Fluoroquinolones and the Risk of Serious Arrhythmia: A Population-Based Study

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Background. Fluoroquinolones have been suspected to cause cardiac arrhythmia but data are lacking, particularly for the individual fluoroquinolones. We assessed the risk of serious arrhythmia, defined as ventricular arrhythmia or sudden/unattended death identified in hospital discharge diagnoses, related to fluoroquinolones as a class as well as for each individual molecule.

Methods. We used a cohort of patients treated for respiratory conditions from 1 January 1990 to 31 December 2005, identified using the healthcare databases from the province of Quebec (Canada), with follow-up until 31 March 2007. A nested case-control analysis was performed within this cohort, with all cases of serious arrhythmia occurring during follow-up identified from hospitalization records. These cases were matched with up to 20 controls. Conditional logistic regression was used to compute adjusted rate ratios (RRs) of serious arrhythmia associated with fluoroquinolone use.

Results. Within the cohort of 605 127 subjects, 1838 cases were identified (incidence rate = 4.7/10 000 person-years). The rate of serious arrhythmia was elevated with current fluoroquinolone use (RR = 1.76; 95% confidence interval [CI], 1.19–2.59), in particular with new current use (RR = 2.23; 95% CI, 1.31–3.80). Gatifloxacin use was associated with the highest rate (RR = 7.38; 95% CI, 2.30–23.70); moxifloxacin and ciprofloxacin were also associated with elevated rates of serious arrhythmia (RR = 3.30; 95% CI, 1.47–7.37 and RR = 2.15; 95% CI, 1.34–3.46, respectively).

Conclusions. The use fluoroquinolones is associated with an elevated risk of serious arrhythmia, with some differences among molecules. Given that the individual fluoroquinolones share various indications, the relative risks of serious arrhythmia could inform the choice of different molecules in high-risk patients.

Fluoroquinolones are antibiotics frequently used in the treatment of bacterial infections in both primary and secondary care [1, 2]. From a clinical viewpoint, fluoroquinolones offer several advantages because of their broad spectrum of activity and a high bioavailability for oral administration [3, 4]. Despite their proven efficacy, however, the risk/benefit profile of these antibiotics still requires careful evaluation

wherever they are prescribed. Their association with various adverse drug reactions, such as QTc interval prolongation and torsades de pointes, which can lead to ventricular fibrillation, cardiac arrest, and sudden cardiac death [5], has resulted in revising the indication for use of some fluoroquinolones (ie, moxifloxacin) while certain antibiotics in this class have been withdrawn from the European and US markets entirely (ie, sparfloxacin, grepafloxacin) [6, 7].

Establishing a causal link between fluoroquinolones and serious arrhythmia has been difficult owing to the rarity of adverse events, poor quality of data emanating from randomized clinical trials [1, 4, 8], and the limitations of pharmacovigilance surveys [9, 10]. To date, only one population-based study has been conducted, reporting a >3-fold higher risk of developing ventricular arrhythmia and cardiac arrest with the use

of fluoroquinolones [11]. This study, however, did not evaluate the risk separately for the different fluoroquinolone antibiotics and did not control for certain key confounders such as the occurrence of exacerbations of chronic respiratory disease [12, 13].

In this study, we assessed the risk of serious arrhythmia related to fluoroquinolones as a class as well as for each individual fluoroquinolone antibiotic.

METHODS

Data Source

Data were drawn from the RAMQ and MedEcho databases, for which demographic and healthcare utilization information are currently collected for all 7 million of residents of the province of Quebec (Canada).

Before 1 January 1997, the RAMQ prescription drug insurance plan covered residents who were either aged ≥65 years, or welfare recipients and their children. After this date, the drug plan was modified to give access to employed residents and their spouse/children who did not have access to alternate private drug insurance coverage [14]. The RAMQ database also provides the dates of death. The MedEcho database contains information pertaining to all hospital admissions and in-hospital deaths in Quebec obtained from the data recorded by archivists on the hospitalization discharge summary sheet. These databases have been previously used to conduct epidemiological studies [14–16].

