# Fluoroquinolones and the risk of serious arrhythmia: a population-based study

Francesco Lapi PharmD PhD[1,2,3], Machelle Wilchesky PhD[1,4], Abbas Kezouh PhD[1], Jacques I. Benisty MD MPH[1], Pierre Ernst MD MSc[1,5], Samy Suissa PhD[1,2]

[1]*Centre for Clinical Epidemiology, Lady Davis Research Institute, Jewish General Hospital, Montreal, Quebec (Canada);*
[2]*Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec (Canada);*
[3]*Department of Preclinical and Clinical Pharmacology, University of Florence, Florence (Italy);*
[4]*Donald Berman Maimonides Geriatric Centre, McGill University, Montreal, Quebec (Canada);*
[5]*Department of Medicine, McGill University, Montreal, Quebec (Canada)*

*Corresponding author*
Dr. Samy Suissa
Centre for Clinical Epidemiology
Jewish General Hospital
3755 Côte Sainte-Catherine
H3T 1E2, Montreal, Quebec, Canada
Tel: 514.340.7563
Fax: 514.340.7564
email: samy.suissa@mcgill.ca



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**Key points:**

Few observational studies have been conducted on fluoroquinolone-related cardiac rhythm disorders. Our results demonstrate that patients newly exposed to fluoroquinolones had a greater risk of developing serious arrhythmias. This effect was due predominantly to gatifloxacin, moxifloxacin and ciprofloxacin.


**Abstract**

**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 January 1, 1990 to December 31, 2005, identified using the healthcare databases from the province of Quebec (Canada), with follow-up until March 31, 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 to up to 20 controls. Conditional logistic regression was used to compute adjusted rate ratios (RR) of serious arrhythmia associated with fluoroquinolone use.

**Results.** Within the cohort of 605,127 subjects, 1,838 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% 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.

**Background**

Fluoroquinolones are antimicrobial drugs frequently used in the treatment of bacterial infections in both primary and secondary care. [1, 2] From a clinical viewpoint, fluoroquinolones offer several advantages due to 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 whenever 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 (i.e., moxifloxacin) while certain antibiotics in this class have been withdrawn from the European and US markets entirely (i.e., 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 more than 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 fluroquinolone 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 January 1, 1997, the RAMQ prescription drug insurance plan covered residents who were either 65 years and older, 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. The protocol number is: 11-039.

### *Cohort definition*

We used a cohort of patients (n=1,410,211) treated for respiratory conditions from January 1, 1997 to December 31, 2005, identified using the RAMQ database, with follow-up until March 31, 2007. Respiratory medications comprised bronchodilators, nasal or orally-inhaled corticosteroids, and anti-asthma medications (cromoglycate, nedocromil, montelukast, zafirkulast, and ketotifen).

Subjects with fewer than two 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 (t0) 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 (i.e., ventricular or atrial arrhythmia at any diagnosis position, primary or otherwise) or medical services (i.e., 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, death (if not registered as sudden or unattended death in MedEcho) or until March 31, 2004 (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 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 (i.e. implantation, replacement or removal of cardioverter-defibrillator; ventricular tachycardia ablation; electrophysiological studies) as well as pharmacological treatments (i.e. 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 months 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 three 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 31-365 day time period before the index date were considered as 'past' prescriptions. Finally, current use was further classified as being use which was either "new" or "not new" depending on whether or not they 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, ACE Inhibitors, angiotensin receptors blockers), cardiotonics, thyroid and lipids lowering medications, non-steroidal anti-inflammatory drugs (NSAIDs), and inhaled corticosteroids was also adjusted for within the same time-window.

Given the fact that COPD exacerbations are both an independent risk factor for serious arrhythmia [12, 13] and as well potentially associated with our exposure, 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 non-macrolide; 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 which can potentially induce arrhythmia (i.e. antiarrhythmic drugs (if not used to define cases), macrolides, pirimetamine, sulfamethoxazole/trimethoprim (if not used to define

'moderate' exacerbation), antiviral and antifungal medications, antidepressants, other central nervous systems (CNS) drugs, antiemetic drugs, and antimigraine medications) [21, 22] were included and adjusted for in our multivariate models.

***Nested case-control analysis***

Up to 20 controls 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 on 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 was 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 intervals (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 arrhythmia" or "sudden/unattended death" were restricted to only those which were preceded or followed by cardiac surgical/interventional procedures or pharmacological treatments. Statistical analyses were conducted using SAS version 9.2 TS2M3 (SAS Institute Inc, Cary, North Carolina).

**Results**

A total of 605,127 patients met the study inclusion criteria. During follow-up, 1,838 cases of serious arrhythmia were identified, giving an incidence rate equal to 4.7 per 10,000 person-years at risk (**Figure 1**).

**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, cardiotonics, 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 non-fatal. 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: 0.92-1.93), recent (RR=1.24; 95% CI: 0.82-1.86), or past (RR=1.14; 95% CI: 1.00-1.32) users. When current use was further broken down into current use which was "new" and "not new", patients newly exposed appeared at greater risk (RR=1.62; 95% CI: 0.97-2.71) 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 which 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 (i.e., 21 days: adjusted RR=2.10; 95% CI: 1.53-2.88; for 28 days: adjusted RR=1.9[illegible] 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% [illegible] 03-2[illegible]3).

