteria and exposures 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. 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.
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6	Outcome definition 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.
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.

				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.

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		No missing data
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—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
Results				
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.
			20	Figure 1
		(b) Give reasons for non-participation at each stage	5, 6	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) *Cohort study*—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*	*Cohort study*—Report numbers of outcome events or summary measures over time	18	Table 2, Table 3
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		
		Cross-sectional study—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		

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	19	Table 4
Discussion				
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

				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	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.

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.
Other information				
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.

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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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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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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

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. To reduce potential confounding by indication, oral cefixime was used as a control. Both fluoroquinolones and cefixime are frequently prescribed for respiratory diseases and urinary tract infections in Korea. Other studies used β-lactam antibiotics, such as amoxicillin, amoxicillin-clavulanate, and penicillin V, as controls.[21–23] However, in Korea, β-lactam antibiotics are not commonly used in UTI treatment; thus, cefixime was used in this study as a comparator. Cefixime is a medication with no pro-arrhythmic effects and is not in the list of drug-induced QT prolongation or torsades de pointes.[24–29]

Data source and ethics

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

Inclusion criteria and exposures

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.

Exclusion criteria

We excluded patients who were hospitalized within 30 days of the index date, which was defined as the date on which the study medication was prescribed. We also excluded patients who were prescribed antibiotics within 30 days prior to the index date, who were 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, or who were already diagnosed with serious ventricular arrhythmia before the index date.

Outcome definition

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 I469) were used to identify the patients with serious ventricular arrhythmias. Only the main diagnostic codes were used. Because diagnostic codes are sometimes used in patients with existing arrhythmias, only the first diagnosis was used when patients had more than one diagnostic code for serious ventricular arrhythmia to focus on incidence outcomes. 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. Follow-up began on the index date and ended on the date of serious arrhythmia or 14 days after starting treatment, whichever came first.

Covariates

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

Statistical analyses

The number of serious ventricular arrhythmias was identified, and the incidence per 1,000,000 patients was calculated. Each patient group prescribed ciprofloxacin, levofloxacin, ofloxacin, or moxifloxacin was compared with the group prescribed cefixime to assess the risk of ventricular arrhythmia. Using logistic regression with inverse probability treatment weighting (IPTW), we calculated the odds ratios (OR) and 95% confidence intervals (CIs) of serious ventricular arrhythmia compared with cefixime for days 1-7 and 8-14 after the index date.

We calculated the propensity scores of being prescribed ciprofloxacin, levofloxacin, ofloxacin, or moxifloxacin compared with cefixime using logistic regression. Age, sex, prescription month, all covariate-related comorbidities, and antibiotic indications were included in the propensity models. Inverse probability treatment weights were calculated with propensity scores to adjust for baseline differences and control for confounding by indication.[32] IPTW weights the inverse of the estimated propensity score for treated patients and the inverse of one minus the estimated propensity score for control patients.[33] Propensity score matching has the disadvantage of including only a subset of subjects and controls in the analysis, but IPTW can be used without reducing sample number. We evaluated the baseline covariate balance between groups with standardized differences before and after IPTW. A standardized difference <0.1 indicated that covariates were well balanced between

treatment and control patients.[34]

For the subgroup analyses, we divided patients by age, sex, and cardiovascular disease history. Acute myocardial infarction, ischaemic heart disease, cardiomyopathy, valve disorder, arrhythmia, congestive heart failure, and congenital heart disease were included as cardiovascular diseases. We defined cardiovascular disease using the same ICD-10 code as that used to define baseline comorbidities. The propensity score for each subgroup and drug type was calculated and the odds ratios were calculated, respectively. No data were missing in this study. Statistical analyses were performed using R, version 3.1.1 (www.R-project.org).

Patient and public involvement

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

Results

Study population characteristics

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) diagnosed with serious ventricular arrhythmia before the index date (n=4,471), 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.

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

Development of serious ventricular arrhythmia

Serious ventricular arrhythmia incidence, weighted ORs and 95% CIs for days 1-7 after antibiotic initiation are presented in Table 2. ORs for serious ventricular arrhythmia compared with cefixime 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% CI, 1.15-3.11) for ciprofloxacin, levofloxacin, ofloxacin, and moxifloxacin, respectively. Ciprofloxacin and levofloxacin were not associated with an increased risk, while moxifloxacin was associated with a 1.87-fold increased risk of serious ventricular arrhythmia. Ofloxacin was associated with a 59% reduced risk of serious ventricular arrhythmia compared with cefixime for 1-7 days after the index date.

The serious ventricular arrhythmia incidence and weighted OR for the 8-14 days post-prescription are presented in Table 3. ORs for serious ventricular arrhythmia compared with cefixime 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), and 1.78 (95% CI, 0.86-3.88) for ciprofloxacin, levofloxacin, ofloxacin, and moxifloxacin, respectively. Risk reductions of 66% and 42% were found for ciprofloxacin and ofloxacin, respectively. No evidence of an increased risk was found for levofloxacin. Moxifloxacin was associated with a 1.78-fold increased risk of serious ventricular arrhythmia for 8-14 days after the index date; however, this increased risk was not statistically significant.

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

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. Overall, standard ciprofloxacin, levofloxacin, and ofloxacin doses have little effect on increased QT intervals, while moxifloxacin has the highest effect.

Comparison with other population-based studies

In a study on veterans in the United States,[21] levofloxacin use was associated with a 3.13-fold increased risk of cardiac arrhythmias and a 2.49-fold increased risk of all-cause death compared with

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

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

determine whether fluoroquinolones increase the risk of arrhythmias in patients with these risk factors.