The Research Ethics Committee of the Jewish General Hospital has granted approval for this protocol (number 11–039).

Cohort Definition

We used a cohort of patients (N = 1 410 211) treated for respiratory conditions from 1 January 1990 to 31 December 2005, identified using the RAMQ database, with follow-up until 31 March 2007. Respiratory medications comprised bronchodilators, nasal or orally inhaled corticosteroids, and antiasthma medications (cromoglycate, nedocromil, montelukast, zafirlukast, and ketotifen).

Subjects with <2 complete years of RAMQ coverage before the date of their first respiratory medication prescription were excluded from the study. Thus, the date of cohort entry occurred 730 days after a patient's first eligible day of coverage, assuming that they were not excluded at any point in time between day 0 and day 729. Subjects were excluded if they had a previous history of arrhythmia before or on the day of cohort entry based on the identification of codes for hospitalization (ie, ventricular or atrial arrhythmia at any diagnosis position, primary or otherwise) or medical services (ie, arrhythmia-related surgical/interventional procedures) or on recorded use of antiarrhythmic drugs. Patients were followed

from cohort entry until they left the drug plan, had an event of serious arrhythmia, or died (if not registered as sudden or unattended death in MedEcho), or until 31 March 2007 (the end of cohort follow-up), whichever came first.

Case Definition

Cases of serious arrhythmia, defined as ventricular arrhythmia or sudden/unattended death, were identified using *International Classification of Diseases, Ninth Revision* (*ICD-9*) and *ICD-10* codes (primary diagnosis position) for hospitalizations. First, diagnoses of paroxysmal ventricular tachycardia, ventricular fibrillation and/or flutter, cardiac arrest [11, 17, 18], other unspecified forms of arrhythmia, and sudden or unattended death (including sudden cardiac death) were identified. These diagnosis codes were then coupled for each individual with specific cardiac surgical/interventional procedures (ie, implantation, replacement, or removal of cardioverter-defibrillator; ventricular tachycardia ablation; electrophysiological studies) as well as pharmacological treatments (ie, beta-blockers, mexiletine, and magnesium) [19]. Codes pertaining to cardiac interventions used in the treatment of rhythm disorders (±3 months from the date of diagnosis) identified within the hospitalization data and all prescriptions for an antiarrhythmic drug (±1 month from the date of diagnosis) were examined with respect to each acute event of serious arrhythmia. The index date was then defined as the earlier date from either hospital admission (or the date of death) or the occurrence of a surgical/interventional procedure or pharmacological treatment.

Exposure Definition

All prescriptions for fluoroquinolones (ciprofloxacin, gatifloxacin, grepafloxacin, levofloxacin, moxifloxacin, norfloxacin, ofloxacin, trovafloxacin) dispensed to cases and controls were extracted from the RAMQ database. We classified fluoroquinolones use during 3 mutually exclusive time periods, nominally the "current," "recent," and "past" time windows. A prescription was defined as being current if it occurred within the 14-day time period immediately preceding the index date; a prescription was defined as being recent if it occurred at any point during the 15–30-day time window before the index date; those prescriptions recorded within the 31–365-day time period before the index date were considered past prescriptions. Finally, current use was further classified as use that was either "new" or "not new" depending on whether or not the individuals had also been recent users. Current (either new or not new), recent, and past use was then compared with no use of fluoroquinolones.

