A Thesis for Degree of Master

Association between Oral Fluoroquinolone Use and Serious Ventricular Arrhythmia

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This thesis has been examined and approved.

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Abstract

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Background: Fluoroquinolones are broad-spectrum antibiotics widely prescribed in the outpatient setting. However, whether oral fluoroquinolone use is associated with the risk of serious ventricular arrhythmia is controversial.

Methods: We conducted a retrospective cohort study using the Korean Health Insurance Review and Assessment Service-National Inpatients Sample (HIRA-NIS) from 1 February 2014 to 30 November 2014. We

extracted outpatients who were prescribed oral fluoroquinolone and amoxicillin-clavulanate, then we identified serious ventricular arrhythmia using ICD-10 codes. We estimated cumulative incidence, and Cox regression was used to compute the adjusted hazard ratios [HR] and 95% confidence intervals [CI] of serious ventricular arrhythmia associated with fluoroquinolone use compared to amoxicillin-clavulanate use.

Results: During the 1 to 7 days after the prescription date, the cumulative incidence of serious ventricular arrhythmia was 60.1 per 1 million prescriptions among fluoroquinolone users and 25.4 among amoxicillin-clavulanate users. Fluoroquinolone use was not associated with serious ventricular arrhythmia, when compared to amoxicillin-clavulanate use (HR, 1.56; 95% CI, 0.43-5.70). Furthermore, subgroup analysis showed no association between the type of fluoroquinolone and the risk of serious ventricular arrhythmia compared to amoxicillin-clavulanate. The HRs of ofloxacin, levofloxacin and ciprofloxacin were 3.93 (95% CI, 0.96-16.1), 0.77 (95% CI, 0.08-7.29) and 1.02 (95% CI, 0.11-9.54), respectively.

Conclusions: Oral fluoroquinolone use was not associated with an increased risk of serious ventricular arrhythmia in the sample of the general Korean population.

Keywords: fluoroquinolone, ventricular arrhythmia, ofloxacin, levofloxacin, ciprofloxacin

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Ⅰ. Introduction

Fluoroquinolones are broad-spectrum antibiotics widely prescribed to treat various infections in the outpatient setting. Although fluoroquinolones have generally been considered to be well-tolerated, they may increase the risk of cardiac adverse cardiac events such as torsades de pointes, ventricular arrhythmia and cardiac arrest.[1-10] For this reason sparfloxacin and grepafloxacin were withdrawn from the markets entirely.[11]

However there is controversy among researchers about the adverse effects of fluoroquinolones. A nested case-control study in Canada showed a 2- to 7-fold increased risk of serious arrhythmia associated with gatifloxacin, moxifloxacin, and ciprofloxacin compared to non-users. However, levofloxacin was not associated with an increase in the risk of serious arrhythmia.[2] Another study in Taiwan reported a 3-fold increase in the risk for ventricular arrhythmia with moxifloxacin but not ciprofloxacin or levofloxacin, compared to amoxicillin-clavulanate.[1] In contrast, a recent observational study in Denmark and Sweden showed that the use of fluoroquinolones was not associated with an increased risk of serious arrhythmia. However, we cannot exclude whether fluoroquinolones influence the risk of serious arrhythmia because 82% of oral

fluoroquinolone use in this study were ciprofloxacin.[12]

Further research is needed to assess the cardiac risk of fluoroquinolones and thus, resolve this debate. So, we conducted a retrospective cohort study using the Korean National Inpatient Sample database. The present study aimed to determine the association between oral fluoroquinolone use and serious ventricular arrhythmia.

Ⅱ. Method

1. Data sources

We conducted a study using the 2014 Korean Health Insurance Review and Assessment Service-National Inpatients Sample (HIRA-NIS-2014). The National Health Insurance of South Korea covers ~98% of the population. The claim data of the HIRA contains diagnoses, procedures, and prescription drugs. The HIRA-NIS database is a gender and an age-stratified random sample of the HIRA claim data and consists of 13% of the inpatient claims (~700,000 individuals) and 1% of outpatient claims (~400,000 individuals).[13]

2. Study design and population

We conducted a retrospective cohort study. We identified all patients aged

20 years or older who had been prescribed fluoroquinolones in the outpatient department from 1 February 2014 to 30 November 2014. Potential confounding by indication was addressed by including patients who had been prescribed amoxicillin-clavulanate as a control group. Amoxicillin-clavulanate is known as a medication without any pro-arrhythmic effects and is not in the list of drug-induced QT prolongation or torsades de pointes.[14-17] We included only the first prescription of study antibiotics during the evaluation period for each patient. The "index date" was defined as the first prescription date of the study medication

We excluded all patients who (1) were prescribed drugs associated with QT prolongation or at increased risk for developing torsades de pointes[14] from 30 days before the index date to 14 days after the index date (Appendix Table 1); (2) had been hospitalized within 30 days before the index date; and (3) had a prior diagnosis of ventricular arrhythmia or sudden cardiac arrest before the index date.