**Discussion**

We found that after appropriate adjustment for immeasurable time-bias, patients newly exposed to fluoroquinolones had a greater risk of developing serious arrhythmia when compared with non-users. 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 "real world use" of such medications, because they most often exclude subjects with significant co-morbidities. Pharmacovigilance data, on the other hand, is 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 pharmacological effects 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]

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 (similarly 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 due to 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 pre-clinical findings [33] and pharmacovigilance reports. [10, 29] Furthermore, our findings confirm the EMA 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 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] and this would require further research.

This study has several limitations. Firstly, 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 "unspecified arrhythmias" and "sudden/unattended death", we observed similar results with regard to the RR of serious arrhythmia, which suggests that misclassification was not a significant issue. Furthermore the overall incidence rate of the outcome which was in line with published estimates. [39] Secondly, 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. Thirdly, 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. Fourthly, we were not able to estimate the difference in risk of serious arrhythmia between new and ongoing use for the individual fluoroquinolone molecules due 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.

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**Table 1.** Comparison of cases of serious arrhythmia and their matched controls.

| | **Cases (n=1,838)** | **Controls (n=36,760)** |
|---|---|---|
| Age in years (mean±SD) | 75.3±12.2 | 7[illegible]±12.0 |
| Follow-up in years (mean±SD) | [illegible]3±4.[illegible] | 5.3±4.0 |
| Gender, female, % | 56.[illegible] | 56.7 |
| ***1 year before the index date*** | | |
| Number 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 |
| Anaemia, % | `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 |
| | **Cases (n=1838)** | **Controls (n=36,760)** |
| Cardiotonic drugs, % | 30.6 | 8.3 |
| Oral corticosteroids, % | 17.7 | 12.2 |
| Inhaled corticosteroids, % | 36.5 | 33.4 |
| Other respiratory medications, % | 53.7 | 1.3 |
| Lipid lowering drugs, % | 18.5 | 14.2 |
| Thyroid medications, % | 14.2 | 12.1 |
| NSAIDs, % | 5.6 | 47.3 |
| ***30 days before the index date*** | | |
| COPD exacerbation, % | | |
| Severe (COPD hospitalizations) | 7.3 | 1.5 |
| Moderate* | | |
| Macrolide and OCS (on the same date) | 0.05 | 0.08 |
| Non-macrolide 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 |
| Others* | 0.9 | 1.0 |
| Macrolide antibiotics (not on the same day of OCS) , % | 0.20 | 0.01 |
| Non-macrolide antibiotics* (not on the same day of OCS), % | 0.4 | 0.3 |

SD, standard deviation; NSAIDs, non steroidal anti-inflammatory drugs; COPD, chronic obstructive pulmonary disease; CNS, central nervous system; OCS, oral corticosteroids; *excluding fluoroquinolones as the exposure under study

**Table 2.** Distribution of cases of serious arrhythmias by type.

| | Overall N=1,838 | With surgical/interventional procedure** N=121 | With pharmacotherapy*** N=272 |
|---|---|---|---|
| Non-fatal cases | 1,209 (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 | 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* | 55 (3.0) | 1 (0.8) | 2 (0.7) |

*including sudden cardiac death **±3 months within the hospitalization ***±1 months within the hospitalization

**Table 3.** Crude and adjusted Rate Ratios (RRs) of serious arrhythmia for the current (within 14 days before the index date), recent (from 15 to 30 days before the index date) and past (from 31-365 days before the index date) use of fluoroquinolones.

| | **Cases (n=1,838)** | **Controls (n=36,670)** | **Crude** | **Adjusted*** |
|---|---|---|---|---|
| Recency of use, n (%) | | | | |
| Current, New | 20 (1.1) | 215 (0.6) | 2.04 | 1.62 (0.97-2.71) |
| Current, not New | 18 (1.0) | 229 (0.6) | 1.75 | 1.12 (0.66-1.89) |
| All current | 38 (2.1) | 444 (1.2) | 1.89 | 1.34 (0.92-1.93) |
| Moxifloxacin | 7 (0.4) | 67 (0.2) | 2.40 | 1.82 (0.78-4.22) |
| Levofloxacin | 5 (0.3) | 69 (0.2) | 1.66 | 0.78 (0.29-2.13) |
| Ciprofloxacin | 20 (1.1) | 245 (0.7) | 1.78 | 1.32 (0.80-2.18) |
| 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 (0.19-3.60) |
| Recent | 30 (1.6) | 398 (1.1) | 1.68 | 1.24 (0.82-1.86) |
| Past | 332 (18.1) | 4,778 (13.0) | 1.53 | 1.14 (1.00-1.32) |
| Unexposed | 1,438 (78.2) | 31,140 (84.7) | Reference | Reference |