Covariates

Variables pertaining to risk factors for serious arrhythmia as well as those identified as being potential confounders of the

fluoroquinolone-arrhythmia association were identified from the RAMQ and MedEcho databases. Specifically, comorbidities such as congestive heart failure, valvular disease, coronary artery disease, enlarged heart, congenital structural cardiovascular abnormalities, other cardiovascular diseases, atherosclerosis, hyperlipidemia, chronic and/or acute renal failure, diabetes mellitus (diagnosis and/or prescriptions of antidiabetic drugs), respiratory diseases, anemia, thyroid diseases, septicemia, and the overall number of hospitalizations were captured in the year before the index date. Additionally, concurrent use of various medication classes such as antihypertensives (beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers), cardiotonics, thyroid and lipid-lowering medications, nonsteroidal anti-inflammatory drugs (NSAIDs), and inhaled corticosteroids was also adjusted for within the same time window.

Given the fact that chronic obstructive pulmonary disease (COPD) exacerbations are both an independent risk factor for serious arrhythmia [12, 13] and potentially associated with the exposure to fluoroquinolones, we considered exacerbations occurring during the 30-day time window leading to the index date as possible confounders. "Moderate" exacerbations were identified when a prescription of an oral corticosteroid and an antibiotic (macrolide or nonmacrolide; excluding fluoroquinolones as the exposure under study) was filled on the same day; "serious" exacerbation was defined as a primary diagnosis of hospitalization for COPD [20]. Finally, prescriptions for medications filled within 30 days before the index date that could potentially induce arrhythmia (ie, antiarrhythmic drugs [if not used to define cases], macrolides, pyrimethamine, sulfamethoxazole/trimethoprim [if not used to define moderate exacerbation], antiviral and antifungal medications, antidepressants, other central nervous systems drugs, antiemetic drugs, and antimigraine medications) [21, 22] were included and adjusted for in our multivariate models.

Nested Case-Control Analysis

Up to 20 control subjects per case were randomly selected within each risk set. Eligible controls who were alive and event-free on the calendar date of the serious arrhythmia case (the index date) were matched to their respective cases by age (±5 years), sex, and cohort year of entry. Matched controls were assigned the same index date as their respective case. Current use, recent use, past use, and no use of fluoroquinolones were compared between cases and their matched controls, and the association between serious arrhythmia and fluoroquinolone use was estimated.

Data Analysis

The incidence density for the outcome of interest was computed in the cohort. Conditional logistic regression was used to compute odds ratios of serious arrhythmia which, for the time-matched nested case-control method used here, provide an accurate estimate of the rate ratio (RR) and the related 95% confidence interval (CI) [23]. In addition to age, sex, and calendar year of cohort entry on which the logistic regression was conditioned, we adjusted for the risk factors and confounders described above. Furthermore, we computed the attributable risk of serious arrhythmia due to fluoroquinolones by applying the RRs to the background incidence rate derived from our cohort.

Three sensitivity analyses were conducted in order to further clarify our results. Firstly, we controlled for immeasurable time bias [24] by repeating the analyses after excluding patients who had been hospitalized during the current time window. Secondly, the definition of current use was modified by varying the duration of the current time window from 14 to 21 and 28 days. Finally, all models were re-run using a more strict case definition whereby cases identified via diagnoses pertaining to unspecific arrhythmias or sudden/unattended death were restricted to only those that were preceded or followed by cardiac surgical/interventional procedures or pharmacological treatments (Figure 1). Statistical analyses were conducted using SAS software, version 9.2 TS2M3 (SAS Institute Inc, Cary, North Carolina).

RESULTS

A total of 605 127 patients met the study inclusion criteria (Figure 1). During follow-up, 1838 cases of serious arrhythmia were identified, giving an incidence rate of 4.7 per 10 000 person-years at risk.

Table 1 depicts demographic and clinical characteristics of cases and controls. Mean age was 75.3 years (SD, 12.2) and 56.7% of cases were women. Cases were more likely to have cardiovascular and renal diseases along with asthma, anemia, and a history of septicemia. Furthermore, cases were more likely to have been using antihypertensive, cardiotonic, or lipid-lowering drugs as well as NSAIDs and respiratory medications. Frequency of hospitalizations for COPD exacerbations were also proportionally higher among cases than controls (7.3% vs 1.5%), as well as the use of medications known to be potentially pro-arrhythmic. As shown in Table 2, most of the cases were nonfatal. Overall, 121 and 272 cases were combined with a surgical/interventional procedure or pharmacotherapy, respectively.

