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ORIGINAL RESEARCH ARTICLE

Fluoroquinolones and Cardiovascular Risk: A Systematic Review, Meta-analysis and Network Meta-analysis

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Abstract

Introduction Several fluoroquinolone antibiotics have been associated with cardiac adverse effects, leading to the withdrawal of some of these agents from the market. Cardiac side effects such as QT prolongation and torsades de pointes (TdP) have also been observed with fluoroquinolones currently on the market. In order to evaluate the cardiac risk of fluoroquinolones as a class, and the comparative risk for each individual drug, we conducted a systematic review, meta-analysis, and network meta-analysis.

Methods MEDLINE, EMBASE and the Cochrane Library were searched, up to March 2018, for randomized controlled trials, cohort studies, and case–control studies that investigated the association between fluoroquinolone treatment and the risk of cardiovascular events and cardiovascular mortality. We followed the PRISMA 2009 guidelines for data selection and extraction. Outcomes were pooled using random effects models. Direct and indirect comparisons in network meta-analysis were performed using frequentist methods.

Results Thirteen studies were included in our analyses. Fluoroquinolone use was associated with a statistically significant 85% increase in the risk for arrhythmia (odds ratio [OR] 1.85; 95% confidence interval [CI] 1.22–2.81) and 71% increase in the risk for cardiovascular mortality (OR 1.71; 95% CI 1.39–2.09). Moxifloxacin ranked most likely to have the highest risk for arrhythmia (P-score 0.99) and for cardiovascular mortality (P-score 0.95) by network meta-analysis.

Conclusions Our findings show a significant association between fluoroquinolone use and an increased risk for arrhythmia and cardiovascular mortality. Moxifloxacin ranked with the highest probability for cardiovascular adverse events. Further study is required to determine how to reduce the risk for fluoroquinolone-associated cardiac toxicity.

Key Points

Fluoroquinolone use is associated with a statistically significant increase in the risk for arrhythmia and the risk for cardiovascular mortality.

This risk was especially pronounced with moxifloxacin.

1 Introduction

Fluoroquinolone antibiotics have a wide spectrum of antibacterial coverage and are commonly used for a variety of infections, including respiratory tract infections, urinary tract infections, skin and soft tissue infections [1]. Nevertheless, several fluoroquinolones have been removed from the market due to safety issues such as hepatic toxicity (e.g.,

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trovafloxacin) [2], hypoglycemia (e.g., gatifloxacin) [3], and cardiotoxicity (e.g., grepafloxacin) [4].

Cardiac side effects such as QT prolongation and torsades de pointes (TdP) have also been observed in patients using fluoroquinolones currently on the market [4–6]. The proposed mechanism for the QT prolongation and possible increased risk for TdP is the fluoroquinolones blockade of the rapid delayed rectifier potassium current (I_{Kr}), resulting in an accumulation of potassium ions in cardiac myocytes and delayed cardiac repolarization [7, 8].

The available case reports and clinical studies suggest that moxifloxacin carries the greatest risk of QT prolongation compared with all other fluoroquinolones currently available in clinical practice, whereas ciprofloxacin appears to be associated with the lowest risk for QT prolongation and TdP [9, 10]. However, several case reports of ciprofloxacin cardiotoxicity have been published [11].

Two recent observational studies regarding clinical cardiovascular adverse events of fluoroquinolones reported conflicting results. Lapi et al. reported an association between fluoroquinolone use and the risk for serious arrhythmia [12]. In contrast, a cohort study conducted by Inghammar et al. didn't find such an association [13].

A single meta-analysis has reported that, as a class, fluoroquinolones are associated with an increased risk of serious arrhythmia [14]. Nevertheless, the relative risk for cardiac toxicity with the use of individual fluoroquinolone agents has not been evaluated by any of the published studies.

We conducted a systematic review, a meta-analysis, and a network meta-analysis to estimate the cardiac risk of fluoroquinolones as a class, and the comparative risk for the three commonly used individual fluoroquinolones [9, 10] moxifloxacin, levofloxacin and ciprofloxacin.

2 Materials and Methods

2.1 Data Source and Searches

We followed the Preferred Reporting Items for Systematic reviews and Meta-analysis framework guidelines (PRISMA 2009) [15]. The systematic review was performed by searching all publications indexed in MEDLINE (from 1966), EMBASE (from 1974), and the Cochrane Library (from1993) that investigated the association between fluoroquinolone treatment and the risk of cardiovascular events and cardiovascular mortality. We performed this search on March 14, 2018, with no date restriction. Our search included randomized controlled trials (RCTs), cohort studies, and case control studies. Searches were performed using Medical Subject Headings (MeSH) terms and free keywords: levofloxacin, ofloxacin, ciprofloxacin, moxifloxacin, delafloxacin, fluoroquinolone, cardiovascular, cardiac, heart, arrest, death, mortality, tachycardia, ventricular, tachyarrhythmia, arrhythmia, torsades de pointes, myocardial infarction (MI), and stroke. A manual search of reference lists of review articles and original studies was performed to identify additional reports. No language was applied in the search. The protocol was registered in the PROSPERO registry (registration number CRD42018094087)

2.2 Selection Criteria

Published studies were considered eligible if they reported on the risk of arrhythmia, cardiovascular mortality, or MI in fluoroquinolone users compared with non-fluoroquinolone users with no time limitation. We included observational studies and RCTs. When the results of a study were reported in more than one publication, the most informative and recent publication was included in the analysis.