Strengths and limitations

One of the strengths of this study is that it is the largest study to date evaluating the association between oral fluoroquinolone use and serious ventricular arrhythmia. This study was a nationwide population-based study including 4,888,890 patients who were prescribed oral fluoroquinolone or cefixime. In addition, the datasets had no missing values, thus minimizing the number of subjects. Second, propensity score weighting was performed to adjust the underlying characteristics and antibiotic indications of both the fluoroquinolone and cefixime groups. In the propensity score matching, unmatched subjects occur and subject numbers decreased. In this study, all subjects can be included for comparison using IPTW.

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 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%.[38] 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.

Conclusion

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

Contributors

Y.C. contributed to the study design; cleaned, analysed, and interpreted the data; and drafted and revised the manuscript.

H.P. contributed to the study design, interpreted the data, and critically revised the paper.

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Competing interests

All authors declare no competing interests.

Data sharing

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

References

1 Owens RC, Ambrose PG. Antimicrobial safety: focus on fluoroquinolones. *Clin Infect Dis* 2005;41(Suppl 2):S144-S157. doi:10.1086/428055.

2 Singh S, Nautiyal A. Aortic dissection and aortic aneurysms associated with fluoroquinolones: a systematic review and meta-analysis. *Am J Med* 2017;130:1449–1457.e9. doi:10.1016/j.amjmed.2017.06.029.

3 Pasternak B, Svanström H, Melbye M, et al. Association between oral fluoroquinolone use and retinal detachment. *JAMA* 2013;310:2184–90. doi:10.1001/jama.2013.280500.

4 Raguideau F, Lemaitre M, Dray-Spira R, et al. Association between oral fluoroquinolone use and retinal detachment. *JAMA Ophthalmol* 2016;134:415–21. doi:10.1001/jamaophthalmol.2015.6205.

5 Kuo SC, Chen YT, Lee YT, et al. Association between recent use of fluoroquinolones and rhegmatogenous retinal detachment: a population-based cohort study. *Clin Infect Dis* 2014;58:197–203. doi:10.1093/cid/cit708.

6 Daneman N, Lu H, Redelmeier DA. Fluoroquinolones and collagen associated severe adverse events: a longitudinal cohort study. *BMJ Open* 2015;5:e010077. doi:10.1136/bmjopen-2015-010077.

7 Wise BL, Peloquin C, Choi H, et al. Impact of age, sex, obesity, and steroid use on quinolone-associated tendon disorders. *Am J Med* 2012;125:1228.e23–8. doi:10.1016/j.amjmed.2012.05.027.

8 Lee CC, Lee MT, Chen YS, et al. Risk of aortic dissection and aortic aneurysm in patients taking oral fluoroquinolone. *JAMA Intern Med* 2015;175:1839–47. doi:10.1001/jamainternmed.2015.5389.

9 Démolis JL, Kubitza D, Tennezé L, et al. Effect of a single oral dose of moxifloxacin (400 mg and 800 mg) on ventricular repolarization in healthy subjects. *Clin Pharmacol Ther* 2000;68:658–66. doi:10.1067/mcp.2000.111482.

10 Tsikouris JP, Peeters MJ, Cox CD, et al. Effects of three fluoroquinolones on QT analysis after standard treatment courses. *Ann Noninvasive Electrocardiol* 2006;11:52–6. doi:10.1111/j.1542-474X.2006.00082.x.

11 Noel GJ, Natarajan J, Chien S, et al. Effects of three fluoroquinolones on QT interval in healthy adults after single doses. *Clin Pharmacol Ther* 2003;73:292–303.

12 Noel GJ, Goodman DB, Chien S, et al. Measuring the effects of supratherapeutic doses of levofloxacin on healthy volunteers using four methods of QT correction and periodic and continuous ECG recordings. *J Clin Pharmacol* 2004;44:464–73.

13 Haq S, Khaja M, Holt JJ, et al. The effects of intravenous levofloxacin on the QT interval and QT dispersion. *Int J Angiol* 2006;15:16–9.

14 Bloomfield DM, Kost JT, Ghosh K, et al. The effect of moxifloxacin on QTc and implications for the design of thorough QT studies. *Clin Pharmacol Ther* 2008;84:475–80.

15 Daya SK, Gowda RM, Khan IA. Ciprofloxacin- and hypocalcemia-induced torsade de pointes triggered by hemodialysis. *Am J Ther* 2004;11:77–9.

16 Ibrahim M, Omar B. Ciprofloxacin-induced torsade de pointes. *Am J Emerg Med* 2012;30:252.e5-9. doi:10.1016/j.ajem.2010.09.039.

17 Nair MK, Patel K, Starer PJ. Ciprofloxacin-induced torsades de pointes in a methadone-dependent patient. *Addiction* 2008;103:2062–4. doi:10.1111/j.1360-0443.2008.02390.x.

18 Gandhi PJ, Menezes PA, Vu HT, et al. Fluconazole- and levofloxacin-induced torsades de pointes in an intensive care unit patient. *Am J Health Syst Pharm* 2003;60:2479–83.

19 Dale KM, Lertsburapa K, Kluger J, et al. Moxifloxacin and torsade de pointes. *Ann Pharmacother* 2007;41:336–40. doi:10.1345/aph.1H474.