Table 3 shows that, when the exposure to fluoroquinolones was modeled according to recency of use, the adjusted RR was not significantly elevated among current (RR = 1.34; 95% CI, .92–1.93), recent (RR = 1.24; 95% CI, .82–1.86), or past (RR = 1.14; 95% CI, 1.00–1.32) users. When current use was further broken down into current use that was new or not new, patients newly exposed appeared at greater risk (RR = 1.62; 95%
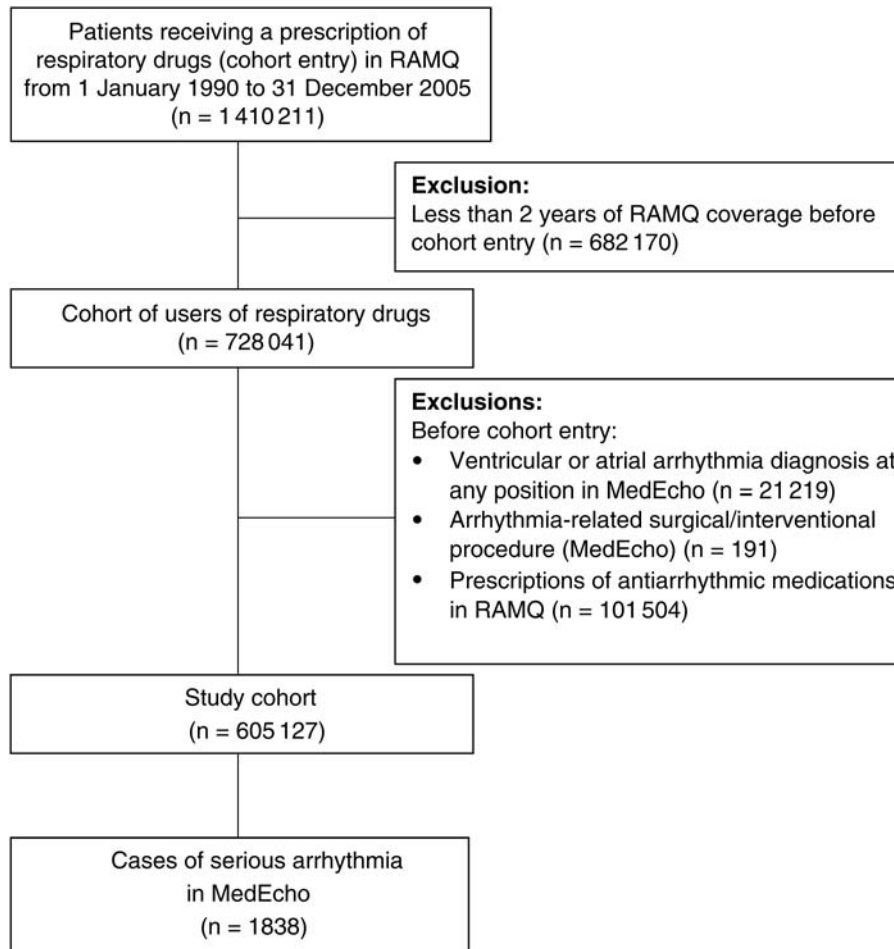
Patients receiving a prescription of
respiratory drugs (cohort entry) in RAMQ
from 1 January 1990 to 31 December 2005
(n = 1 410 211)

Exclusion:
Less than 2 years of RAMQ coverage before
cohort entry (n = 682 170)

Cohort of users of respiratory drugs
(n = 728 041)

Exclusions:
Before cohort entry:
- Ventricular or atrial arrhythmia diagnosis at
  any position in MedEcho (n = 21 219)
- Arrhythmia-related surgical/interventional
  procedure (MedEcho) (n = 191)
- Prescriptions of antiarrhythmic medications
  in RAMQ (n = 101 504)

Study cohort
(n = 605 127)

Cases of serious arrhythmia
in MedEcho
(n = 1838)

Figure 1. Study flow chart.