Case reports, case series, pharmacokinetic studies in healthy adults, reviews, expert opinion, editorials, letters to the editor, and commentaries were excluded. Articles were also excluded from the analysis if they had insufficient published data for determining an estimate of the risk ratio (RR) or odds ratio (OR) and the confidence interval (CI). We excluded articles involving populations with HIV, sepsis, and tuberculosis and intensive care unit patients, to reduce the potential for confounding by indication. Additionally, we excluded studies in which the only comparison group was macrolide users due to their cardiovascular risks [8].

2.3 Data Extraction and Quality Assessment

The studies were obtained through medical databases and were independently screened by two reviewers (EG and RM) based on titles and then selected abstracts. A comprehensive search of reference lists of review articles and original studies was performed to identify additional reports. Disagreements were resolved through consensus or referral to a third reviewer (IM) when no consensus was obtained.

The data were extracted by two independent reviewers (EG and RM). Disagreements were resolved through consensus or referral to a third reviewer (IM) when needed. Data were extracted for the following characteristics: study details (study design, geographical location, publication year, duration of follow up), participants' details (number, study population, age, and gender), intervention and comparator characteristics (drug name, dosage regimen), outcomes, and covariate adjustments. Study authors were not contacted for additional information.

The quality of the observational studies was assessed using the Newcastle–Ottawa Quality Assessment Scale (NOS) scoring [16]. We considered studies with a NOS score of seven or more to be high-quality studies. The risk of bias for RCTs was assessed using the Cochrane tool for

assessing risk of bias for randomized control trials (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) [17].

2.4 Outcomes

Odds ratios were determined for arrhythmia, MI, and cardiovascular mortality.

2.5 Statistical Analysis

Raw data were extracted from individual studies, and the pooled ORs and corresponding 95% CIs were calculated for each primary outcome. The heterogeneity of the data was quantified using the Q statistic and the I^2 statistic. High heterogeneity was considered significant when $p < 0.1$ for the Q statistic or when the I^2 was > 50%. Effect sizes of fluoroquinolones as a class were pooled using random-effects models. These analyses were performed using Comprehensive Meta-Analysis software (CMA), version 3.

Additionally, we conducted a network meta-analysis according to PRISMA-NMA 2015 to pool direct and indirect comparisons between the marketed fluoroquinolones, namely moxifloxacin, levofloxacin, and ciprofloxacin, with regards to their relative arrhythmia and cardiovascular mortality. This analysis and network graphs were performed and generated using the package 'netmeta' within the R environment version 3.4.3 [18].

Moreover, we ranked the arrhythmia and cardiovascular mortality risks of fluoroquinolones using P-scores derived from network point estimates and standard errors. The P-scores of a treatment in this analysis can be interpreted as the mean extent of certainty that the treatment has greater risk of arrhythmia/cardiovascular death among the included treatments, measured on a scale from 1 (worst) to 0 (best) [19].

Inconsistency was assessed by using the Q statistic and comparing the results from direct and indirect estimates using the package 'netmeta' within the R environment version 3.4.3 [18].

Finally, we performed subgroup analyses according to study design: observational and interventional. Due to the limited number of RCTs in each analysis, we didn't perform subgroup analysis for RCTs. Additional sensitivity analysis was performed to examine the association between fluoroquinolone use and arrhythmia or MI excluding studies reporting cardiovascular events as adverse events rather than an outcome. Further, sub-analyses of studies that examined treatment for acute infections and of the studies that used β-lactam antibiotics as the control group were performed.

3 Results

3.1 Description of the Selected Studies

Our search generated 3491 records for evaluation. Records were screened for inclusion by title, resulting in 131 potentially relevant papers, which were further evaluated by abstract. After exclusion of irrelevant abstracts, 27 articles were selected for full-text evaluation. Thirteen articles were included in our three analyses: five case–control studies, five cohort studies, and three RCTs. The search process is illustrated in Fig. 1. The selected studies involved use of fluoroquinolones as a group and of moxifloxacin, ciprofloxacin, levofloxacin, and gatifloxacin. No studies reporting the cardiovascular risk of ofloxacin and delafloxacin were found. Study characteristics are summarized in Table 1. Additional information including quality assessments of observational studies and the overall risk of bias of RCTs are available online (Tables A1 and A2, respectively, see Electronic Supplementary Material). The comparator group was most commonly a β-lactam antibiotic.

3.2 Meta-analysis

3.2.1 Arrhythmia

Six studies [12, 13, 20–23] with 4,507,132 participants (three cohort studies, two case–control studies, and one RCT) reported arrhythmia among fluoroquinolone users. The pooled analysis showed a significant association between fluoroquinolone use and an increased risk for arrhythmia (OR 1.85 [95% CI 1.22–2.81]) with high heterogeneity $I^2 = 87\%$ (Fig. 2). In the sub-analysis for observational studies [12, 13, 20, 22, 23] (excluding Harms et al. [21], who reported cardiac arrhythmia as part of the safety analysis and not as an outcome, and was the only RCT in the analysis) the significant association was maintained (OR 1.87 [95% CI 1.22–2.87]; $p < 0.001$; $I^2 = 90\%$).

