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Oral Fluoroquinolones and Risk of Mitral and Aortic Regurgitation

Mahyar Etminan, PharmD, MSc,[a,b] Mohit Sodhi, BSc, MSc,[a] Saeed Ganjizadeh-Zavareh, MD, MSc,[c] Bruce Carleton, BPharm, PharmD,[a,d] Abbas Kezouh, PhD,[e] James M. Brophy, MD, PhD[f]

ABSTRACT

BACKGROUND Recent studies have linked fluoroquinolones (FQs) to cardiac adverse events, including aortic dissection and aneurysm. To date, whether FQs can increase the risk of aortic or mitral regurgitation has not been studied.

OBJECTIVES This disproportionality analysis and case-control study examined whether FQs increase the risk of aortic and mitral regurgitation.

METHODS Data from the U.S. Food and Drug Administration's adverse reporting system database was used to undertake a disproportionality analysis, and a random sample of 9,053,240 patients from the U.S. PharMetrics Plus database (IQVIA) was used for the matched nested case-control study. Current FQ exposure implied an active prescription at the index date or 30 days prior to the event date. Recent FQ exposure was defined as FQ use within days 31 to 60 and past within days 61 to 365 prior to the event date. Rate ratios (RRs) were compared to users of amoxicillin and azithromycin. Conditional logistic regression was used to compute RRs adjusting for confounders.

RESULTS The reported odds ratio for the disproportionality analysis was 1.45 (95% confidence interval [CI]: 1.20 to 1.77). A total of 12,505 cases and 125,020 control subjects were identified in the case-control study. The adjusted RRs for current users of FQ compared with amoxicillin and azithromycin users were 2.40 (95% CI: 1.82 to 3.16) and 1.75 (95% CI: 1.34 to 2.29), respectively. The adjusted RRs for recent and past FQ users when compared with amoxicillin were 1.47 (95% CI: 1.03 to 2.09) and 1.06 (95% CI: 0.91 to 1.21), respectively.

CONCLUSIONS These results show that the risk of aortic and mitral regurgitation is highest with current use followed by recent use. No risk was observed with past use of FQs. Future studies are necessary to confirm or refute these associations. (J Am Coll Cardiol 2019;74:1444–50) © 2019 by the American College of Cardiology Foundation.

Fluoroquinolones (FQs) are one of the most prescribed classes of antibiotics and are favored over other agents for their broad spectrum of antibacterial activity and high oral absorption. In recent years, a number of adverse events have been linked to these drugs. Some of these adverse events include retinal detachment, which has produced mixed results (1-3), but others, including aortic aneurysm and dissection (4-6), peripheral neuropathy (7,8), and cardiac arrhythmias (9-11), are more consistent with a causal link with FQs and are now included in a warning from the U.S. Food and Drug Administration (FDA). The putative mechanism behind these adverse events is FQs' in vitro ability to damage connective tissue and collagen throughout the body (4,12-14). A recent case report has described a patient who developed aortic valve prolapse shortly after starting ciprofloxacin (15) for 2 days without any

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From the [a]Department of Ophthalmology and Visual Sciences, University of British Columbia, Vancouver, British Columbia, Canada; [b]Therapeutic Evaluation Unit, British Columbia Provincial Health Services Authority, Vancouver, British Columbia, Canada; [c]Department of Medicine, Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada; [d]Division of Translational Therapeutics, Department of Pediatrics, and Pharmaceutical Outcomes Programme, British Columbia Children's Hospital Research Institute, University of British Columbia, Vancouver, British Columbia, Canada; [e]Department of Epidemiology and Biostatistics, McGill University, Montreal, Quebec, Canada; and the [f]Departments of Medicine, Epidemiology, and Biostatistics, McGill University, Montreal, Quebec, Canada. This study was funded by the Therapeutic Evaluation Unit of the British Columbia Provincial Health Services Authority. The funding source had no role in the design and conduct of the study. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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other reasonable explanation for this acute adverse event.