20 Zambon A, Polo Friz H, Contiero P, et al. Effect of macrolide and fluoroquinolone antibacterials on the risk of ventricular arrhythmia and cardiac arrest: an observational study in Italy using case-control, case-crossover and case-time-control designs. *Drug Saf* 2009;32:159–67.

21 Rao GA, Mann JR, Shoaibi A, et al. Azithromycin and levofloxacin use and increased risk of cardiac arrhythmia and death. *Ann Fam Med* 2014;12:121–7.

22 Chou HW, Wang JL, Chang CH, et al. Risks of cardiac arrhythmia and mortality among patients using new-generation macrolides, fluoroquinolones, and β-lactam/β-lactamase inhibitors: a Taiwanese nationwide study. *Clin Infect Dis* 2015;60:566–77. doi:10.1093/cid/ciu914.

23 Inghammar M, Svanström H, Melbye M, et al. Oral fluoroquinolone use and serious arrhythmia: bi-national cohort study. *BMJ* 2016;352:i843.

24 Abo-Salem E, Fowler JC, Attari M, et al. Antibiotic-induced cardiac arrhythmias. *Cardiovasc Ther* 2014;32:19–25. doi:10.1111/1755-5922.12054.

25 Owens RC, Nolin TD. Antimicrobial-associated QT interval prolongation: pointes of interest. *Clin Infect Dis* 2006;43:1603–11. doi:10.1086/508873.

26 Li EC, Esterly JS, Pohl S, et al. Drug-induced QT-interval prolongation: considerations for clinicians. *Pharmacotherapy* 2010;30:684–701. doi:10.1592/phco.30.7.684.

27 Yap YG, Camm AJ. Drug induced QT prolongation and torsades de pointes. *Heart* 2003;89:1363–72.

28 Cubeddu LX. Iatrogenic QT abnormalities and fatal arrhythmias: mechanisms and clinical significance. *Curr Cardiol Rev* 2009;5:166–76. doi:10.2174/157340309788970397.

29 Isbister GK. Risk assessment of drug-induced QT prolongation. *Aust Prescr* 2015;38:20–4.

30 Kim JA, Yoon S, Kim LY, et al. Towards actualizing the value potential of Korea health insurance review and assessment (HIRA) data as a resource for health research: strengths, limitations, applications, and strategies for optimal use of HIRA data. *J Korean Med Sci* 2017;32:718–28. doi:10.3346/jkms.2017.32.5.718.

31 Song SO, Jung CH, Song YD, et al. Background and data configuration process of a nationwide population-based study using the Korean national health insurance system. *Diabetes Metab J* 2014;38:395–403. doi:10.4093/dmj.2014.38.5.395.

32 Mansournia MA, Altman DG. Inverse probability weighting. *BMJ* 2016;352:i189.

33 Brookhart MA, Wyss R, Layton JB, et al. Propensity score methods for confounding control in nonexperimental research. *Circ Cardiovasc Qual Outcomes* 2013;6:604–11. doi:10.1161/CIRCOUTCOMES.113.000359.

34 Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med* 2009;28:3083–107. doi:10.1002/sim.3697.

35 Roden DM. Drug-induced prolongation of the QT interval. *N Engl J Med* 2004;350:1013–22. doi:10.1056/NEJMra032426.

36 Kang J, Wang L, Chen XL, et al. Interactions of a series of fluoroquinolone antibacterial drugs with the human cardiac K+ channel HERG. *Mol Pharmacol* 2001;59:122–6.

37 Ray WA, Murray KT, Hall K, et al. Azithromycin and the risk of cardiovascular death. *N Engl J Med* 2012;366:1881–90. doi:10.1056/NEJMoa1003833.

38 Tamariz L, Harkins T, Nair V. A systematic review of validated methods for identifying ventricular arrhythmias using administrative and claims data. *Pharmacoepidemiol Drug Saf* 2012;21(Suppl 1):148–53. doi:10.1002/pds.2340.

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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 ±SD	49.3 ±17.7	48.5 ±17.3	50.4 ±16.7	50.3 ±16.9	58.4 ±17.4
No. of females (%)	238329 (59.1)	951813 (64.9)	643076 (56.3)	1120119 (61.2)	23586 (50.1)
No. of Comorbidities (%)					
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)
No. of Antibiotic Indications (%)					
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
History of cardiovascular disease					
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)
Without cardiovascular disease					
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)
Age ≥65					
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)
Age <65					
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)
Male					
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)
Female					
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