3.2.2 Cardiovascular Mortality

The pooled analysis of three studies [20, 24, 25] with 3,275,114 participants (two cohort studies and one RCT), resulted in a significant association between fluoroquinolone use and an increased risk for cardiovascular mortality (OR 1.71 [95% CI 1.39–2.09]) with low heterogeneity ($p = 0.4$; $I^2 = 0\%$) (Fig. 3). When we excluded Cannon et al. [25], the only RCT in the analysis, the pooled effect of the two observational studies [20, 24] is OR 1.68 (95% CI 1.26–2.24); $I^2 = 37\%$.

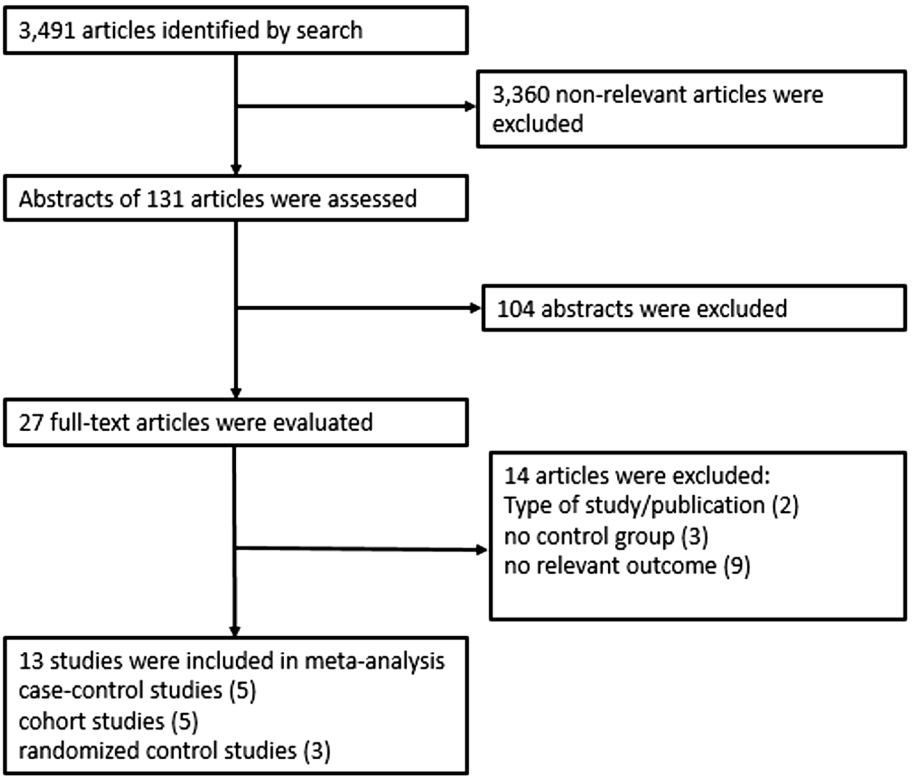

Fig. 1 Selection process: articles retrieved, screened, and selected for the quantitative analysis

3.2.3 Myocardial Infarction

In the pooled analysis of six studies [25–30] with 269,832 participants (one cohort study, three case control studies, and two RCTs, see Table 3) reporting MI risk in fluoroquinolone users, we observed a small but statistically significant association between fluoroquinolone use and an increased risk for MI (OR 1.18 [95% CI 1.00–1.38]), with high heterogeneity ($p=0.01$; $I^2=66\%$) (Fig. 4). In the sensitivity analysis, excluding Fink et al. [30], the association remained significant (OR 1.19 [95% CI 1.02–1.38]; $p=0.018$; $I^2=66\%$) for heterogeneity. In the sub-group analysis for observational studies [26–29], the pooled effect is OR 1.33 (95% CI 1.26–1.39); $I^2=0\%$.

3.3 Network Meta-analysis

3.3.1 Arrhythmia

In the network meta-analysis for arrhythmia (network plot in Fig. 5), moxifloxacin ranked most likely to have the highest risk for arrhythmia among the marketed fluoroquinolones included in the analysis (P-score 0.99), and ciprofloxacin ranked most likely to have the lowest risk for arrhythmia (P-score 0.39) (see Table 2).

Moxifloxacin was associated with a higher risk for arrhythmia compared with levofloxacin and ciprofloxacin (OR 2.19 [95% CI 1.31–3.64] and OR 2.71 [95% CI 1.60–4.59], respectively). Both ciprofloxacin and levofloxacin were associated with higher risk for arrhythmia compared with non-fluoroquinolones (OR 1.51 [95% CI 1.04–2.20] and OR 1.87 [95% CI 1.36–2.58], respectively).

However, analysis of the comparative risk for arrhythmia did not show a significant difference between levofloxacin and ciprofloxacin (OR 1.24 [95% CI 0.79–1.95]) (see Fig. 6).

The inconsistent results for the overall network do not indicate that the direct and indirect comparisons of arrhythmia were inconsistent ($p=0.24$), with heterogeneity of 26%.