Like the aorta, the healthy human aortic and mitral valves are also made up of collagen and connective tissue delicately woven in its extracellular matrix that is integral to its function (16). When the valve connective tissue is compromised, it can lead to mitral valve prolapse and mitral regurgitation (16). For example, in patients with Marfan syndrome, systemic damage of the connective tissue leads to higher rates of mitral valve prolapse (17), which can progress to severe mitral regurgitation via chordal rupture leading to heart failure and, in some cases, sudden death (18).

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We hypothesized that FQs could damage the connective tissue of the aortic and mitral valve apparatus, thus increasing the risk of valvular regurgitation. Given their widespread use, establishing the magnitude of any potential FQ risk of valvular regurgitation is a pertinent question for both clinicians and their patients. To address this question, we first undertook a disproportionality analysis using the U.S. Food and Drug Administration Adverse Events Reporting Systems (FAERS) database to identify cases of FQ-related valvular regurgitation reported to the FDA and compared these cases to valvular regurgitation cases reported for other non-FQ drugs. We also performed a case-control study to further quantify the valvular regurgitation secondary to FQs.

METHODS

DATA SOURCES. For the disproportionality analysis, we accessed the FDA's FAERS database, which captures all prescription drug related adverse events reported by health professionals and patients (19). FAERS was accessed through OpenVigil (2.1) (20), a freely available web-based pharmacovigilance tool that identified all FDA-reported adverse events from 2004 to 2018 (19,20).

For the case-control study, we used the U.S. PharMetrics Plus database (IQVIA), a large health claims database that captures demographics, physician visits, hospitalizations, and prescription drugs for >150 million enrollees. All medical diagnoses are captured through International Classification of Diseases, Ninth and Tenth Editions (ICD-9 and -10). This database also captures all outpatient prescription drugs. This includes drug identification, dose prescribed, and treatment duration. This database provides adequate representation of all geographic areas of the United States (21). The study design was a case-control nested within a random sample of 9,053,240 subjects who we had access to from 2006 to 2016. We followed the reporting of studies conducted using the RECORD-PE (REporting of studies Conducted using Observational Routinely collected health Data statement for PharmacoEpidemiology) (22) reporting guidelines throughout the paper. Ethics approval was obtained from the University of British Columbia research ethics board.

STUDY DESIGN AND ANALYSIS.

Disproportionality analysis. This is a drug adverse event "signal"-driven analysis that compares, in our case, the number of valvular regurgitation reports related to FQ with the number for all other drugs (23) in FAERS. We searched OpenVigil (2.1) for the following terms: *aortic valve replacement, aortic valve repair, aortic valve incompetence, aortic valve disease, mitral valve replacement, mitral valve repair, mitral valve disease, mitral valve incompetence,* and *mitral valve prolapse.* Then, we identified the number of these events reported from 2004 to 2018 with the following oral fluoroquinolones: *ciprofloxacin, levofloxacin, moxifloxacin, gemifloxacin, gatifloxacin, lomefloxacin, and norfloxacin.* Although gatifloxacin has been taken off market, it was still included in the list to examine a class effect. Reported odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were computed comparing the number of valvular regurgitation secondary to FQ use to the same events with all other drugs. A reporting OR >1.0 signaled increased risk.

Case-control study. We identified incident cases of valvular regurgitation identified as those with first physician visit codes for the following conditions: *mitral valve disease or insufficiency, aortic valve disease or insufficiency, aortic valve or mitral valve disorders, and aortic valve or mitral valve regurgitation* (ICD-9 394.9, 396.3, 396.8, 396.9, 424.0, and 424.1; ICD-10, I34, and I35) (**Central Illustration**). Conditions for which FQs can be prescribed and that can independently increase the risk of valvular regurgitation, including rheumatic fever, strep throat, and endocarditis, were excluded prior to the identification of cases and control subjects to prevent protopathic bias (**Central Illustration**). After these exclusions, there were 8,272,981 subjects in our base cohort (**Figure 1**). For each case, the pool of potential control subjects without any history of valvular regurgitation was identified, and 10 control subjects were matched to a case by follow-up time, calendar time (to control for prescribing trends that may lead to differential