3. Outcome definition

The outcome of this study, "serious ventricular arrhythmia", was defined using the International Classification of Diseases, Tenth Revision [ICD-10]

codes. Patients with the main diagnosis code of ventricular tachycardia, fibrillation, flutter (ICD-10 codes : I472, I490) or cardiac arrest (ICD-10 codes : I46, I460, I461, I469) were identified. The first diagnosis was included when the patients had diagnosis codes more than once.

4. Exposures

The fluoroquinolones prescriptions (including ciprofloxacin, levofloxacin, ofloxacin, moxifloxacin, norfloxacin, tosufloxacin, lomefloxacin, balofloxacin, gemifloxacin, enoxacin) were extracted using the Korea Drug Code (Appendix Table 2). Only outpatient prescriptions were included, and inpatient prescriptions were excluded. We used observation periods that were defined as 1-7 days and 1-14 days, respectively, after the index dates to evaluate the acute effect of the medications.

5. Statistical analysis

Risk factors (hypertension, diabetes mellitus, acute myocardial infarction, congestive heart failure, cancer, cerebrovascular disease, renal disease, chronic obstructive pulmonary disease, liver disease) in patients were

identified as potential confounders by diagnosis codes (Appendix Table 3). All risk factors, age, and gender were analyzed as covariates. The number of cases and cumulative incidence per 1million prescriptions was identified. The risk of serious ventricular arrhythmia of fluoroquinolone compared to amoxicillin-clavulanate was calculated, with adjustment for the covariates, as hazard ratio [HR] and 95% confidence interval [CI] using Cox proportional regression. Additionally, we calculated the HR according to the types of oral fluoroquinolones for a subgroup analysis. R statistical software (version 3.3.0, Vienna, Austria) was used for data manipulation and analysis.

6. Ethics

In the HIRA-NIS 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 (Jeju-do, South Korea) and the board waived informed consent. (IRB No. JEJUNUH 2016-07-002-001)

Ⅲ. Result

1. Characteristics of the study population

From 1,100,000 individuals in the HIRA-NIS-2014 dataset, we extracted 257,049 outpatient who were prescribed oral fluoroquinolone and amoxicillin-clavulanate between 1 February 2014 and 30 November 2014. Included in the analysis, were 99,835 users of fluoroquinolone and 157,214 users of amoxicillin-clavulanate were included in the analysis (Figure 1).

The baseline characteristics of the two groups(fluoroquinolone and amoxicillin-clavulanate users) are shown in Table 1. Fluoroquinolone users had a mean age of 53.6 years, and they were primarily female (61.0%). When compared to amoxicillin-clavulanate users, fluoroquinolone users were more likely to have cardiovascular, cerebrovascular and other diseases.

Ofloxacin (33.5%), levofloxacin (30.3%) and ciprofloxacin (29.7%) were

frequently prescribed (Table 2). Baseline characteristics of patients according to the types of fluoroquinolones, are shown in Table 3. The main diagnosis codes in the patients prescribed fluoroquinolones were urinary, respiratory and gastrointestinal infections (Appendix Table 4). The main diagnosis code in the patients prescribed amoxicillin-clavulanate was upper respiratory tract infection (Appendix Table 5).