Figure Legends

Figure 1. Study flow chart

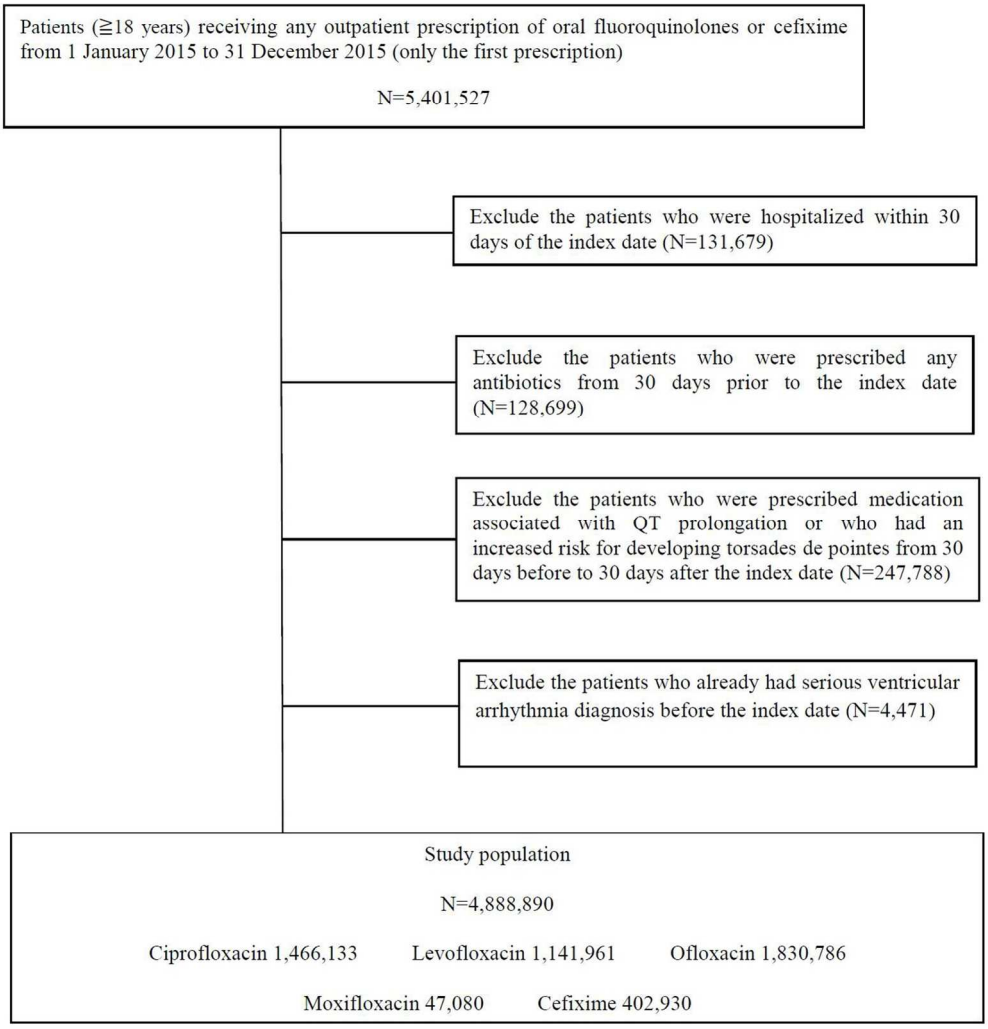

Figure 1. Study flow chart

121x126mm (300 x 300 DPI)

Supplementary appendix

Table S1. ICD-10 covariate codes

Comorbidities	
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
Indications for antibiotics	
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

			Standardized difference	
	Cefixime	Ciprofloxacin	Before IPTW	After IPTW
No. of subjects	402930	1466133		
Age, mean ±SD	49.3 ±17.7	48.5 ±17.3	0.041	0.046
No. of females (%)	238329 (59.1)	951813 (64.9)	0.119	0.042
No. of Comorbidities (%)				
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
No. of Antibiotic Indications (%)				
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
Month, No (%)				
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

			Standardized difference	
	Cefixime	Levofloxacin	Before IPTW	After IPTW
No. of subjects	402930	1141961		
Age, mean ±SD	49.3 ±17.7	50.4 ±16.7	0.068	0.042
No. of females (%)	238329 (59.1)	643076 (56.3)	0.057	0.064
No. of Comorbidities (%)				
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
No. of Antibiotic Indications (%)				
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
Month, No (%)				
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

			Standardized difference	
	Cefixime	Ofloxacin	Before IPTW	After IPTW
No. of subjects	402930	1830786		
Age, mean ±SD	49.3 ±17.7	50.3 ±16.9	0.061	0.009
No. of females (%)	238329 (59.1)	1120119 (61.2)	0.042	0.006
No. of Comorbidities (%)				
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
No. of Antibiotic Indications (%)				
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
Month, No (%)				
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

			Standardized difference	
	Cefixime	Moxifloxacin	Before IPTW	After IPTW
No. of subjects	402930	47080		
Age, mean ±SD	49.3 ±17.7	58.4 ±17.4	0.521	0.007
No. of females (%)	238329 (59.1)	23586 (50.1)	0.183	0.024
No. of Comorbidities (%)				
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
No. of Antibiotic Indications (%)				
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
Month, No (%)				
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
Title and abstract	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	
Introduction				
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
Methods				
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	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—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 *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5, 6,	Inclusion criteria and exposures 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. Follow-up began on the index date and ended on the date of serious arrhythmia or 14 days after starting treatment, whichever came first.
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6	Outcome definition 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

				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*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—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
Results				
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 Table 1	Study population characteristics
		(b) Indicate number of participants with missing data for each variable of interest		No missing data
		(c) *Cohort study*—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*	*Cohort study*—Report numbers of outcome events or summary measures over time	21	Table 2, Table 3
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		
		Cross-sectional study—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		

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	22	Table 4
Discussion				
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

				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

				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%.[38] 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.
Other information				
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.

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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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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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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

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 (see online supplementary table 1). To reduce potential confounding by indication, oral cefixime was used as a control. Both fluoroquinolones and cefixime are frequently prescribed for respiratory diseases and urinary tract infections in Korea. Other studies used β-lactam antibiotics, such as amoxicillin, amoxicillin-clavulanate, and penicillin V, as controls.[21–23] However, in Korea, β-lactam antibiotics are not commonly used in UTI treatment; thus, cefixime was used in this study as a comparator. Cefixime is a medication with no pro-arrhythmic effects and is not in the list of drug-induced QT prolongation or torsades de pointes.[24–29]

Data source and ethics

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

Inclusion criteria and exposures

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.