ABBREVIATIONS AND ACRONYMS

CI = confidence interval

FAERS = U.S. Food and Drug Administration Adverse Events Reporting System

FDA = U.S. Food and Drug Administration

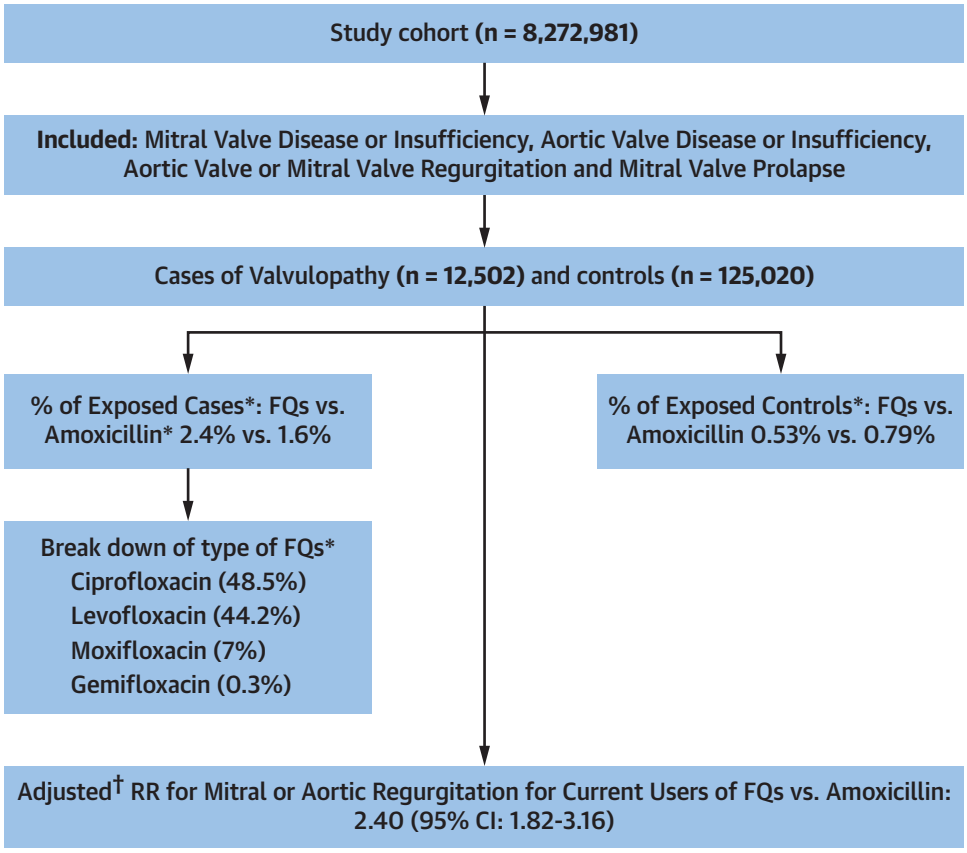
FQ = fluoroquinolones

ICD = International Classification of Diseases

OR = odds ratio

RR = rate ratio

CENTRAL ILLUSTRATION **Oral Fluoroquinolones and Mitral and Aortic Regurgitation Risk: Inclusion and Exclusion Criteria**