3.3.2 Cardiovascular Mortality

In network meta-analysis for cardiovascular mortality (network plot in Fig. 7), moxifloxacin was ranked most likely to have the highest risk for cardiovascular mortality (P-score 0.95) (Table 3) and was associated with a significantly higher risk for cardiovascular mortality compared with ciprofloxacin (OR 3.50 [95% CI 1.78–6.91]) (Fig. 8). Our results didn't suggest a significant association between moxifloxacin and cardiovascular mortality compared with levofloxacin use (OR 1.38 [95% CI 0.72–2.65]). Levofloxacin was associated with a significantly higher risk for cardiovascular mortality compared with ciprofloxacin use (OR 2.53 [95% CI 1.55–4.14]). Ciprofloxacin was ranked most likely to have the lowest risk for cardiovascular mortality (P-score 0.15) (Table 3) and was the only fluoroquinolone that was

Table 1 Study characteristics

Study	Year	Study design	Relevant outcome	FQ	Control	Events FQ users/control	FQ users/control	Duration of follow-up
Chou et al. [20]	2015	Cohort	Arrhythmia, cardiovascular mortality	Moxifloxacin Ciprofloxacin Levofloxacin	Amoxicillin-clavulanate	82/127 88/142	361,390/1,102,358	7 days
Inghammar et al. [32]	2016	Cohort	Arrhythmia	NS	Penicillin	105/113	909,656/909,656	14 days
Harms et al. [21]	2008	RCT	Arrhythmia	Moxifloxacin	Placebo	1/1	39/40	6 months
Lapi et al. [12]	2012	Nested case control	Arrhythmia	Moxifloxacin Ciprofloxacin Levofloxacin Gatifloxacin	FQ non-users	35/1293	427/31,933	Within 14 days before the index date
Rao et al. [22]	2014	Cohort	Arrhythmia	Levofloxacin	Amoxicillin + clavulanate potassium	59/166	201,789/979,380	10 days
Zambon et al. [33]	2009	Case control	Arrhythmia	NS	FQ non-users	NA	NA/NA (total 10,464)	Recent/immediately prior to the date of the event
Cannon et al. [25]	2005	RCT	Cardiovascular mortality, MI	Gatifloxacin	Placebo	31/19 137/154	2076/2086	18–32 months (mean 2 years)
Ray et al. [24]	2012	Cohort	Cardiovascular mortality	Ciprofloxacin Levofloxacin	Amoxicillin	38/80	458,532/1,348,672	10 days
Bjerrum et al. [26]	2006	Case control	MI	NS	FQ non-users	227/3858	968/19,509	3 years
Fink et al. [30]	1994	RCT	MI	Ciprofloxacin	Imipenem–cilastatin	0/4	200/200	7 days of discontinuation
Karter et al. [27]	2003	Case control	MI	NS	Penicillin	33/129	132/570	6 months prior to the index date
Luchsinger et al. [28]	2002	Cohort	MI	NS	Non users of macrolides, quinolones, tetracycline, penicillin, cephalosporin, trimethoprim-sulfamethoxazole	NA	70,801/152,475	NA
Monster et al. [29]	2005	Case control	MI	NS	Penicillin	34/1954	296/20,519	3 years

FQ fluoroquinolones, *MI* myocardial infarction, *NA* not applicable, *NS* not specified, *RCT* randomized controlled trial

not associated with a risk for cardiac mortality compared with non-users (Fig. 8).

The results of inconsistency for the overall network do not indicate that the direct and indirect comparisons of cardiac death were inconsistent ($p = 0.16$), with heterogeneity of 45%.

Additional sub-analyses of studies that examined treatment for acute infections and of the studies that used β-lactam antibiotics as the control group were performed. The two subgroup analyses support our primary findings of a significant association between cardiovascular mortality and fluoroquinolones use. The association between fluoroquinolone and arrhythmia was statistically significant in the first analysis. In the second analysis, we couldn't

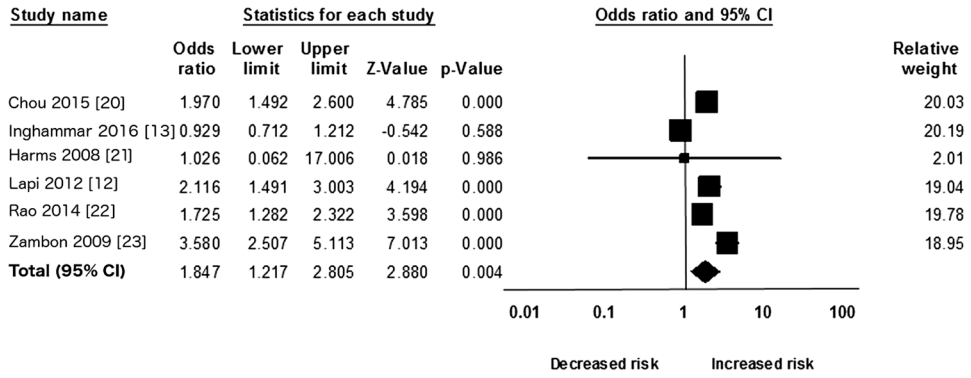

Fig. 2 Arrhythmia in fluoroquinolone users versus non-users. The forest plot demonstrates point estimates of the odds ratio surrounded by 95% confidence intervals (CI) calculated by random-effects model