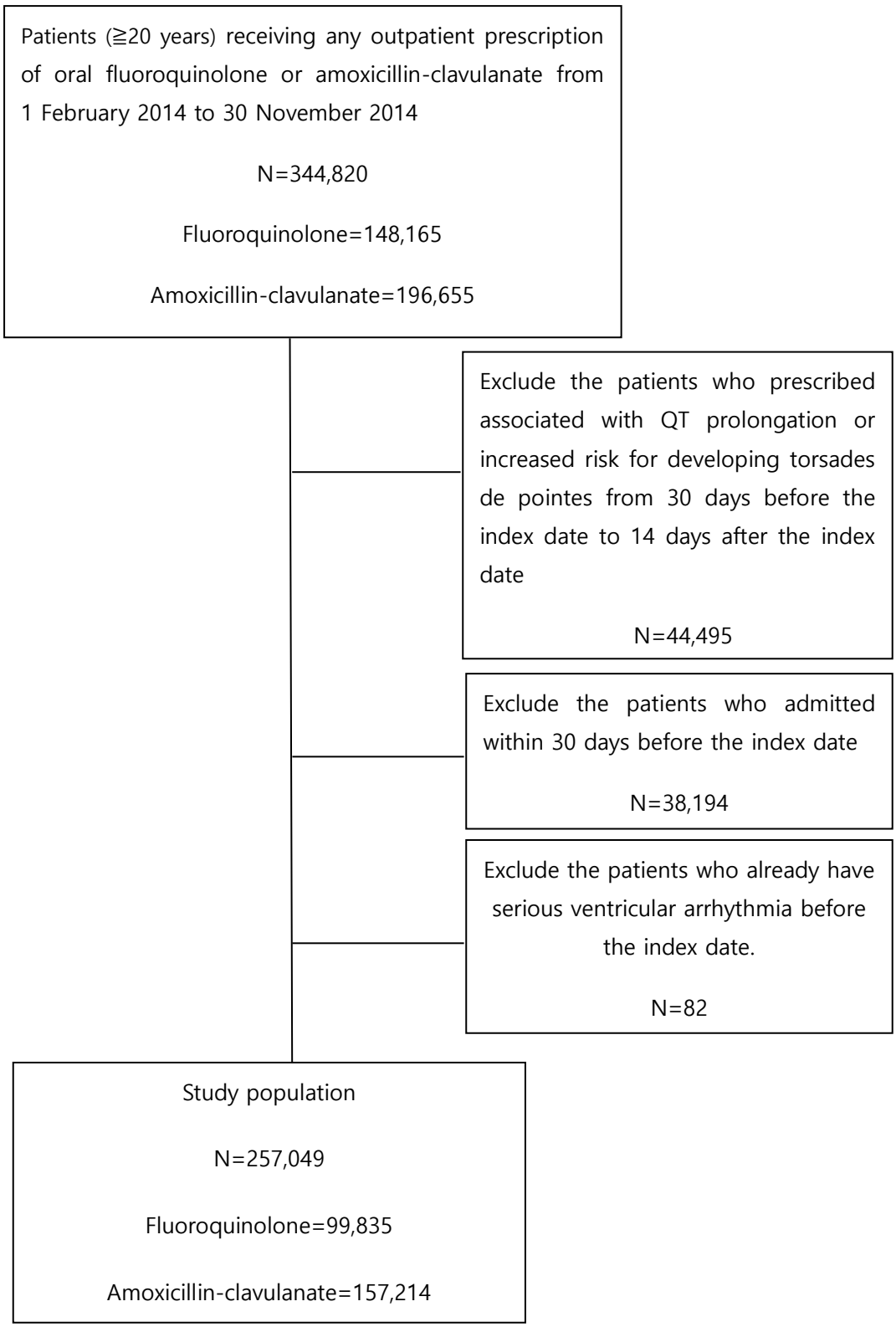

Figure 1. Study flow diagram

Table 1. Baseline characteristics of patients using fluoroquinolone versus amoxicillin−clavulanate

Characteristics	Fluoroquinolone (N=99,835)	Amoxicillin-clavulanate (N=157,214)
Mean age (yr)	53.6	47.8
Female (%)	61.0	56.6
Medical history (%)		
Hypertension	36.0	26.6
Diabetes mellitus	25.8	19.1
Acute myocardia infarction	2.0	1.4
Congestive heart failure	5.4	3.5
Cancer	12.5	8.2
Cerebrovascular disease	11.5	7.7
Renal disease	13.2	7.7
†COPD	39.3	36.8
Liver disease	29.3	23.3

† COPD: chronic obstructive pulmonary disease

Table 2. Number of patients according to the types of fluoroquinolones

Types of fluoroquinolone	No. of patients (%)
Ofloxacin	33,471 (33.5%)
Levofloxacin	30,238 (30.3%)
Ciprofloxacin	29,608 (29.7%)
Tosufloxacin	1,675 (1.7%)
Balofloxacin	1,333 (1.3%)
Norfloxacin	1,259 (1.3%)
Moxifloxacin	1,198 (1.2%)
Gemmifloxacin	713 (0.7%)
Lomefloxacin	285 (0.3%)
Enoxacin	55 (0.1%)

Table 3. Baseline characteristics of patients using fluoroquinolone according to the types of fluoroquinolones, versus patients using amoxicillin-clavulanate

Characteristics	Ofloxacin (N=33,471)	Levofloxacin (N=30,238)	Ciprofloxacin (N=29,608)	Amoxicillin-clavulanate (N=157,214)
Mean age (yr)	53.6	54.1	52.5	47.8
Female (%)	61.7	55.9	68.7	56.6
Medical history (%)				
Hypertension	35.4	37.1	34.8	26.6
Diabetes mellitus	24.2	26.7	26.2	19.1
Acute myocardia infarction	1.7	2.2	2.0	1.4
Congestive heart failure	4.7	6.0	5.3	3.5
Cancer	9.3	14.3	12.9	8.2
Cerebrovascular disease	10.9	12.3	10.8	7.7
Renal disease	8.8	14.4	16.6	7.7
COPD	36.6	44.5	35.5	36.8
Liver disease	26.6	30.1	31.1	23.3