Exclusion criteria

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

Outcome definition

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 I469) were used to identify the patients with serious ventricular arrhythmias. Only the main diagnostic codes were used. Because diagnostic codes are sometimes used in patients with existing arrhythmias, only the first diagnosis was used when patients had more than one diagnostic code for serious ventricular arrhythmia to focus on incidence outcomes. 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. Follow-up began on the index date and ended on the date of serious arrhythmia or 14 days after starting treatment, whichever came first.

Covariates

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

Statistical analyses

The number of serious ventricular arrhythmias was identified, and the incidence per 1,000,000 patients was calculated. Each patient group prescribed ciprofloxacin, levofloxacin, ofloxacin, or moxifloxacin was compared with the group prescribed cefixime to assess the risk of ventricular arrhythmia. Using logistic regression with inverse probability treatment weighting (IPTW), we calculated the odds ratios (OR) and 95% confidence intervals (CIs) of serious ventricular arrhythmia compared with cefixime for days 1-7 and 8-14 after the index date.

We calculated the propensity scores of being prescribed ciprofloxacin, levofloxacin, ofloxacin, or moxifloxacin compared with cefixime using logistic regression. Age, sex, prescription month, all covariate-related comorbidities, and antibiotic indications were included in the propensity models. Inverse probability treatment weights were calculated with propensity scores to adjust for baseline differences and control for confounding by indication.[32] IPTW weights the inverse of the estimated propensity score for treated patients and the inverse of one minus the estimated propensity score for control patients.[33] Propensity score matching has the disadvantage of including only a subset of subjects and controls in the analysis, but IPTW can be used without reducing sample number. We evaluated the baseline covariate balance between groups with standardized differences before and after IPTW. A standardized difference <0.1 indicated that covariates were well balanced between

treatment and control patients.[34]

For the subgroup analyses, we divided patients by age, sex, and cardiovascular disease history. Acute myocardial infarction, ischaemic heart disease, cardiomyopathy, valve disorder, arrhythmia, congestive heart failure, and congenital heart disease were included as cardiovascular diseases. We defined cardiovascular disease using the same ICD-10 code as that used to define baseline comorbidities. The propensity score for each subgroup and drug type was calculated and the odds ratios were calculated, respectively. No data were missing in this study. Statistical analyses were performed using R, version 3.1.1 (www.R-project.org).

Patient and public involvement

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

Results

Study population characteristics

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 increased risk for developing torsades de pointes from 30 days before to 30 days after the index date (n=247,788), or (4) diagnosed with serious ventricular arrhythmia before the index date (n=4,471), 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.

The baseline characteristics of the study population before weighting are presented in Table 1. Compared with cefixime users, moxifloxacin users were older and had more comorbidities. Ciprofloxacin, levofloxacin, and ofloxacin users had similar baseline comorbidities as cefixime users, except that chronic lung disease was less prevalent among ciprofloxacin and ofloxacin users and cancer was less prevalent among ofloxacin users. After the study population had been weighting using the IPTW, all baseline differences were less than 0.1 standardized differences (see online supplementary table 4-7).

Development of serious ventricular arrhythmia

Serious ventricular arrhythmia incidence, weighted ORs and 95% CIs for days 1-7 after antibiotic initiation are presented in Table 2. ORs for serious ventricular arrhythmia compared with cefixime 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% CI, 1.15-3.11) for ciprofloxacin, levofloxacin, ofloxacin, and moxifloxacin, respectively. Ciprofloxacin and levofloxacin were not associated with an increased risk, while moxifloxacin was associated with a 1.87-fold increased risk of serious ventricular arrhythmia. Ofloxacin was associated with a 59% reduced risk of serious ventricular arrhythmia compared with cefixime for 1-7 days after the index date.

The serious ventricular arrhythmia incidence and weighted OR for the 8-14 days post-prescription are presented in Table 3. ORs for serious ventricular arrhythmia compared with cefixime 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), and 1.78 (95% CI, 0.86-3.88) for ciprofloxacin, levofloxacin, ofloxacin, and moxifloxacin, respectively. Risk reductions of 66% and 42% were found for ciprofloxacin and ofloxacin, respectively. No evidence of an increased risk was found for levofloxacin. Moxifloxacin was associated with a 1.78-fold increased risk of serious ventricular arrhythmia for 8-14 days after the index date; however, this increased risk was not

statistically significant.

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

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

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

In this study, ciprofloxacin and levofloxacin were not associated with increased ventricular arrhythmia risk, however, some case reports exist on QT interval prolongation and torsades de pointes after fluoroquinolone use.[15–19] Most of these cases were patients with concomitant use of other medications associated with QT interval prolongation or with multiple risk factors associated with drug-induced arrhythmia. The risk factors for drug-induced arrhythmia are baseline QT interval prolongation, rapid intravenous drug infusion, digitalis therapy, bradycardia, organic heart disease, and electrolyte imbalances.[35] Our study excluded patients who were prescribed drugs associated with QT interval prolongation, and we could not confirm whether the risk of ventricular arrhythmia was increased by the concomitant fluoroquinolone use with drugs that increase the risk of torsades de pointes. We also could not assess whether intravenous use was associated with increased risk because this study was conducted only in oral fluoroquinolone users. Furthermore, no baseline ECG or electrolyte data were available. Further studies are needed to determine whether fluoroquinolones

increase the risk of arrhythmias in patients with these risk factors.