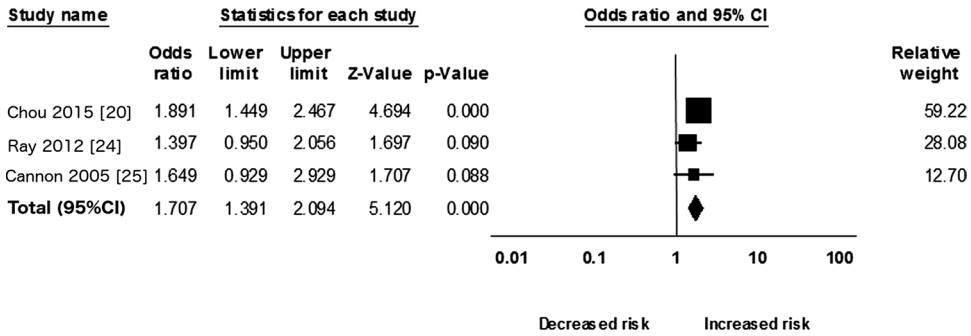

Fig. 3 Cardiovascular mortality in fluoroquinolone users versus non-users. The forest plot demonstrates point estimates of the odds ratio surrounded by 95% confidence intervals (CI) calculated by random-effects model

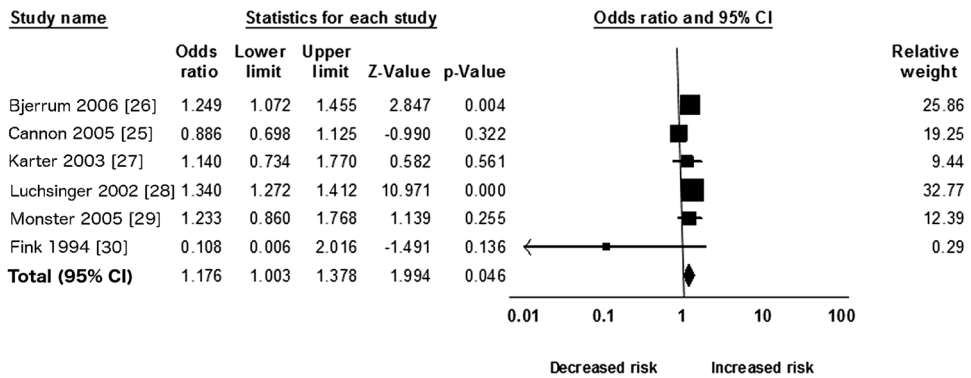

Fig. 4 Myocardial infarction in fluoroquinolone users versus non-users. The forest plot demonstrates point estimates of the odds ratio surrounded by 95% confidence intervals (CI) calculated by random-effects model

reach statistical significance, only a trend (see Electronic Supplementary Material).

4 Discussion

The results of our meta-analysis indicate an association between the use of fluoroquinolones and the risk for arrhythmia and cardiovascular mortality compared with non-fluoroquinolone treatment. In network meta-analyses, moxifloxacin treatment was associated with the highest probability to be associated with the risk for both arrhythmia and cardiovascular mortality as compared to other fluoroquinolones and non-fluoroquinolone treatments, and ciprofloxacin was associated with the lowest probability to be associated with the risk for both outcomes.

Our results suggest an association between fluoroquinolone use and cardiovascular adverse events, and are consistent with Liu et al.'s results [14]; however, the association in our analysis was somewhat weaker. Liu et al. included in their analysis a study based on the US FDA adverse event reporting system (FAERS). As the data in FAERS cannot be used to directly infer the OR or RR of an event [31], this study was not included in the calculation of the pooled effect in our meta-analysis. In the network meta-analysis, which included only

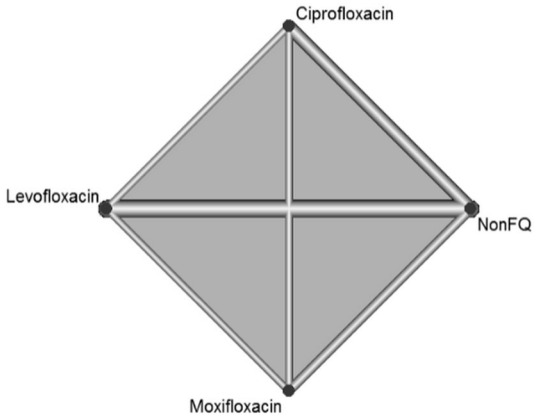

Fig. 5 Network plot for arrhythmia analysis: nodes represent treatments and edges represent the available direct comparisons between pairs of treatments. *FQ* fluoroquinolones

Table 2 Treatment ranked by probability of highest risk of arrhythmia

Medication	P-score[a]
1. Moxifloxacin	0.99
2. Levofloxacin	0.61
3. Ciprofloxacin	0.39
4. Non-fluoroquinolone	0.005

[a]P-score derived from network meta-analysis. It represents the mean extent of certainty that a given treatment has greater risk of arrhythmia among the included treatments, measured on a scale from 0 (best) to 1 (worst)

marketed fluoroquinolones, we found a significant difference between the risk for arrhythmia associated with individual fluoroquinolones: moxifloxacin was associated with > 2-fold increase in the risk of arrhythmia compared with ciprofloxacin or levofloxacin. The higher risk observed with moxifloxacin use is consistent with in-vitro findings suggesting a more potent blockade of I_{Kr} current than ciprofloxacin and levofloxacin [8] and with previous clinical studies [12, 14]. Interestingly, a higher risk was observed for levofloxacin compared with ciprofloxacin in the analysis of cardiac mortality, while the risk of arrhythmia was not statistically significantly different, though a consistent trend was observed. Furthermore, levofloxacin ranked more likely to have higher risk for both outcomes than ciprofloxacin. These findings are consistent with the fact that ciprofloxacin is often considered as having the lowest potential to cause cardiovascular side effects [8, 9]. Our results suggest a very weak association between the use of fluoroquinolone antibiotics and MI. Due to the relatively small number of participants in the analysis, and the lack of biological plausibility, we believe this finding can be attributed to residual confounding rather than a causal association.