† COPD: chronic obstructive pulmonary disease

2. Development of serious ventricular arrhythmia

Serious ventricular arrhythmia was recorded in 214 patients during the study period. During the 1−7 days after the fluoroquinolone prescription, 6 patients underwent serious ventricular arrhythmia, and the cumulative incidence was 60.1 per 1 million prescriptions. Among amoxicillin−clavulanate users, 4 patients underwent serious ventricular arrhythmia and the cumulative incidence was 25.4 per million prescriptions. The adjusted HR, compared to amoxicillin−clavulanate, was 1.56 (95% CI, 0.43−5.70). Oral fluoroquinolones were not significantly associated with the risk of serious ventricular arrhythmia (Table 4) (Figure 2).

Table 4. Risk of serious ventricular arrhythmia associated with fluoroquinolone use compared to amoxicillin−clavulanate use during the 7 days after the index date

1-7 days after the index date	**Fluoroquinolone** (N=99,835)	**Amoxicillin-clavulanate** (N=157,214)
Number of patients	6	4
Cumulative incidence (no./1 million)	60.1	25.4
Adjusted hazard ratio (95% CI)	1.56 (0.43-5.70)	1
P value for Adjusted hazard ratio	0.50	

During the 1-14 days after the fluoroquinolone prescription, 8 patients underwent serious ventricular arrhythmia and the cumulative incidence was 80.1 per 1 million prescriptions among patients who took fluoroquinolone. There were 7 serious ventricular arrhythmia patients among amoxicillin-clavulanate users and the cumulative incidence was 44.5 per 1 million prescriptions. The adjusted HR was 1.27(95% CI, 0.45-3.59) among patients who took fluoroquinolone compared to amoxicillin-clavulanate users. There was no significant difference. (Table 5) (Figure 3).

Table 5. Risk of serious ventricular arrhythmia associated with fluoroquinolone use compared to amoxicillin-clavulanate use during the 14 days after the index date

1-14 days after the index date	**Fluoroquinolone** (N=99,835)	**Amoxicillin-clavulanate** (N=157,214)
Number of patients	8	7
Cumulative incidence (no./1 million)	80.1	44.5
Adjusted hazard ratio (95% CI)	1.27 (0.45-3.59)	1
P value for Adjusted hazard ratio	0.65	

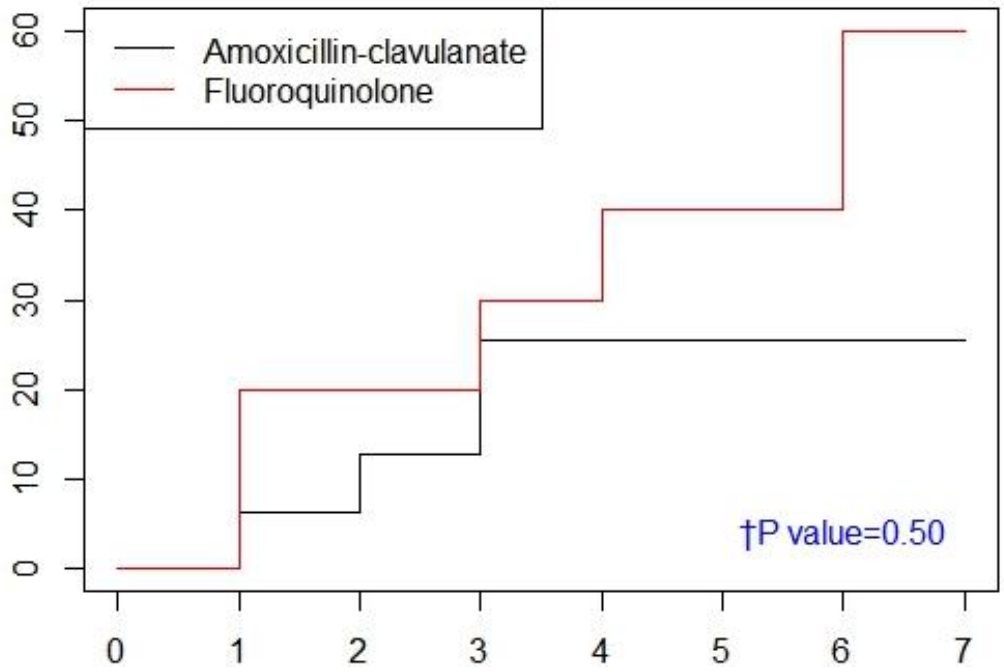

Figure 2. Cumulative incidence of serious ventricular arrhythmia among patients who took fluoroquinolone versus amoxicillin-clavulanate during the 1-7 days period after the index date