In this study, ofloxacin users had a reduced risk of serious ventricular arrhythmia. However, it is not possible to conclude that ofloxacin has an anti-arrhythmic effect. In fact, cases of torsades de pointes had been reported to occur after taking ofloxacin.[37,39] A study with US FDA Adverse Event Reporting System data reported a reduced risk of torsades de pointes, but the adjusted odds ratio was not statistically significant (OR, 0.67; 95% CI, 0.03-4.38).[39] In addition, reason for the reduced risk of arrhythmia in ofloxacin users cannot be clearly explained. Additional clinical and population-based studies are needed.

Strengths and limitations

One of the strengths of this study is that it is the largest study to date evaluating the association between oral fluoroquinolone use and serious ventricular arrhythmia. This study was a nationwide population-based study including 4,888,890 patients who were prescribed oral fluoroquinolone or cefixime. In addition, the datasets had no missing values, thus minimizing the number of subjects. Second, propensity score weighting was performed to adjust the underlying characteristics and antibiotic indications of both the fluoroquinolone and cefixime groups. In the propensity score matching, unmatched subjects occur and subject numbers decreased. In this study, all subjects can be included for comparison using IPTW.

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 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%.[40] 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.

Conclusion

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

Contributors

Y.C. contributed to the study design; cleaned, analysed, and interpreted the data; and drafted and revised the manuscript.

H.P. contributed to the study design, interpreted the data, and critically revised the paper.

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Competing interests

All authors declare no competing interests.

Data sharing

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

References

1 Owens RC, Ambrose PG. Antimicrobial safety: focus on fluoroquinolones. *Clin Infect Dis* 2005;41(Suppl 2):S144-S157. doi:10.1086/428055.

2 Singh S, Nautiyal A. Aortic dissection and aortic aneurysms associated with fluoroquinolones: a systematic review and meta-analysis. *Am J Med* 2017;130:1449–1457.e9. doi:10.1016/j.amjmed.2017.06.029.

3 Pasternak B, Svanström H, Melbye M, et al. Association between oral fluoroquinolone use and retinal detachment. *JAMA* 2013;310:2184–90. doi:10.1001/jama.2013.280500.

4 Raguideau F, Lemaitre M, Dray-Spira R, et al. Association between oral fluoroquinolone use and retinal detachment. *JAMA Ophthalmol* 2016;134:415–21. doi:10.1001/jamaophthalmol.2015.6205.

5 Kuo SC, Chen YT, Lee YT, et al. Association between recent use of fluoroquinolones and rhegmatogenous retinal detachment: a population-based cohort study. *Clin Infect Dis* 2014;58:197–203. doi:10.1093/cid/cit708.

6 Daneman N, Lu H, Redelmeier DA. Fluoroquinolones and collagen associated severe adverse events: a longitudinal cohort study. *BMJ Open* 2015;5:e010077. doi:10.1136/bmjopen-2015-010077.

7 Wise BL, Peloquin C, Choi H, et al. Impact of age, sex, obesity, and steroid use on quinolone-associated tendon disorders. *Am J Med* 2012;125:1228.e23–8. doi:10.1016/j.amjmed.2012.05.027.

8 Lee CC, Lee MT, Chen YS, et al. Risk of aortic dissection and aortic aneurysm in patients taking oral fluoroquinolone. *JAMA Intern Med* 2015;175:1839–47. doi:10.1001/jamainternmed.2015.5389.

9 Démolis JL, Kubitza D, Tennezé L, et al. Effect of a single oral dose of moxifloxacin (400 mg and 800 mg) on ventricular repolarization in healthy subjects. *Clin Pharmacol Ther* 2000;68:658–66. doi:10.1067/mcp.2000.111482.

10 Tsikouris JP, Peeters MJ, Cox CD, et al. Effects of three fluoroquinolones on QT analysis after standard treatment courses. *Ann Noninvasive Electrocardiol* 2006;11:52–6. doi:10.1111/j.1542-474X.2006.00082.x.

11 Noel GJ, Natarajan J, Chien S, et al. Effects of three fluoroquinolones on QT interval in healthy adults after single doses. *Clin Pharmacol Ther* 2003;73:292–303.

12 Noel GJ, Goodman DB, Chien S, et al. Measuring the effects of supratherapeutic doses of levofloxacin on healthy volunteers using four methods of QT correction and periodic and continuous ECG recordings. *J Clin Pharmacol* 2004;44:464–73.

13 Haq S, Khaja M, Holt JJ, et al. The effects of intravenous levofloxacin on the QT interval and QT dispersion. *Int J Angiol* 2006;15:16–9.

14 Bloomfield DM, Kost JT, Ghosh K, et al. The effect of moxifloxacin on QTc and implications for the design of thorough QT studies. *Clin Pharmacol Ther* 2008;84:475–80.

15 Daya SK, Gowda RM, Khan IA. Ciprofloxacin- and hypocalcemia-induced torsade de pointes triggered by hemodialysis. *Am J Ther* 2004;11:77–9.

16 Ibrahim M, Omar B. Ciprofloxacin-induced torsade de pointes. *Am J Emerg Med* 2012;30:252.e5-9. doi:10.1016/j.ajem.2010.09.039.

17 Nair MK, Patel K, Starer PJ. Ciprofloxacin-induced torsades de pointes in a methadone-dependent patient. *Addiction* 2008;103:2062–4. doi:10.1111/j.1360-0443.2008.02390.x.

18 Gandhi PJ, Menezes PA, Vu HT, et al. Fluconazole- and levofloxacin-induced torsades de pointes in an intensive care unit patient. *Am J Health Syst Pharm* 2003;60:2479–83.