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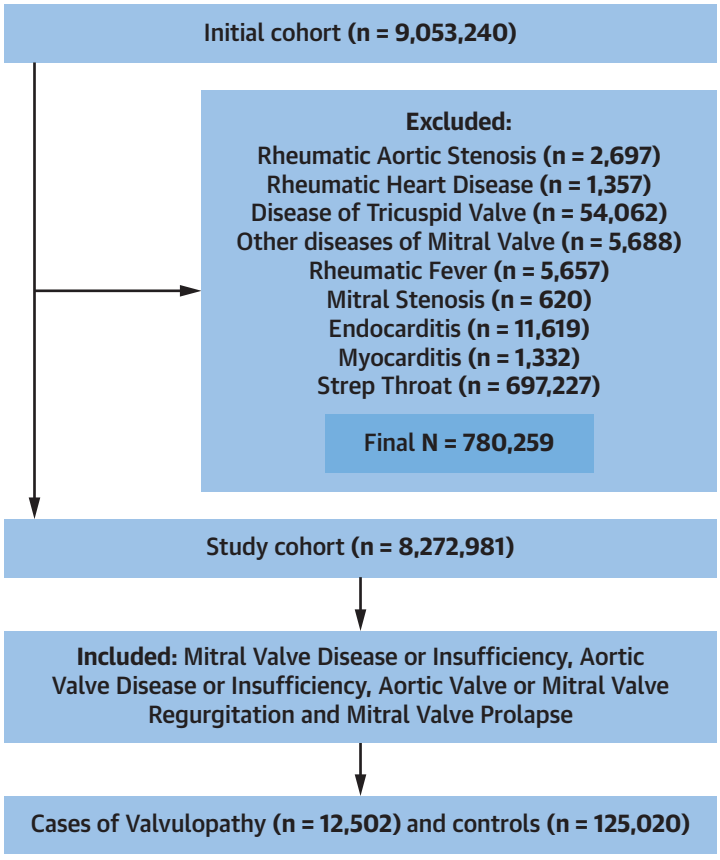
The initial cohort included >9 million patients from the PharMetrics Plus Database. We then proceeded to exclude conditions that might have been potential confounders (780,000 patients). The final cohort included 12,502 cases of valvular regurgitation and >125,020 control subjects. We then report the percentage exposed to fluoroquinolones (FQs) and amoxicillin among the cases and control subjects and present the breakdown of the type of FQs among the cases. The final adjusted rate ratio (RR) for mitral or aortic regurgitation for current FQ users versus amoxicillin users was 2.40 (95% confidence interval [CI]: 1.82 to 3.16). *For the comparison of current FQ users versus current amoxicillin users. †Adjusted for variables in Table 2.

prescribing of FQs among cases and control subjects), age, and index date (date of registration of the case in the database). Control subjects were allowed to be future cases and could have been selected more than once. This incident density-based sampling approach for control selection generates ORs that are close approximations of the rate ratios (RRs) (24). Separate analyses were done looking at all valvular regurgitation events as well as a stratified analysis looking at the type of regurgitation (aortic vs. mitral).

We identified all oral fluoroquinolone prescriptions (ciprofloxacin, gemifloxacin, levofloxacin, moxifloxacin, ofloxacin, and norfloxacin) in the year prior to the index date. We created 3 distinct risk periods. Current FQ exposure implied an active prescription at the index date or in the 30 days preceding that date. Recent FQ exposure was defined as FQ use within days 31 to 60 and past within days 61 to 365. These risk periods were created to reflect potential etiological windows as the damage to the connective tissue of the heart valve by FQs has been shown to occur within a few days (15). To control for confounding by infection, we also identified users of 2 antibiotics with distinct spectra of coverage.

FIGURE 1 Description of Included and Excluded Conditions in the Primary Cohort



Amoxicillin was used as it is a commonly prescribed, narrow spectrum antibiotic that has not been associated with valvular regurgitation. We further controlled for confounding by infection by also comparing the risk of valvular regurgitation with users of azithromycin, a macrolide with a broad spectrum of activity used for more severe community-acquired bacterial infections. A conditional logistic regression model was used to compute crude and adjusted RRs. RRs were adjusted for the following variables: sex, age, atrial fibrillation, diabetes, hypertension, coronary artery disease, stroke, chronic heart failure, chronic renal failure, and drugs that might increase the risk of valvular regurgitation including statins, cabergoline, pergolide, and phentermine. Finally, we estimated the magnitude of an unmeasured confounder that is needed to reverse a potential harmful association between FQ use and valvular regurgitation by using the metric E value (25) where $E = RR + \sqrt{(RR[RR-1])}$ and RR is the rate ratio for users of FQ compared with amoxicillin or azithromycin users.

RESULTS

In the disproportionality analysis, there were a total of 102 reported events of FQ valvular regurgitation and 6,099 reports with other drugs from 2004 to 2018

TABLE 1 Results of the Disproportionality Analysis

Drug	Number of Cases	ROR	95% CI
Ciprofloxacin	44	1.67	1.24–2.25
Gatifloxacin	6	2.87	1.29–6.39
Levofloxacin	52	1.80	1.37–2.37
Moxifloxacin	11	0.73	0.41–1.32
Lomefloxacin	0	N/A	N/A
Gemifloxacin	0	N/A	N/A
Norfloxacin	0	N/A	N/A
Total	113		
*Combined	102	1.45	1.20–1.77

*When searching all exposures and all outcomes, it is possible that a patient was prescribed multiple fluoroquinolones, therefore the combined number may be smaller.