CI, .97–2.71) than those who had received these medications in both current and recent time periods; although again, these RRs were not statistically significantly different from no increase in risk. Among individual fluoroquinolones, gatifloxacin was the only molecule to be significantly associated with a higher risk of serious arrhythmia (RR = 3.97; 95% CI, 1.15–13.62).

To account for immeasurable time bias, we limited the analysis to those patients who were not hospitalized during the current time window. In this analysis, the overall risk of serious arrhythmia was significantly higher among current users (RR = 1.76; 95% CI, 1.19–2.59) as compared with recent and past users. Furthermore, new current users reported an even greater risk (RR = 2.23; 95% CI, 1.31–3.80) when compared with current use that was not new. After stratifying our analyses by individual fluoroquinolone molecules, gatifloxacin reported the highest point estimate (RR = 7.38; 95% CI, 2.30–23.70) while moxifloxacin and ciprofloxacin were also associated with a significantly increased risk of serious arrhythmia

(RR = 3.30; 95% CI, 1.47–7.37 and RR = 2.15; 95% CI, 1.34–3.46, respectively; Table 4). The additional cases of serious arrhythmia for the new current users were 5.8 per 10 000 person-years, while moxifloxacin, ciprofloxacin, and gatifloxacin reported an attributable risk of 10.8, 5.4, and 30 per 10 000 person-years, respectively.

When we varied the duration of the current time window from 14 to 21 and 28 days, the overall risk of serious arrhythmia among users of fluoroquinolones decreased (21 days: adjusted RR = 2.10; 95% CI, 1.53–2.88; for 28 days: adjusted RR = 1.94; 95% CI, 1.44–2.71).

Finally, sensitivity analyses using the more strict case definition still provided consistent results (adjusted RR for current users was 1.65; 95% CI, 1.03–2.63).

DISCUSSION

We found that after appropriate adjustment for immeasurable time bias, patients newly exposed to fluoroquinolones had a

Table 1. Comparison of Cases of Serious Arrhythmia and Matched Controls

	Cases (n = 1838)	Controls (n = 36 760)
Age, years, mean ± SD	75.3 ± 12.2	75.2 ± 12.0
Follow-up, years, mean ± SD	5.3 ± 4.0	5.3 ± 4.0
Sex, female, %	56.7	56.7
1 year before the index date		
No. of hospitalizations, mean ± SD	0.3 ± 0.4	0.2 ± 0.4
Heart failure, %	34.2	7.2
Stroke, %	4.3	2.8
Atrial fibrillation, %	26.3	4.4
Valvular disease, %	8.5	1.7
Coronary artery disease, %	47.6	16.7
Congenital structural cardiovascular abnormalities, %	1.1	0.2
Enlarged heart, %	4.4	0.5
Diabetes, %	20.7	11.4
Hypertension, %	36.8	28.7
Hyperlipidemia, %	9.3	5.1
Atherosclerosis, %	8.9	3.6
Renal failure (chronic disease and/or acute episodes), %	13.4	4.0
Anemia, %	14.4	7.1
Asthma, %	12.7	10.7
Thyroid diseases, %	15.9	12.9
Septicemia, %	1.4	0.4
Comedications		
Antihypertensive drugs, %	80.1	56.2
Cardiotonic drugs, %	30.6	8.3
Oral corticosteroids, %	17.7	12.2
Inhaled corticosteroids, %	36.5	33.4
Other respiratory medications, %	53.7	45.3
Lipid-lowering drugs, %	18.5	14.2
Thyroid medications, %	14.2	12.1
NSAIDs, %	56.6	47.3
30 days before the index date		
COPD exacerbation, %		
Severe (COPD hospitalizations)	7.3	1.5
Moderate[a]		
Macrolide and OCS (on the same date)	0.05	0.08
Nonmacrolide and OCS (on the same date)	1.0	0.6
Potentially inducing arrhythmia medications, %		
Antiarrhythmic drugs	5.5	0.8
Antidepressants	8.7	6.5
Antiemetic drugs	3.4	1.9
Antiprotozoal drugs	2.5	1.6
Other CNS medications	4.4	3.1

Table 1 continued.