19 Dale KM, Lertsburapa K, Kluger J, et al. Moxifloxacin and torsade de pointes. *Ann Pharmacother* 2007;41:336–40. doi:10.1345/aph.1H474.

20 Zambon A, Polo Friz H, Contiero P, et al. Effect of macrolide and fluoroquinolone antibacterials on the risk of ventricular arrhythmia and cardiac arrest: an observational study in Italy using case-control, case-crossover and case-time-control designs. *Drug Saf* 2009;32:159–67.

21 Rao GA, Mann JR, Shoaibi A, et al. Azithromycin and levofloxacin use and increased risk of cardiac arrhythmia and death. *Ann Fam Med* 2014;12:121–7.

22 Chou HW, Wang JL, Chang CH, et al. Risks of cardiac arrhythmia and mortality among patients using new-generation macrolides, fluoroquinolones, and β-lactam/β-lactamase inhibitors: a Taiwanese nationwide study. *Clin Infect Dis* 2015;60:566–77. doi:10.1093/cid/ciu914.

23 Inghammar M, Svanström H, Melbye M, et al. Oral fluoroquinolone use and serious arrhythmia: bi-national cohort study. *BMJ* 2016;352:i843.

24 Abo-Salem E, Fowler JC, Attari M, et al. Antibiotic-induced cardiac arrhythmias. *Cardiovasc Ther* 2014;32:19–25. doi:10.1111/1755-5922.12054.

25 Owens RC, Nolin TD. Antimicrobial-associated QT interval prolongation: pointes of interest. *Clin Infect Dis* 2006;43:1603–11. doi:10.1086/508873.

26 Li EC, Esterly JS, Pohl S, et al. Drug-induced QT-interval prolongation: considerations for clinicians. *Pharmacotherapy* 2010;30:684–701. doi:10.1592/phco.30.7.684.

27 Yap YG, Camm AJ. Drug induced QT prolongation and torsades de pointes. *Heart* 2003;89:1363–72.

28 Cubeddu LX. Iatrogenic QT abnormalities and fatal arrhythmias: mechanisms and clinical significance. *Curr Cardiol Rev* 2009;5:166–76. doi:10.2174/157340309788970397.

29 Isbister GK. Risk assessment of drug-induced QT prolongation. *Aust Prescr* 2015;38:20–4.

30 Kim JA, Yoon S, Kim LY, et al. Towards actualizing the value potential of Korea health insurance review and assessment (HIRA) data as a resource for health research: strengths, limitations, applications, and strategies for optimal use of HIRA data. *J Korean Med Sci* 2017;32:718–28. doi:10.3346/jkms.2017.32.5.718.

31 Song SO, Jung CH, Song YD, et al. Background and data configuration process of a nationwide population-based study using the Korean national health insurance system. *Diabetes Metab J* 2014;38:395–403. doi:10.4093/dmj.2014.38.5.395.

32 Mansournia MA, Altman DG. Inverse probability weighting. *BMJ* 2016;352:i189.

33 Brookhart MA, Wyss R, Layton JB, et al. Propensity score methods for confounding control in nonexperimental research. *Circ Cardiovasc Qual Outcomes* 2013;6:604–11. doi:10.1161/CIRCOUTCOMES.113.000359.

34 Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med* 2009;28:3083–107. doi:10.1002/sim.3697.

35 Roden DM. Drug-induced prolongation of the QT interval. *N Engl J Med* 2004;350:1013–22. doi:10.1056/NEJMra032426.

36 Kang J, Wang L, Chen XL, et al. Interactions of a series of fluoroquinolone antibacterial drugs with the human cardiac K+ channel HERG. *Mol Pharmacol* 2001;59:122–6.

37 Frothingham R. Rates of torsades de pointes associated with ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin, and moxifloxacin. *Pharmacotherapy 2001;21:1468–72.*

38 Ray WA, Murray KT, Hall K, et al. Azithromycin and the risk of cardiovascular death. *N Engl J Med* 2012;366:1881–90. doi:10.1056/NEJMoa1003833.

39 Poluzzi E, Raschi E, Motola D, *et al.* Antimicrobials and the risk of torsades de pointes: the contribution from data mining of the US FDA Adverse Event Reporting System. *Drug Saf* 2010;**33**:303–14. doi:10.2165/11531850-000000000-00000

40 Tamariz L, Harkins T, Nair V. A systematic review of validated methods for identifying ventricular arrhythmias using administrative and claims data. *Pharmacoepidemiol Drug Saf* 2012;21(Suppl 1):148–53. doi:10.1002/pds.2340.

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 ±SD	49.3 ±17.7	48.5 ±17.3	50.4 ±16.7	50.3 ±16.9	58.4 ±17.4
No. of females (%)	238329 (59.1)	951813 (64.9)	643076 (56.3)	1120119 (61.2)	23586 (50.1)
No. of Comorbidities (%)					
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)
No. of Antibiotic Indications (%)					
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
History of cardiovascular disease					
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)
Without cardiovascular disease					
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)
Age ≥65					
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)
Age <65					
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)
Male					
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)
Female					
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