CI = confidence interval; N/A = not applicable; ROR = reporting odds ratio.

TABLE 2 Characteristics of Cases and Control Subjects

	Cases (n = 12,502)	Control Subjects (n = 125,020)
Follow-up, yrs	3.4 ± 2.5	3.4 ± 2.5
Age, yrs	58.1 ± 12.7	58.1 ± 12.7
Male	7,037 (56.3)	70,370 (56.3)
Atrial fibrillation	2,159 (17.3)	3,298 (2.6)
Diabetes mellitus	4,148 (33.2)	18,519 (14.8)
Hypertension	9,014 (72.1)	49,084 (39.3)
Coronary artery disease	3,929 (31.4)	10,368 (8.3)
Stroke	1,455 (11.6)	1,277 (1.0)
Chronic heart failure	2,728 (21.8)	2,903 (2.3)
Chronic renal failure	1,060 (8.5)	1,739 (1.4)
Use of the following drugs		
Statins	3,397 (27.2)	25,512 (20.4)
Cabergoline	5 (0.04)	21 (0.02)
Pergolide	0 (0.00)	3 (0.00)
Phentermine	14 (0.11)	164 (0.13)

Values are mean ± SD or n (%).

reported to FAERS with a reporting OR of 1.45 (95% CI: 1.20 to 1.77) (Table 1). Additional data regarding individual FQs can be found in Table 1.

In the case-control study, there were 12,502 cases and 125,020 control subjects (Table 2, Figure 1). The average age among the cases and control subjects was 58.1 ± 12.7 (Table 2). Cases had a higher prevalence of atrial fibrillation and coronary artery disease (Table 2). The adjusted RR for current users of FQ compared with amoxicillin users was 2.40 (95% CI: 1.82 to 3.16) (Table 3). For the current user analysis, the breakdown of the specific FQ agents among the exposed cases was ciprofloxacin (48.5%), levofloxacin (44.2%), moxifloxacin (7%), and gemifloxacin (0.3%). The adjusted RR for current users of FQs when compared with current users of azithromycin was 1.75 (95% CI: 1.34 to 2.29) (Table 3). The adjusted RR compared with recent users of amoxicillin was 1.47 (95% CI: 1.03 to 2.09) (Table 3). The adjusted RR when compared with recent users of azithromycin was 1.37 (95% CI: 0.95 to 1.98) (Table 3). The risk for past users with amoxicillin and azithromycin as reference groups was very close to 1.00 (Table 3).

When the cases of valvular regurgitation were stratified by valvular type, there were 9,774 cases of mitral regurgitation (Table 4) and 2,309 of aortic regurgitation (Table 5). For current use, the adjusted RR for mitral regurgitation compared with amoxicillin and azithromycin was 2.25 (95% CI: 1.77 to 2.87) and 1.75 (95% CI: 1.37 to 2.22), respectively (Table 4). For current use, the adjusted RR for aortic regurgitation compared with amoxicillin and azithromycin was 2.24 (95% CI: 1.30 to 3.87) and 1.90 (95% CI: 1.06 to 3.42) respectively (Tables 5). The RR for past users of FQs for all three analyses (overall and stratified) was close to one (Tables 3 to 5).

Based on the E-value calculation, an unmeasured confounder would need to have an association magnitude (with both regurgitation and FQ) of 4.2 (95% CI: 3.0 to 5.8) to eliminate the observed risk seen with current users of FQs.