	Cases (n = 1838)	Controls (n = 36 760)
Others[a]	0.9	1.0
Macrolide antibiotics (not on the same day of OCS), %	0.20	0.01
Nonmacrolide antibiotics[a] (not on the same day of OCS), %	0.4	0.3

Abbreviations: COPD, chronic obstructive pulmonary disease; CNS, central nervous system; NSAIDs, nonsteroidal anti-inflammatory drugs; OCS, oral corticosteroid; SD, standard deviation.

[a] Excluding fluoroquinolones as the exposure under study.

greater risk of developing serious arrhythmia compared with nonusers. This effect was mainly due to use of gatifloxacin, moxifloxacin, and ciprofloxacin. In contrast, levofloxacin did not seem to increase the risk of serious arrhythmia.

Current clinical information regarding fluoroquinolone-related arrhythmias is primarily based on a handful of randomized clinical trials (RCTs) [8, 25–28] and pharmacovigilance data [10, 29, 30]. The RCTs, which reported on prolongation of the QT interval as a proxy for arrhythmia, found that QT prolongation did not occur in the vast majority of subjects receiving levofloxacin or ciprofloxacin. Only moxifloxacin appeared to be associated with a potentially clinically significant prolongation of the QT interval [8, 25–27]. On the other hand, the most recent pharmacovigilance analyses [10, 29] raised concerns of an excess of torsades de pointes among moxifloxacin, [10, 29] gatifloxacin, [10] levofloxacin, [10, 29], and ciprofloxacin [29] users.

RCTs provide only limited information on the actual use of such medications, because they most often exclude subjects with significant comorbidities. Pharmacovigilance data, on the other hand, are limited by selective reporting. Hence, observational studies are needed to complement these findings [31].

To date, only one other observational study on the ventricular arrhythmia or cardiac arrest risk associated with fluoroquinolones has been conducted. Although an elevated risk was found, we believe that this study by Zambon and coworkers [11] has several limitations which we have tried to address. First, we adopted a shorter time window for current exposure, to be more consistent with the rapid effect of fluoroquinolones on cardiac rhythm. We were also able to examine the risk of arrhythmia for several of these antibiotics individually. We further controlled for COPD exacerbations, a potentially strong confounder of the association of fluoroquinolones with ventricular arrhythmia [12, 13].

Table 2. Distribution of Cases of Serious Arrhythmias by Type

	Overall (n = 1838)	With Surgical/Interventional Procedure[a] (n = 121)	With Pharmacotherapy[b] (n = 272)
Nonfatal cases, No. (%)	1209 (65.8)	117 (96.7)	270 (99.3)
Paroxysmal ventricular tachycardia	512 (27.9)	80 (66.1)	106 (39.0)
Cardiac arrest	160 (8.7)	8 (6.6)	47 (17.3)
Ventricular fibrillation and/or flutter	92 (5.0)	12 (9.9)	29 (10.7)
Unspecific arrhythmia	445 (24.2)	17 (14.0)	88 (32.4)
Fatal cases, No. (%)	629 (34.2)	2 (1.7)	2 (0.7)
Paroxysmal ventricular tachycardia	33 (1.8)	…	…
Cardiac arrest	395 (21.5)	1 (0.8)	…
Ventricular fibrillation and/or flutter	55 (3.0)	…	…
Unspecific arrhythmia	91 (5.0)	…	…
Sudden or unattended death[c]	55 (3.0)	1 (0.8)	2 (0.7)

[a] Procedure performed ± 3 months from the date of diagnosis.