† P value for adjusted hazard ratio

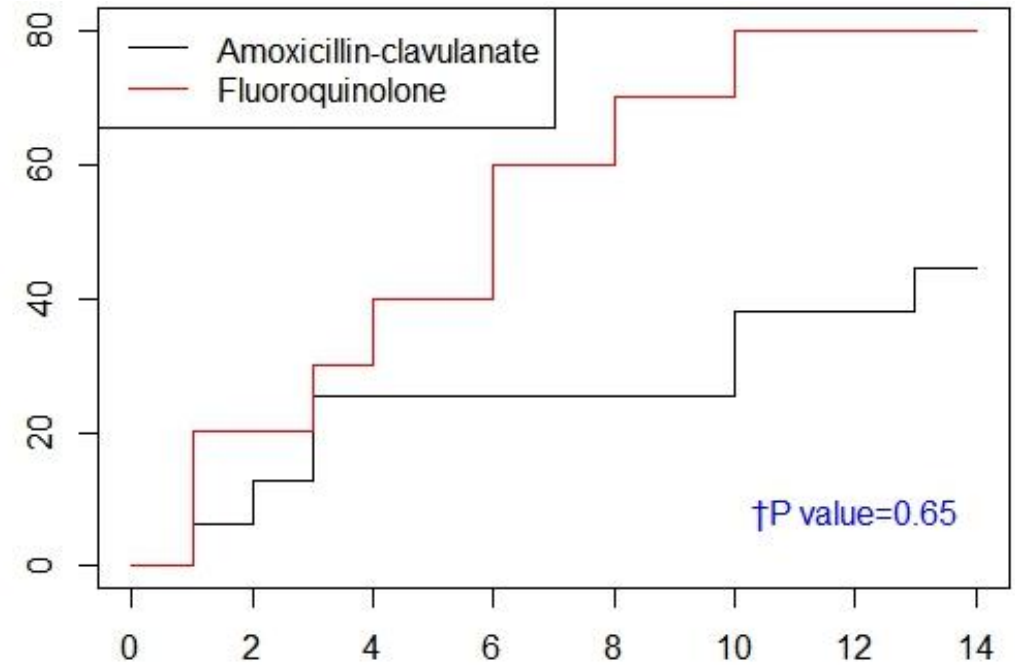

Figure 3. Cumulative incidence of serious ventricular arrhythmia among patients who took fluoroquinolone versus amoxicillin-clavulanate during the 1-14 days period after the index date

† P value for adjusted hazard ratio

3. Subgroup analysis

Table 6 shows the cumulative incidence and the HRs of serious ventricular arrhythmia according to the types of oral fluoroquinolones compared to amoxicillin-clavulanate. The risk of serious ventricular arrhythmia in ofloxain, levofloxacin or ciprofloxacin users did not differ significantly from that in amoxicillin-clavulanate users.

The adjusted HR of ofloxacin 3.93 (95% CI, 0.96-16.1) and 2.32 (95% CI, 0.67-8.10) in days 1-7 and 1-14, respectively. However, neither results was statistically significant. During the 1-7 days after the index date, the adjusted HRs of levofloxacin and ciprofloxacin were 0.77 (95% CI, 0.08-7.29) and 1.02 (95% CI, 0.11-9.54), respectively. During the 1-14 days after the index date, the adjusted HRs of levofloxacin and ciprofloxacin were 0.51 (95% CI, 0.06-4.30) and 1.19 (95% CI, 0.24-5.92), respectively.

Table 6. Risk of serious ventricular arrhythmia associated with fluoroquinolone use according to the types of fluoroquinolones compared to amoxicillin−clavulanate use

Types of fluoroquinolones	1-7 days after the index date	1-14 days after the index date
Ofloxacin		
Adjusted hazard ratio	3.93	2.32
(95% CI)	(0.96-16.1)	(0.67-8.10)
No. of patients	4	4
Cumulative incidence (no./1 million)	119.5	119.5
Levofloxacin		
Adjusted hazard ratio	0.77	0.51
(95% CI)	(0.08-7.29)	(0.06-4.30)
No. of patients	1	1
Cumulative incidence (no./1 million)	33.1	33.1
Ciprofloxacin		
Adjusted hazard ratio	1.02	1.19
(95% CI)	(0.11-9.54)	(0.24-5.92)
No. of patients	1	2
Cumulative incidence (no./1 million)	33.8	67.5
Amoxicillin-clavulanate		
Adjusted hazard ratio	1	1
No. of patients	4	7
Cumulative incidence (no./1 million)	25.4	44.5

Ⅳ. Discussion

1. Findings

In this study, we found no association between oral fluoroquinolone use and serious ventricular arrhythmia. We found no increased hazard of oral fluoroquinolones with developing serious ventricular arrhythmia within 7 or 14 days compared to amoxicillin-clavulanate. Moreover, three types of fluoroquinolones (ofloxacin, levofloxacin or ciprofloxacin) were not associated with a significantly increased risk.