Our study has several strengths. First, the results are generalizable due to the large number of participants in the arrhythmia and cardiovascular mortality analyses and the use of raw data. The subgroup analyses performed according to study design and baseline indication support these findings. Furthermore, to our knowledge, we are the first to conduct indirect comparisons using a network meta-analysis to assess differences between individual fluoroquinolones regarding their cardiovascular risk.

There are several limitations of our analysis. Firstly, our study was not designed to explore the interaction between co-morbidity and fluoroquinolones' cardiovascular adverse effects and therefore the observed risk does not reflect the risk in special populations such as patients with conduction disorders and patients with prior major cardiovascular events. Secondly, confounding by indication is a possible limitation of observational studies such as those included in our analyses. Although many of

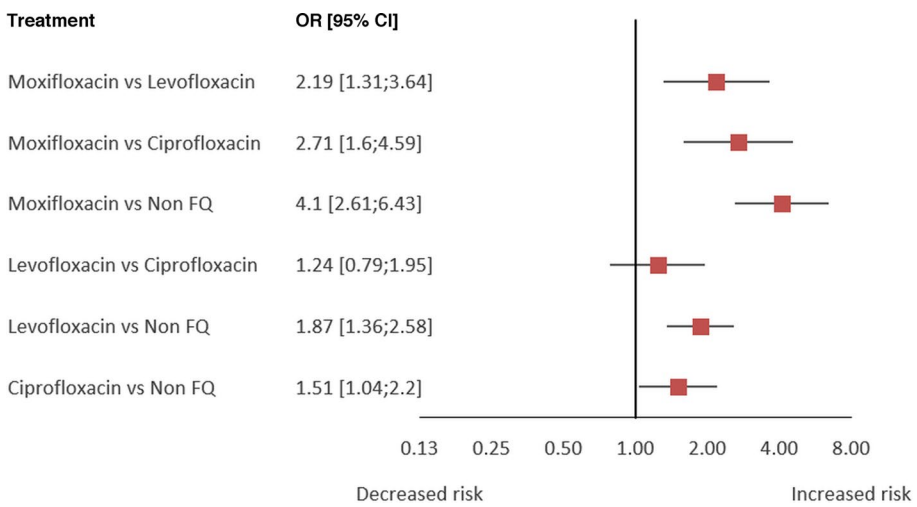

Fig. 6 Comparative odds ratio (OR) for arrhythmia in different fluoroquinolones. The forest plot demonstrates point estimates of risk ratio surrounded by 95% confidence intervals (CI) calculated by random-effects model. *FQ* fluoroquinolones

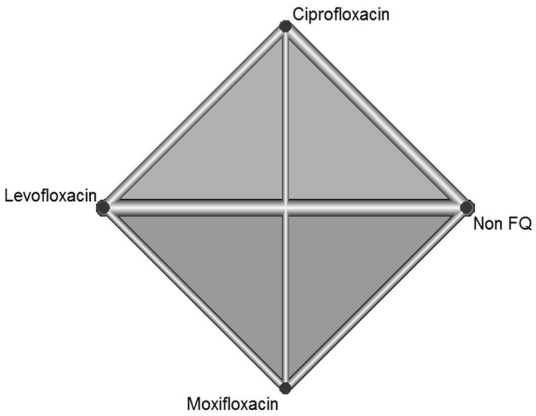

Fig. 7 Network plot for cardiovascular mortality analysis. Nodes represent treatments and edges represent the available direct comparisons between pairs of treatments. *FQ* fluoroquinolones

Table 3 Treatment ranked by probability of highest risk of cardiovascular mortality

Medication	P-score[a]
1. Moxifloxacin	0.95
2. Levofloxacin	0.72
3. Non fluoroquinolone	0.18
4. Ciprofloxacin	0.15

[a]P-score derived from network meta-analysis. It represents the mean extent of certainty that a given treatment has greater risk of cardiovascular mortality among the included treatments, measured on a scale from 0 (best) to 1 (worst)

the observational studies compared fluoroquinolone use to other antibacterial agents for similar indications, the potential for residual confounding remains. Thirdly, we had no information regarding important lifestyle factors that influence patients' cardiovascular risk, compliance, and antibiotics regimen in many of the studies. Lastly, there was evidence of high heterogeneity among the trials for some of the outcomes. The high heterogeneity can be attributed to different indications of antibiotics, different control exposure, different drug regimens (dose and treatment duration), different study design, different coexisting conditions, concomitant drugs, age, and gender. We used a random effects model in our computations in order to account for the possibility of study-dependent variations in effect, and conducted sensitivity analyses excluding studies that reported on cardiac outcomes only as part the assessment of side effects.