[b] Pharmacotherapy administered ± 1 month from the date of diagnosis.

[c] Including sudden cardiac death.

Our results further demonstrate the importance of immeasurable time bias [24] in this specific context. This bias arises when a study includes exposure times during periods where exposure cannot be measured. Given that the RAMQ database (similar to many health administrative databases) does not include information on medications dispensed to hospital inpatients, patients would incorrectly appear as unexposed during hospitalizations, which could incidentally occur during the etiological time period under study.

With respect to the analyses performed to identify risks associated with the individual fluoroquinolone molecules, a greater effect size was expectedly higher for moxifloxacin. Interestingly, it was gatifloxacin, a drug that was withdrawn in 2006 because of serious hyperglycemic events [32], which we found to be associated with the highest risk of arrhythmia. These results on moxifloxacin and gatifloxacin are in keeping with previous preclinical findings [33] and pharmacovigilance reports [10, 29]. Furthermore, our findings confirm those of the European Medicines Agency report [34], which assessed a "low potential" for arrhythmia with levofloxacin. Finally, this study adds new information on the serious arrhythmia risk associated with the use of ciprofloxacin, whose

Table 3. Crude and Adjusted Rate Ratios of Serious Arrhythmia for Current, Recent, and Past Use of Fluoroquinolones

	Cases (n = 1838)	Controls (n = 36 670)	Crude RR	Adjusted RR (95% CI)[a]
Recency of use, No. (%)[b]				
Current, new	20 (1.1)	215 (0.6)	2.04	1.62 (.97–2.71)
Current, not new	18 (1.0)	229 (0.6)	1.75	1.12 (.66–1.89)
All current	38 (2.1)	444 (1.2)	1.89	1.34 (.92–1.93)
Moxifloxacin	7 (0.4)	67 (0.2)	2.40	1.82 (.78–4.22)
Levofloxacin	5 (0.3)	69 (0.2)	1.66	0.78 (.29–2.13)
Ciprofloxacin	20 (1.1)	245 (0.7)	1.78	1.32 (.80–2.18)
Gatifloxacin	4 (0.22)	17 (0.05)	5.69	3.97 (1.15–13.62)
Others	2 (0.1)	46 (0.1)	0.93	0.83 (.19–3.60)
Recent	30 (1.6)	398 (1.1)	1.68	1.24 (.82–1.86)
Past	332 (18.1)	4778 (13.0)	1.53	1.14 (1.00–1.32)
Unexposed	1438 (78.2)	31 140 (84.7)	Reference	Reference

Abbreviations: CI, confidence interval; RR, rate ratio.

[a] Adjusted for all covariates reported in Table 1.

[b] Current: within 14 days before the index date; recent: 15–30 days before the index date; past: 31–365 days before the index date.

Table 4. Crude and Adjusted Rate Ratios of Serious Arrhythmia for Current, Recent, and Past Use of Fluoroquinolones

	Cases (n = 1649)	Controls[a] (n = 36 051)	Crude RR	Adjusted RR (95% CI)[b]
Recency of use, No. (%)[c]				
Current, new	18 (1.1)	186 (0.5)	2.37	2.23 (1.31–3.80)
Current, not new	17 (1.0)	206 (0.6)	2.08	1.41 (.82–2.44)
All current	35 (2.1)	392 (1.1)	2.22	1.76 (1.19–2.59)
Moxifloxacin	7 (0.4)	56 (0.2)	3.30	3.30 (1.47–7.37)
Levofloxacin	3 (0.2)	61 (0.2)	1.30	1.29 (.40–4.17)
Ciprofloxacin	19 (1.2)	216 (0.6)	2.15	2.15 (1.34–3.46)
Gatifloxacin	4 (0.24)	15 (0.04)	7.40	7.38 (2.30–23.70)
Others	2 (0.1)	44 (0.1)	1.05	1.05 (.25–4.33)
Recent	26 (1.6)	372 (1.1)	1.70	1.26 (.80–1.93)
Past	295 (17.9)	4647 (12.9)	1.53	1.15 (1.00–1.34)
Unexposed	1293 (78.4)	30 640 (85.0)	Reference	Reference

Patients hospitalized during the current time window were excluded.