2. Drug-induced arrhythmia

Many drugs cause prolongation of the QT interval and potentially lead to fatal arrhythmias such as torsades de pointes.[11,15,17,18] The drug-related QT prolongation occurs via inhibition of potassium channels, particularly the

rapid component of the delayed rectifier potassium channel [I_{Kr}]. I_{Kr} is encoded by human ether-a-go-go-related gene [HERG]. The propensity of drugs to increase transmural dispersion of repolarization across the ventricular wall (which creates a substrate for reentry) and to generate early afterdepolarizations may initiate torsades de pointes.[18] The risk factors for the development of drug-induced torsades de pointes are female, electrolyte abnormalities (hypomagnesemia and hypokalemia), bradycardia, heart failure, digitalis therapy, high drug concentrations, a rapid rate of intravenous infusion, and baseline QT prolongation, for example.[17]

All fluoroquinolones are I_{Kr} antagonists. However, levofloxacin, ciprofloxacin and ofloxacin were found to be significantly less potent inhibitors of HERG channels compared to sparfloxacin, grepafloxacin, moxifloxacin and gatifloxacin.[19] The effect of fluoroquinolones on the QT interval was studied in several randomized controlled trials. Moxifloxacin is associated with the risk of QT prolongation.[20,21] Conversely, ciprofloxacin and levofloxacin were not associated with QT prolongation at the recommended dose.[20,22] There are some case reports of torsades de pointes associated with fluoroquinolones.[4-10] However, most patients in these reports have more than one risk factor for drug-induced torsades de pointes.

3. Comparison to other studies

A few population-based observational studies have investigated the association between fluoroquinolones and ventricular arrhythmia or cardiac arrest. Zambon et al.[3] reported that fluoroquinolones increase the risk of ventricular arrhythmia and cardiac arrest by using case-control, case-crossover and case-time-control methods with respective HRs of 3.58 (95% CI, 2.51-5.12), 1.98 (95% CI, 1.19-3.29) and 1.59 (95% CI, 0.88-2.87). However, they used an extended observation period of 4 weeks. Oral antibiotics use usually does not typically exceed 2 weeks, and the concentration of fluoroquinolones quickly decay after discontinuation. Lapi et al.[2] reported that fluoroquinolone use was associated with a 77% increased risk in patients treated for respiratory conditions. This disagreement with our findings may be due to the difference in the average age of the patients and the severity of comorbidity. Chou et al.[1] reported an odds ratio of 2.07 (95% CI, 1.56–2.76) for ventricular arrhythmia in the Taiwanese population associated with fluoroquinolone use compared to amoxicillin-clavulanate, In the study of Chou et al., moxifloxacin showed a 3-fold increased odds ratio for ventricular arrhythmia, while no association was noted between ciprofloxacin or levofloxacin. The increased odds ratio for fluoroquinolone was mainly due to moxifloxacin and this could be the cause of difference with findings of our study. In our study, we could not

analyze moxifloxacin as a subgroup because there were only 1198(1.2% of all fluoroquinolones) users. Inghammar et al.[12] reported oral fluoroquinolone treatment was not associated with an increased risk of serious arrhythmia compared to penicillin V in the general population of Denmark and Sweden. This result corresponds with our study. However, ciprofloxacin was the most common fluoroquinolone prescribed (82.6%). Therefore, the risk of serious arrhythmia associated with other less frequently used fluoroquinolones could not be confirmed. In our study, the cumulative incidence of serious ventricular arrhythmia in fluoroquinolone users was 60.1 per million prescriptions during days 1−7 after the index date. The respective cumulative incidences in the study of Chou et al.[1] and Inghammar et al.[12] were 226.9 and 72.6 per million prescriptions.