5 Conclusions

Our findings show a significant association between fluoroquinolone use and increased risk for arrhythmia and cardiovascular mortality. This risk was especially pronounced with moxifloxacin, which was associated with a 2- to 3-fold higher risk for these outcomes. These findings are in accordance with previous studies. Due to the widespread use of fluoroquinolones, the findings that we describe are relevant to healthcare professionals. These findings provide the best available evidence on the cardiac risk profile of fluoroquinolones as a class, and on the most likely relative risk of individual agents.

Additional studies are required to investigate the observed risks of individual drugs, and to evaluate fluoroquinolone cardiac safety in special populations with risk factors for cardiac arrhythmias. Until then, prudent

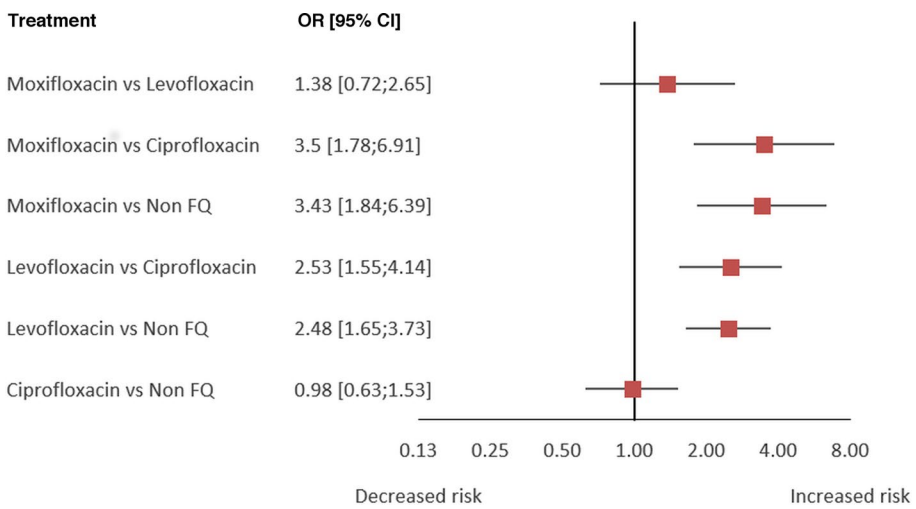

Fig. 8 Comparative odds ratio (OR) for cardiovascular mortality in different fluoroquinolones. The forest plot demonstrates point estimates of risk ratio surrounded by 95% confidence intervals (CI) calculated by random-effects model. *FQ* fluoroquinolones

monitoring should be considered, particularly in high-risk patients.

Compliance with Ethical Standards

Conflict of interest Einat Gorelik, Reem Masarwa, Amichai Perlman, Victoria Rotshild, Momen Abbasi, Mordechai Muszkat, and Ilan Matok have no conflicts of interest that are directly relevant to the content of this study.