*adjusted for all covariates reported in Table 1

**Table 4.** Crude and adjusted Rate Ratios (RRs) of serious arrhythmia for the current (within 14 days before the index date), recent (from 15 to 30 days before the index date) and past (from 31-365 days before the index date) use of fluoroquinolones, when patients hospitalized during the current time-window were excluded.

| | **Cases (n=1,649)** | **Controls* (n=36,051)** | **Crude** | **Adjusted**** |
|---|---|---|---|---|
| Recency of use, n (%) | | | | |
| Current, New | 18 (1.1) | 186 (0.5) | 2.37 | 2.23 (1.31 - 3.80) |
| Current, not New | 17 (1.0) | 306 (0.8) | 2.08 | 1.41 (0.82 – 2.44) |
| All current | 35 (2.1) | 492 (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 (0.40 - 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 (0.25 - 4.33) |
| Recent | 26 (1.6) | 372 (1.1) | 1.70 | 1.26 (0.80 - 1.93) |
| Past | 295 (17.9) | 4,647 (12.9) | 1.53 | 1.15 (1.00 - 1.34) |
| Unexposed | 1,293 (78.4) | 30,640 (85.0) | Reference | Reference |

* % are weighted for the number of controls being matched per case
**adjusted for all covariates reported in Table 1

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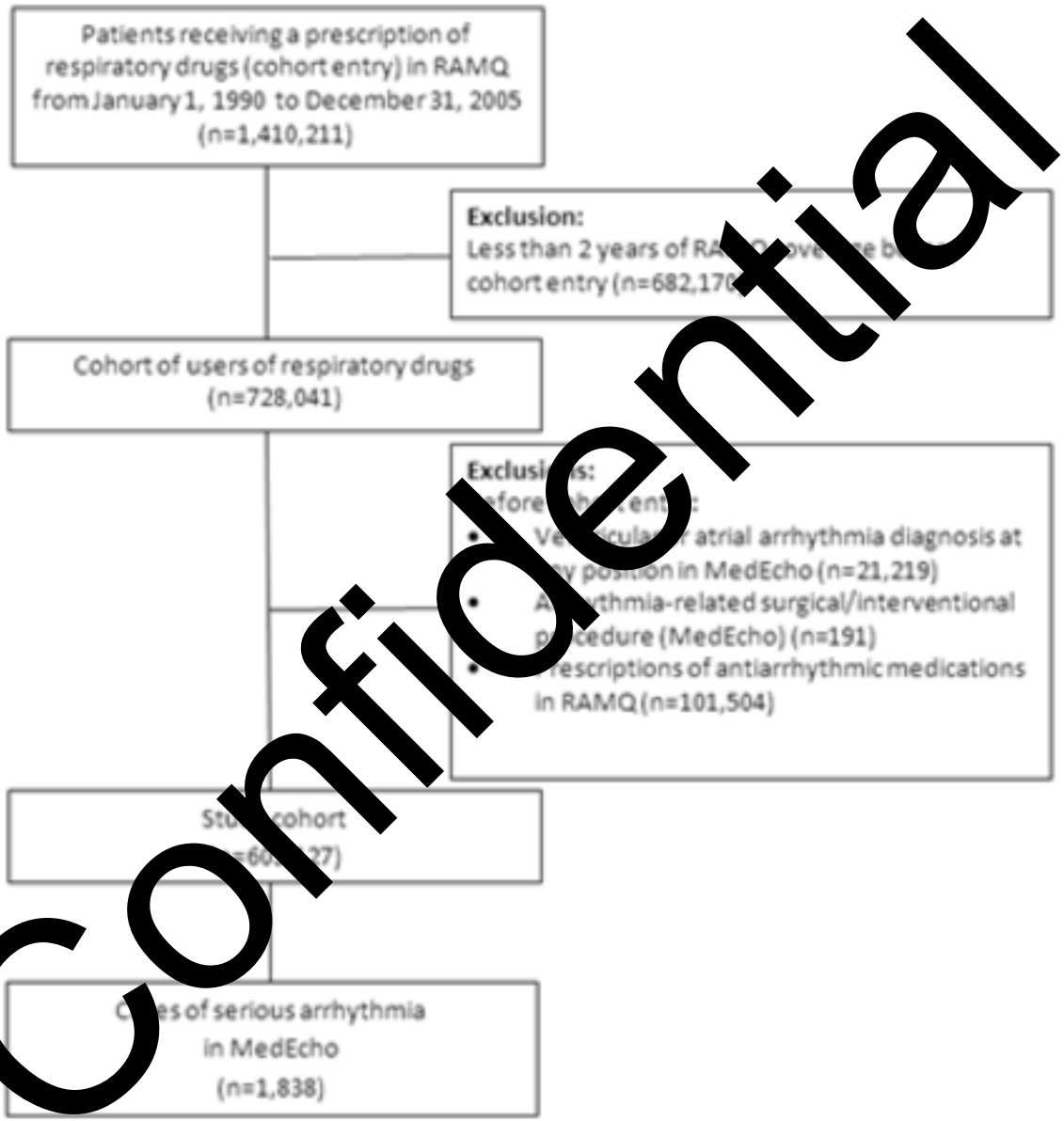




**Figure 1.** Study flow chart.