TABLE 3 Adjusted RRs for Combined Mitral and Aortic Regurgitation Comparing Different Risk Periods for Oral FQ Users Compared With Amoxicillin and Azithromycin Users

	Cases	Control Subjects	Crude RR	Adjusted RR*	Adjusted 95% CI
Drug group	12,502	125,020			
Current amox	153 (1.57)	771 (0.79)	1.00	1.00	Reference
Current FQ	303 (2.42)	662 (0.53)	2.35	2.40	1.82-3.16
Current azithro	174 (1.78)	694 (0.71)	1.00	1.00	Reference
Current FQ	303 (2.42)	662 (0.53)	1.84	1.75	1.34-2.29
Recent amox	103 (1.05)	731 (0.75)	1.00	1.00	Reference
Recent FQ	121 (0.97)	599 (0.48)	1.49	1.47	1.03-2.09
Recent azithro	89 (0.91)	650 (0.67)	1.00	1.00	Reference
Recent FQ	121 (0.97)	599 (0.48)	1.53	1.37	0.95-1.98
Past amox	612 (6.26)	5,220 (5.34)	1.00	1.00	Reference
Past FQ	633 (5.06)	4,363 (3.49)	1.28	1.06	0.91-1.21
Past azithro	524 (5.35)	4,897 (5.01)	1.00	1.00	Reference
Past FQ	633 (5.06)	4,363 (3.49)	1.40	1.18	1.01-1.38

Values are n or n (%) unless otherwise indicated. *Adjusted for variables in Table 2.
amox = amoxicillin; azithro = azithromycin; CI = confidence interval; FQ = fluoroquinolone; RR = rate ratio.

DISCUSSION

The results of this study showed an association between the primary outcome of combined aortic and mitral regurgitation and exposure to oral FQs (Central Illustration). The association between the risk of valvular regurgitation and current users of current FQs was consistently observed in stratified analyses of isolated aortic or mitral regurgitation. A similar prolonged short-term risk was also demonstrated in studies that found a risk of aortic dissection with FQs (5) and may signal a potential delayed effect of regurgitation secondary to FQs in some patients. No association was observed among past users (>60 days since exposure) with respect to mitral or aortic regurgitation.

We found similar results with the disproportionality analysis using the FAERS database. In recent years, drug regulatory agencies including the FDA have issued a number of safety alerts with oral FQs mainly regarding musculoskeletal and neurological adverse events. Recently, the European Medicines Agency issued warnings restricting use of oral FQs to

situations where no alternative antibiotic can be used (26). They also recommend avoiding use of these drugs in patients with a previous history of an FQ-related adverse event.

Mechanistically, FQs are known to damage connective tissue by inducing oxidative stress within the tendon cells (4,12), reducing collagen production (4,13), and stimulating the activity of metalloproteinases (4,14), all of which may lead to reduction in the integrity of the extracellular matrix (4). FQs can damage type I and III collagen (15) that is present in the Achilles tendons (6,27), aorta (6), and aortic valves (28). The putative chain of pathophysiological events would include FQs that, through their high bioavailability and chelating properties, bind to the collagen leading to eventual degradation of the collagen matrix of the aortic or possibly the mitral valve. This can lead to subsequent aortic or mitral valve regurgitation. This hypothesis has been observed in at least 1 case report where a patient who took ciprofloxacin (750 mg twice daily) for 2 days developed symptoms of decompensation as a result of aortic valve prolapse that, following a cardiac work-up, could only be linked to ciprofloxacin use (15). The acute onset of collagen damage with FQs has also been shown to lead to rupture of large tendons within hours (27) and aortic dissection within days (5).

STUDY STRENGTHS AND LIMITATIONS. We were able to identify cases of regurgitation using the FAERS database and generate a signal that was later validated in our case-control study. The large sample size in our cohort study allowed us to exclude confounding conditions and control for confounding by infection by comparing the risk to 2 distinct antibiotics. A number of limitations might also be present. For example, a disproportionality analysis often cannot show cause and effect relation, mainly due to its cross-sectional nature and possible reporting bias. However, we merely used this approach to identify possible case reports and examine a potential signal that could later be tested using a case-control study. Our large sample size allowed us to quantify these relatively rare adverse events. Moreover, we were able to exclude confounding conditions and use 2 different antibiotics to control for confounding by infection. Although the adjusted crude RRs were similar, suggesting that results were robust to measured confounders, we did not have information on unmeasured confounders; however, based on the E value calculation, any unmeasured confounder needs an RR of 3 or greater (with both FQ use and valvular regurgitation) to eliminate the observed harmful association. Although there is no specific validation of valvular regurgitation codes in the PharMetrics database, any potential misclassification would usually be nondifferential, which would have resulted in a bias toward the null. Finally, our study population can only be generalized to those who can afford private health insurance, although we do not think the risk of FQs and valvular regurgitation would necessarily be different in other populations.