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References

1. emc. Ofloxacin SmCP [Internet]. https://www.medicines.org.uk/emc/product/8481/smpc. Accessed 9 May 2018.
2. Lucena MI, Andrade JR, Rodrigo L, Salmerón J, Alvarez A, Lopez-Garrido MJ, Camargo R, Alcantára R. Trovafloxacin-induced acute hepatitis. Clin Infect Dis (Internet). 2000;30(2):400–1.
3. Park-Wyllie LY, Juurlink DN, Kopp A, Shah BR, Stukel TA, Stumpo C, et al. Outpatient gatifloxacin therapy and dysglycemia in older adults. N Engl J Med (Internet). 2006;354(13):1352–61. https://doi.org/10.1056/NEJMoa055191.
4. Rubinstein E, Camm J. Cardiotoxicity of fluoroquinolones. J Antimicrob Chemother (Internet). 2002;49(4):593–6. https://doi.org/10.1093/jac/49.4.593.
5. Nykamp DL, Blackmon CL, Schmidt PE, Roberson AG. QTc prolongation associated with combination therapy of levofloxacin, imipramine, and fluoxetine. Ann Pharmacother (Internet). 2005;39(3):543–6. https://doi.org/10.1345/aph.1E513%0D.
6. Badshah A, Janjua M, Younas F, Halabi AR, Cotant JF. Moxifloxacin-induced QT prolongation and torsades: an uncommon effect of a common drug. Am J Med Sci (Internet). 2009;338(2):164–6.
7. Kannankeril P, Roden DM, Darbar D. Drug-induced long QT syndrome. Pharmacol Rev (Internet). 2010;62(4):760–81.
8. Abo-Salem E, Fowler JC, Attari M, Cox CD, Perez-Verdia A, Panikkath R, et al. Antibiotic-induced cardiac arrhythmias. Cardiovasc Ther (Internet). 2014;32(1):19–25. https://doi.org/10.1111/1755-5922.12054.
9. Falagas ME, Rafailidis PI, Rosmarakis ES. Arrhythmias associated with fluoroquinolone therapy. Int J Antimicrob Agents (Internet). 2007;29(4):374–9.
10. Mehrzad R, Barza M. Weighing the adverse cardiac effects of fluoroquinolones: a risk perspective. J Clin Pharmacol (Internet). 2015;55(11):1198–206.
11. Bolognesi M, Bolognesi D. Ciprofloxacin-induced paroxysmal atrial fibrillation. OA Case Rep (Internet). 2014;1–3. http://www.oapublishinglondon.com/images/article/pdf/1410967708.pdf. Accessed 8 May 2018.
12. Lapi F, Wilchesky M, Kezouh A, Benisty JI, Ernst P, Suissa S. Fluoroquinolones and the risk of serious arrhythmia: a population-based study. Clin Infect Dis (Internet). 2012;55(11):1457–65. https://doi.org/10.1093/cid/cis664.
13. Inghammar M, Svanström H, Melbye M, Pasternak B, Hviid A. Oral fluoroquinolone use and serious arrhythmia : bi-national cohort study. BMJ. 2016;352(i843):1–8.
14. Liu X, Ma J, Huang L, Zhu W, Yuan P, Wan R, et al. Fluoroquinolones increase the risk of serious arrhythmias: a systematic review and meta-analysis. Medicine (Baltimore) (Internet). 2017;96(44):e8273.
15. Moher D. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. Ann Intern Med 2009;151:264
16. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos MPT. The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses (Internet). http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed 2 Aug 2017.
17. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ (Internet). 2011;343(7303):d5928.
18. Rücker G, Schwarzer G, Krahn U, König J. Netmeta: network meta-analysis using frequentist methods. 2017. https://cran.r-project.org/web/packages/netmeta/netmeta.pdf. Accessed 9 May 2018.
19. Rücker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. BMC Med Res Methodol. 2015;15(1):1–9.
20. Chou HW, Wang JL, Chang CH, Lai CL, Lai MS, Chan KA. Risks of cardiac arrhythmia and mortality among patients using new-generation macrolides, fluoroquinolones, and β-lactam/β-lactamase inhibitors: a Taiwanese nationwide study. Clin Infect Dis (Internet). 2015;60(4):566–77.
21. Harms H, Prass K, Meisel C, Klehmet J, Rogge W, Bereswill S, et al. Preventive antibacterial therapy in acute ischemic stroke: a randomized controlled trial. PLoS One (Internet). 2008;3(5):e2158.
22. Rao GA, Mann JR, Shoaibi A, Bennett CL, Nahhas G, Sutton SS, et al. Azithromycin and levofloxacin use and increased risk of cardiac arrhythmia and death. Ann Fam Med (Internet). 2014;12(2):121–7.
23. Zambon A, Polo Friz H, Contiero P, Corrao G. Effect of macrolide and fluoroquinolone antibacterials on the risk of ventricular arrhythmia and cardiac arrest: an observational study in Italy using case–control, case–crossover and case–time–control designs. Drug Saf (Internet). 2009;32(2):159–67.
24. Ray WA, Ph D, Murray KT, Hall K, Arbogast PG, Ph D, et al. Azithromycin and the risk of cardiovascular death. N Engl J Med (Internet). 2012;367(8):772–5. https://doi.org/10.1056/NEJMc1207269.
25. Cannon CP, Braunwald E, Mccabe CH, Grayston JT, Muhlestein B, Giugliano RP, et al. Antibiotic Treatment of Chlamydia pneumoniae after Acute Coronary Syndrome. J Med (Internet). 2005;352(16):1646–54. https://doi.org/10.1056/NEJMoa043528.
26. Bjerrum L, Andersen M, Hallas J. Antibiotics active against Chlamydia do not reduce the risk of myocardial infarction. Eur J Clin Pharmacol. 2006;62:43–9.
27. Karter AJ, Thom DH, Liu J, Moffet HH, Ferrara ASJ. Use of antibiotics is not associated with decreased risk of myocardial infarction. Diabetes Care. 2003;26:2100–6.
28. Luchsinger A, Pablos-me A, Knirsch C, Rabinowitz D, Shea S. Relation of antibiotic use to risk of myocardial infarction in the general population. Am J Cardiol. 2002;89(01):18–21.
29. Monster TB, Johnsen SP, Olsen ML, Østergaard L, Friis S, McLaughlin JK, et al. Antibiotics and risk of first-time hospitalization for myocardial infarction: a population-based case–control study. Am J Ther (Internet). 2005;12(3):226–32.
30. Fink MP, Snydman DR, Niederman MS, Leeper KV, Johnson RH, Heard S, et al. Treatment of severe pneumonia in hospitalized patients : results of a multicenter, randomized, double-blind trial comparing intravenous ciprofloxacin with imipenem-cilastatin. Antimicrob Agents Chemother. 1994;38(3):547–57.
31. Raschi E, Poluzzi E, Salvo F, Pariente A, De Ponti F, Marchesini GMU. Pharmacovigilance of sodium-glucose co-transporter-2 inhibitors: What a clinician should know on disproportionality analysis of spontaneous reporting systems. Nutr Metab Cardiovasc Dis (Internet). 2018;28(6):533–42.

32. Inghammar M, Svanström H, Melbye M, Pasternak B, Hviid A. Oral fluoroquinolone use and serious arrhythmia : bi-national cohort study. BMJ (Internet). 2016;352(i843):1–8.
33. Zambon A, Polo Friz H, Contiero P, Corrao G. Effect of macrolide and fluoroquinolone antibacterials on the risk of ventricular arrhythmia and cardiac arrest: an observational study in Italy using case–control, case–crossover and case–time–control designs. Drug Saf. 2009;32(2):159–67.