Overall, ciprofloxacin and levofloxacin seem to be safe, while moxifloxacin appears to be associated with arrhythmia. Our findings indicate that the risk of arrhythmia with ciprofloxacin or levofloxacin use could not be generalized and these fluoroquinolones can be prescribed in office practice without concern about ventricular arrhythmia in the general population. However, supratherapeutic doses of ciprofloxacin or levofloxacin induced the increased QTc interval in randomized controlled trials (less than moxifloxacin).[23,24] Moreover, there are several case reports of torsades de pointes among ciprofloxacin and levofloxacin users in high−risk patients.[4−9] Clinicians should consider the benefits and the risk of fluoroquinolones

among patients with high risk of drug-induced arrhythmia.

Our study showed ofloxacin was associated with a 2-3 fold increased risk of serious arrhythmia (not statistically significant). In a laboratory study, ofloxacin was the least potent inhibitor of HERG compared to the other fluoroquinolones tested.[25] However, there is no published report about ofloxacin in population-based studies.

4. Strengths and limitations

This study has several strengths. Using population-based claims databases, we could collect a large number of exposures. We were able to identify rare arrhythmia cases, which showed a cumulative incidence of 60.1 per 1 million prescriptions. Furthermore, this study identified the precise time of exposure using medical claims database without recall bias.

This study has several limitations. First, patients whose conditions were not associated with serious ventricular arrhythmia could be included because the diagnosis codes for the outcome definition were not validated. However, Tamariz et al.[26] reported a 78-100% positive predictive value of identifying ventricular arrhythmia when using codes of ventricular arrhythmia and cardiac arrest (ICD-9 codes 427.x). These codes correspond to the codes of this study (ICD-10 code I472, I490, I46.x). Second, the number of cases in the subgroup analyses was not sufficient.

The 95% CIs of the subgroup analysis were broad, and this means low statistical power. The adjusted HR of ofloxacin was 3.93 and 95% CI was 0.96−16.1. If the sample size had been larger, ofloxacin would have shown a statistically significant result. We need further studies with more patients to confirm the association of ofloxacin use with ventricular arrhythmia. Third, we adjusted several covariates but there could be residual confounding factors such as severity of the patients, lab data, baseline QTc intervals and other factors associated with ventricular arrhythmia. However, we excluded patients who were prescribed drugs associated with QT prolongation or at increased risk of developing torsades de pointes and had been hospitalized, thereby reducing the effects of other factors related to ventricular arrhythmia. Fourth, confounding by indication was not fully controlled. We used amoxicillin−clavulanate as a comparative medication to minimize confounding by indication. However, the main diagnosis codes of the patients prescribed fluoroquinolones were urinary, respiratory and gastrointestinal infections, whereas the main diagnosis code of the patients prescribed amoxicillin−clavulanate was upper respiratory tract infection. This different indication for treatment between two groups could be associated with the risk of outcomes. Consequently, we need other comparative medications or more advanced methods to reduce confounding by indication in future studies.

Ⅴ. Conclusion

In this study, we found no association between oral fluoroquinolone use and serious ventricular arrhythmia in the sample of the general Korean population. Ofloxacin, levofloxacin and ciprofloxacin were not associated with ventricular arrhythmia, but the statistical power was low. Moreover, other types of fluoroquinolone were not confirmed due to lack of a sufficient sample size. An additional study involving larger population data is needed to determine the risk of serious ventricular arrhythmia associated with the types of fluoroquinolones used.

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국문요약

경구 플루오로퀴놀론과 심실성 부정맥의 연관성

배경: 플루오로퀴놀론은 다양한 감염성 질환을 치료하기 위해 외래에서 흔히 처방되는 항생제이다. 하지만, 경구 플루오르퀴놀론이 심각한 심실성 부정맥의 위험성을 높이는지 여부는 논란이 있다.

방법: 2014년 건강보험심사평가원 입원환자표본자료를 사용하여 2014년 2월 1일부터 2014년 11월 30일까지 후향적 코호트 연구를 진행했다. 외래에서 경구 플루오르와 아목시실린-클라불란산을 처방 받은 추출한 후 ICD-10 코드로 심각한 심실성 부정맥 환자를 확인했다. 누적 발생률을 추정하고, 콕스 비례위험모형을 이용하여 아목시실린-클라불란산과 비교한 경구 플루오로퀴놀론의 심각한 심실성 부정맥 위험비와 95% 신뢰구간을 산출하였다.

결과: 처방 후 1일에서 7일동안 플루오로퀴놀론 사용자의 심각한 심실성 부정맥 누적 발생률은 처방 100만건당 60.1명 이었으며, 아목시실린-클라불란산 사용자는 25.4명이었다. 플루오로퀴놀론은 심각한 아목시실린-클라불란산과 비교하여 심각한 심실성 부정맥과 관련이 있지 않았다. (위험비, 1.56; 95% 신뢰구간, 0.43-5.70). 어느 종류의 플루오로퀴놀론도 아목시실린-클라불란산과 비교하여 심각한 심실성 부정맥과 관련이 있지 않았다. 오플록사신, 레보플록사신, 시프로플록사신의 위험비는 각각 3.93 (95% 신뢰구간, 0.96-16.1), 0.77 (95% 신뢰

구간, 0.08−7.29) and 1.02 (95% 신뢰구간, 0.11−9.54)이었다.