TABLE 4 Adjusted RRs for Mitral Regurgitation Comparing Different Risk Periods for Oral FQ Users Compared With Amoxicillin and Azithromycin Users

	Cases	Control Subjects	Crude RR	Adjusted RR*	Adjusted 95% CI
Drug group	9,774	97,740			
Current amox	198 (1.58)	974 (0.78)	1.00	1.00	Reference
Current FQ	240 (2.46)	518 (0.53)	2.26	2.25	1.77–2.87
Current azithro	211 (1.69)	855 (0.68)	1.00	1.00	Reference
Current FQ	240 (2.46)	518 (0.53)	1.85	1.75	1.37–2.22
Recent amox	132 (1.06)	927 (0.74)	1.00	1.00	Reference
Recent FQ	97 (0.99)	573 (0.48)	1.44	1.45	1.06–1.99
Recent azithro	113 (0.90)	834 (0.67)	1.00	1.00	Reference
Recent FQ	97 (0.99)	573 (0.48)	1.51	1.39	1.00–1.93
Past amox	772 (6.18)	6,609 (5.29)	1.00	1.00	Reference
Past FQ	496 (5.07)	3,335 (3.43)	1.25	1.03	0.91–1.18
Past azithro	669 (5.35)	6,102 (4.88)	1.00	1.00	Reference
Past FQ	496 (5.07)	3,335 (3.43)	1.34	1.14	0.99–1.30

Values are n or n (%) unless otherwise indicated. *Adjusted for variables in Table 2.
Abbreviations as in Table 3.

CONCLUSIONS

The results of this study found an association between oral fluoroquinolones and an increased risk of

TABLE 5 Adjusted RRs for Aortic Regurgitation Comparing Different Risk Periods for Oral FQ Users Compared With Amoxicillin and Azithromycin Users

	Cases	Controls	Crude RR	Adjusted RR*	Adjusted 95% CI
Drug group	2,309	23,090			
Current amox	38 (1.65)	177 (0.77)	1.00	1.00	Reference
Current FQ	58 (2.51)	115 (0.50)	2.33	2.24	1.30–3.87
Current azithro	31 (1.34)	128 (0.55)	1.00	1.00	Reference
Current FQ	58 (2.51)	115 (0.50)	2.07	1.90	1.06–3.42
Recent amox	26 (1.13)	166 (0.72)	1.00	1.00	Reference
Recent FQ	22 (0.95)	108 (0.47)	1.32	1.46	0.72–2.97
Recent azithro	20 (0.87)	156 (0.68)	1.00	1.00	Reference
Recent FQ	22 (0.95)	108 (0.47)	1.61	1.59	0.74–3.44
Past amox	131 (5.67)	1,182 (5.12)	1.00	1.00	Reference
Past FQ	122 (5.28)	836 (3.62)	1.33	1.09	0.80–1.47
Past azithro	116 (5.02)	1,005 (4.35)	1.00	1.00	Reference
Past FQ	122 (5.28)	836 (3.62)	1.28	1.07	0.78–1.47

Values are n or n (%) unless otherwise indicated. *Adjusted for variables in Table 2.
Abbreviations as in Table 3.

mitral and aortic regurgitation. As such, it might be prudent to consider antibiotics that are chemically distinct to FQs in patients with a previous history of valvular regurgitation who require antibacterial therapy. Future studies are urgently required to confirm or refute these findings.

ADDRESS FOR CORRESPONDENCE: Dr. Mahyar Etminan, The University of British Columbia, The Eye Care Center, Room 323-2550 Willow Street, Vancouver, British Columbia V5Z 3N9, Canada. E-mail: etminanm@mail.ubc.ca.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Exposure to fluoroquinolone antibiotics is associated with an increased risk of developing left-sided valvular regurgitation.

TRANSLATIONAL OUTLOOK: Further studies are needed to fully characterize the incremental risk of valvular heart disease and other adverse events in patients treated with fluoroquinolones.

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