Figure Legends

Figure 1. Study flow chart

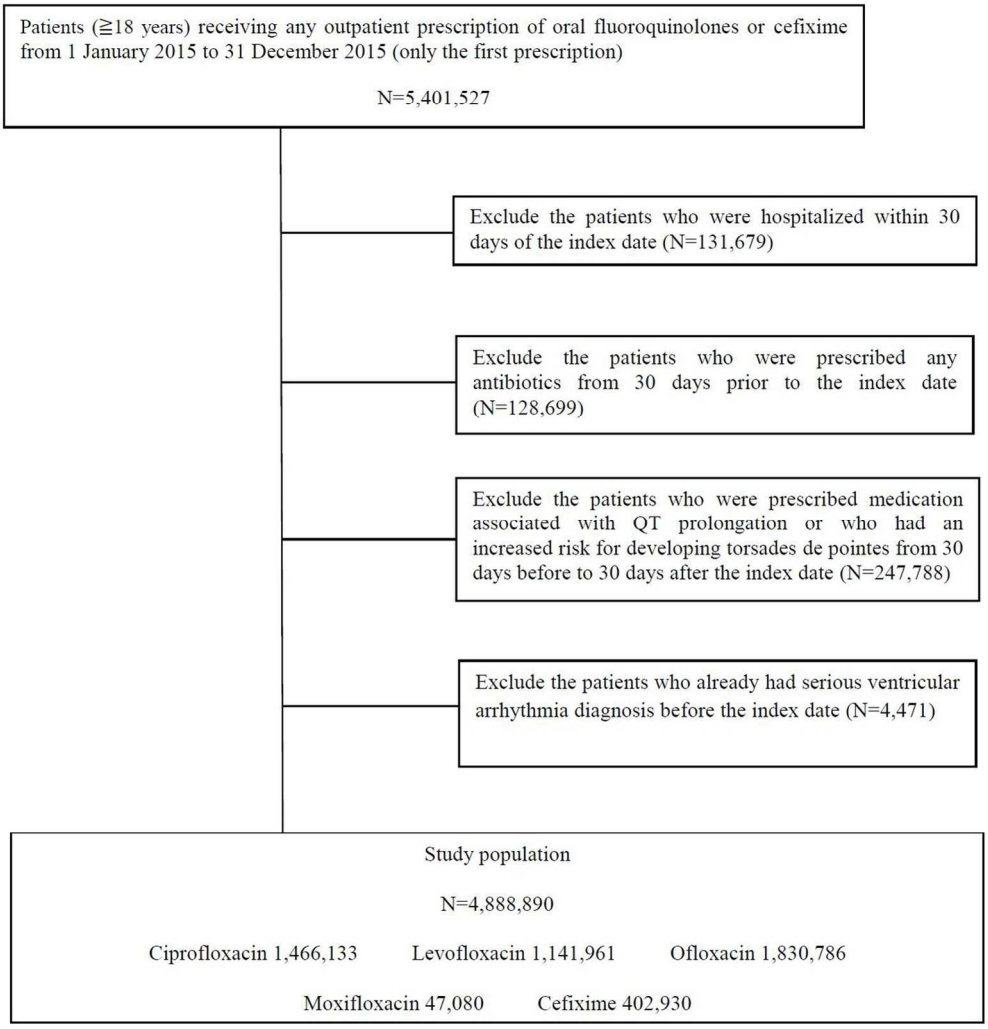

Figure 1. Study flow chart

121x126mm (300 x 300 DPI)

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

Comorbidities	
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
Indications for antibiotics	
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

			Standardized difference	
	Cefixime	Ciprofloxacin	Before IPTW	After IPTW
No. of subjects	402930	1466133		
Age, mean ±SD	49.3 ±17.7	48.5 ±17.3	0.041	0.046
No. of females (%)	238329 (59.1)	951813 (64.9)	0.119	0.042
No. of Comorbidities (%)				
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
No. of Antibiotic Indications (%)				
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
Month, No (%)				
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

			Standardized difference	
	Cefixime	Levofloxacin	Before IPTW	After IPTW
No. of subjects	402930	1141961		
Age, mean ±SD	49.3 ±17.7	50.4 ±16.7	0.068	0.042
No. of females (%)	238329 (59.1)	643076 (56.3)	0.057	0.064
No. of Comorbidities (%)				
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
No. of Antibiotic Indications (%)				
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
Month, No (%)				
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

			Standardized difference	
	Cefixime	Ofloxacin	Before IPTW	After IPTW
No. of subjects	402930	1830786		
Age, mean ±SD	49.3 ±17.7	50.3 ±16.9	0.061	0.009
No. of females (%)	238329 (59.1)	1120119 (61.2)	0.042	0.006
No. of Comorbidities (%)				
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
No. of Antibiotic Indications (%)				
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
Month, No (%)				
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

			Standardized difference	
	Cefixime	Moxifloxacin	Before IPTW	After IPTW
No. of subjects	402930	47080		
Age, mean ±SD	49.3 ±17.7	58.4 ±17.4	0.521	0.007
No. of females (%)	238329 (59.1)	23586 (50.1)	0.183	0.024
No. of Comorbidities (%)				
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
No. of Antibiotic Indications (%)				
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
Month, No (%)				
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
Title and abstract	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	
Introduction				
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
Methods				
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	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—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 *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5, 6,	Inclusion criteria and exposures 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. Follow-up began on the index date and ended on the date of serious arrhythmia or 14 days after starting treatment, whichever came first.
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6	Outcome definition 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

				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*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—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
Results				
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 Table 1	Study population characteristics
		(b) Indicate number of participants with missing data for each variable of interest		No missing data
		(c) *Cohort study*—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*	*Cohort study*—Report numbers of outcome events or summary measures over time	21	Table 2, Table 3
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		
		Cross-sectional study—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
Discussion				
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

				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

				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%.[38] 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.
Other information				
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.