Abbreviations: CI, confidence interval; RR, rate ratio.

[a] Percentages are weighted for the number of controls being matched per case.

[b] Adjusted for all covariates reported in Table 1.

[c] Current: within 14 days before the index date; recent: 15–30 days before the index date; past: 31–365 days before the index date.

previous data were less consistent than for other fluoroquinolones [29, 30, 35].

There is a sound biologic rationale for the association between fluoroquinolone use and serious arrhythmias. Cardiac QT interval is regulated by an interplay of ionic currents through various ion channels, and its prolongation can degenerate into torsades de pointes, which might be followed by ventricular fibrillation, cardiac arrest, and sudden death. Fluoroquinolones are able to prolong the QT interval by interfering with the electrophysiological function of potassium channels that contribute to the regulation of action potentials in the cardiac cells. These changes can result in ventricular arrhythmias. Therefore, the risk of cardiovascular events with fluoroquinolones depends on the degree to which any single molecule inhibits the potassium channels [5, 33]. Chemically, although the substitution in position 5 (as per moxifloxacin and gatifloxacin) of the quinolone nucleus seems to affect cardiotoxicity, researchers have not yet identified a definite structural moiety that significantly increases the QT prolongation, so differentiating the risk profile [3]. Along these lines, our results indicated a greater risk of serious arrhythmia for ciprofloxacin, which does not carry any functional group in position 5. It is possible that genetic variants [36], acting as modifiers in the susceptibility to rhythm disorders, may be associated with the risk of individual molecules [37, 38]. This possibility requires further research.

This study has several limitations. First, the diagnoses of serious arrhythmia have not been formally validated. However, misclassification of the outcome should not differ according to use of fluoroquinolones, and therefore such misclassification can be expected to reduce the association, suggesting that risks may be underestimated in the present study. In addition, after operationally modifying the event definition as a sensitivity analysis so that a more strict definition of cases was used for the diagnoses of unspecific arrhythmias and sudden/unattended death, we observed similar results with regard to the risk ratio of serious arrhythmia, which suggests that misclassification was not a significant issue. Furthermore, the overall incidence rate of the outcome was in line with published estimates [39]. Second, it is possible that residual confounding may still play a role and partially bias our results. However, given the magnitude of the estimates of effect, it would be hard to imagine how greater variability due to residual confounders could explain the elevated risks associated with the use of moxifloxacin, gatifloxacin, and ciprofloxacin. Third, the small number of exposed subjects prevented the definition of an etiologically relevant exposure time window shorter than 2 weeks, which might also have resulted in an underestimation of the true effect. However, the progressive risk reduction that we observed after extending the exposure time window confirms a biologically plausible acute effect. Fourth, we were not able to estimate the difference in risk of serious arrhythmia between new and ongoing use for the individual fluoroquinolone molecules owing to a lack of statistical power. Finally, given our study cohort, the generalizability of our findings may be limited to populations treated at least once with a respiratory medication.

From a public health perspective, the use of these antibiotics, especially ciprofloxacin and levofloxacin, has been increasing in the last decades [2, 40]. As a consequence, it is possible that we may observe a corresponding increase in the number of serious and unintended adverse effects. Given that the individual fluoroquinolones share various indications, the relative risks of serious arrhythmia could inform the choice of molecules in high-risk patients. Given that serious arrhythmias are rare, future studies conducted in a larger population of patients with these outcomes would be beneficial in order to provide confirmation of our findings.

Notes

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