결론: 경구 플로오로퀴놀론은 한국의 일반인구 표본자료에서 심각한 심실성 부정맥의 위험을 높이지 않았다.

핵심어: 플루오로퀴놀론, 심실성 부정맥, 오플록사신, 레보플록사신, 시프로플록사신

Appendix

Appendix Table 1. Korea Drug Codes for medications used in the exclusion criteria

Medications	Korea Drug Codes
Amidarone	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

Appendix Table 2. Korea Drug Codes for fluoroquinolones

Ofloxacin	203901ATB, 203904ATB
Levofloxacin	183201ATB, 183202ATB, 183203ATB
Ciprofloxacin	134101ATB, 134103ATB, 134105ATB 134105ATR, 134108ATR
Tosufloxacin	242201ATB
Balofloxacin	428901ATB
Norfloxacin	203301ATB, 203302ACH, 203303ATB
Moxifloxacin	380301ATB
Gemmifloxacin	442901ATB
Lomefloxacin	184901ATB, 184904ATB, 184903ATB
Enoxacin	152001ATB

Appendix Table 3. Diagnosis codes for covariates

Hypertension	I10-I13.x, I15.x
Diabetes mellitus	E10.x-E14.x
Acute myocardial infarction	I21.x, I22.x, I25.2
Congestive heart failure	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43.x, I50.x, P29.0
Cancer	C00.x–C99.x
Cerebrovascular disease	G45.x, G46.x, H34.0, I60.x–I69.x
Renal disease	N00.x-N19.x, N25.x, N26.x, E102, E112, E122, E132, E142, Z940, Z992
COPD	I27.8, I27.9, J40.x–J47.x, J60.x–J67.x, J68.4, J70.1, J70.3
Liver disease	B18.x, K70.x, , K71.1, K71.3–K71.5, K71.7, K72.x, K73.x, K74.x, K76.0, K76.2–K76.9, Z94.4, I85.0, I85.9, I86.4, I98.2

Appendix Table 4. Top 20 diagnosis codes for fluoroquinolone prescriptions

Codes	Diagnosis	Number of patients
N300	Acute cystitis	9186
J209	Acute bronchitis, unspecified	8623
N309	Cystitis, unspecified	3151
A090	Other and unspecified gastroenteritis and colitis of infectious origin	2748
A049	Bacterial intestinal infection, unspecified	2238
A099	Gastroenteritis and colitis of unspecified origin	1867
N400	Hyperplasia of prostate without complication	1803
J40	Bronchitis, not specified as acute or chronic	1770
J0390	Acute tonsillitis, unspecified, not specified as recurrent	1763
N390	Urinary tract infection, site not specified	1693
I109	Other and unspecified primary hypertension	1665
N411	Chronic prostatitis	1615
N341	Nonspecific urethritis	1357
N10	Acute tubulo-interstitial nephritis	1193
H001	Chalazion	931
J189	Pnemonia, unspecified	931
H0001	Hordeolum internum	860
N201	Calculus of ureter	853
J029	Acute pharyngitis, unspecified	762
J459	Asthma, unspecified	688

Appendix Table 5. Top 20 diagnosis codes for amoxicillin-clavulanate prescriptions

Codes	Diagnosis	Number of patients
J209	Acute pharyngitis, unspecified	27779
J0390	Acute tonsillitis, unspecified, not specified as recurrent	13520
J40	Bronchitis, not specified as acute or chronic	4323
K0531	Chronic complex periodontitis	4043
J060	Acute laryngopharyngitis	3627
J029	Acute pharyngitis, unspecified	3619
K0530	Chronic simplex periodontitis	3429
J0190	Acute sinusitis, unspecified, not specified as recurrent	3415
J36	Peritonsillar abscess	2187
J0100	Acute maxillary sinusitis, not specified as recurrent	2001
J040	Acute laryngitis	1883
I109	Other and unspecified primary hypertension	1802
J304	Allergic rhinitis, unspecified	1770
K047	Periapical abscess without sinus	1754
J329	Chronic sinusitis, unspecified	1624
J0391	Acute tonsillitis, unspecified, recurrent	1442
J22	Unspecified acute lower respiratory infection	1429
J00	Acute nasopharyngitis[common cold]	1416
J320	Chronic maxillary sinusitis	1378
J219	Acute bronchiolitis, unspecified	1360