Fluoroquinolones Are Associated With Increased Risk of Aortic Aneurysm or Dissection: Systematic Review and Meta-analysis

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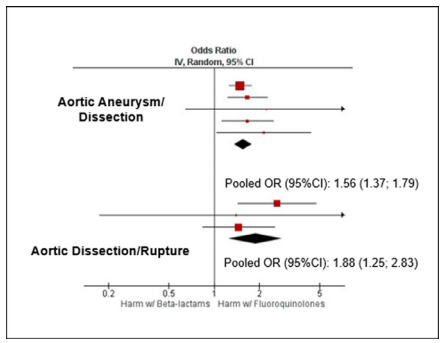
Fluoroquinolone use has been associated with collagen disease events, raising safety concerns. We hypothesized that the use of fluoroquinolones is associated with aortic aneurysm (AA) and aortic dissection or aortic rupture (AD/AR). We performed a systematic review with meta-analysis on studies published until March 2019. Seven observational studies were included, comprising 2,851,646 participants. The studies were evaluated regarding their risk of bias. Results on fluoroquinolone use risk comparing with non-treatment and with beta-lactam antibiotic use were extracted. The estimates were pooled through a random-effects model meta-analysis and heterogeneity assessed through the I^2 statistic. Sensitivity analysis were performed, grouping studies per design and with exclusion of studies with critical risk of bias. Fluoroquinolone use was associated with a higher risk of AA/AD/AR, comparing with a nontreatment intervention (odds ratio = 2.26; 95%CI 1.93–2.65; $I^2 = 30\%$) and comparing with a beta-lactam intervention (odds ratio = 1.56; 95%CI 1.37–1.79; $I^2 = 0\%$). This harm effect remained significant when pooling the results for the AD/AR outcome only and across various study designs. Studies comparing with beta-lactam intervention were considered to have a moderate risk of bias, while the remaining ones were classified as having at least a serious risk of bias. All evaluated outcomes had very low Grading of Recommendation, Assessment, Development and



Harm effect of fluoroquinolone use on aortic disease for beta-lactam use as comparator.

Central Message

Fluoroquinolone use - albeit with very low confidence in the evidence - is still associated with aortic disease, possibly demanding caution on its prescription to potentially susceptible patients.

Abbreviations: AA, aortic aneurysm; AD, aortic dissection; PRISMA, preferred reporting items for systematic reviews and meta-analyses; MOOSE, meta-analyses of observational studies in epidemiology; DAAER, disproportionality analysis of adverse event report studies; CENTRAL, The Cochrane Central Register of Controlled Trials; MeSH, medical subject headings; OR, odds ratio; ROBINS-I, risk of bias in nonrandomized studies - of interventions; GRADE, The Grading of Recommendations Assessment, Development and Evaluation; AR, aortic rupture; FLQ, fluoroquinolones; MMP, matrix metalloproteinases; NNH, number needed to treat; HR, hazard ratio; RR, risk ratio; AMX, amoxicillin; CFX, cefuroxime; ICD, International Statistical Classification of Diseases and Related Health Problems; AER, adverse event reports; MedRA, Medical Dictionary for Regulatory Activities; T-VC, time-varying confounders; B-L, beta-lactams; CI, confidence interval; RCT, randomized controlled trial

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Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interest: DC has participated in educational meetings and/or attended conferences or symposia (including travel, accommodation and/or hospitality) with Bristol-Myers Squibb, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Merck Serono, Ferrer, Pfizer, Novartis and Roche. FJP had consultant and speaker fees with Astra Zeneca, Bayer, BMS, Boehringer Ingelheim and Daiichi Sankyo.

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1043-0679/$–see front matter

https://doi.org/10.1053/j.semtcvs.2020.11.011

Evaluation evidence. Fluoroquinolone use was associated with a significant risk of AA/AD/AR.

Semin Thoracic Surg ■■:■■–■■

Keywords: Fluoroquinolone, Aortic aneurysm, Aortic dissection, Systematic review, Meta-analysis

Perspective Statement

This systematic review with meta-analysis, comprising 7 observational studies and 2,851,646 participants, suggests based on a very low certainty of the evidence that fluoroquinolones use is associated with aortic aneurysm and/or dissection and/or rupture, comparing with nontreatment or beta-lactam use.

INTRODUCTION

Fluoroquinolones (FLQ) are one of the most frequently prescribed antibiotics and its use has substantially increased over the past few decades.[1,2] These drugs are indicated for several types of infections, namely genitourinary, prostatitis, respiratory, some sexually transmitted diseases and gastroenteritis. Commonly prescribed FLQ include[3] ciprofloxacin, levofloxacin, ofloxacin, moxifloxacin and gatifloxacin.

In recent years, several epidemiological concerns regarding the use of FLQ and their association with unexpected side effects — tendon rupture,[4] nervous system damage,[5] and even multisystem toxicity[6] — have been emerging, prompting press releases and establishment of safety policies from various drug regulatory agencies. More recently, diseases of the aorta have been associated as potential side effects related to FLQ, namely aortic aneurysm (AA) and aortic dissection (AD),[7] possibly due to an harmful effect on collagenous structures.[8,9]

Risk factors for both AA[10] and AD[11] include male sex, age older than 60 years, smoking, hypertension and family history. More specific risk factors for AD include AA, collagen congenital disorders and inflammatory disease.

Given the life-threatening condition of the diseases implicated, the widespread and growing use of FLQ, and the recent publication of observational studies, a systematic review with meta-analysis was performed, with the goal of assessing a possible association of FLQ use with aortic disease.

METHODS

We carried out a systematic review and meta-analysis that followed the PRISMA and MOOSE guidelines as standards for reporting data.[12,13] The protocol of this systematic review is available online with DOI 10.17605/OSF.IO/QF9VN.

Eligibility Criteria and Outcomes

We included all types of longitudinal controlled studies that had FLQ as intervention and/or exposure group and a control group. The FLQ group included individuals treated and/or exposed to any FLQ, with any route of administration, dose, treatment duration or indication, without restriction of age. The control group was composed by individuals receiving placebo, no treatment, absence of exposure to FLQ, or exposed to non.FLQ antibiotics. The type of controlled studies allowed for this systematic review were randomized controlled trials, cohort, case-control, within-subject crossover, case-time-control and disproportionality analysis of adverse event report studies (DAAER), being either prospective or retrospective.

The primary outcome for the eligible studies was the risk of short-term AA/AD. Whenever possible the data for the outcome were selected from a time period of 60 days after start of the treatment (due to potential bimodal distribution of aortic disease risk immediately after the exposure and between 30 and 50 days).[14,15] When a time period of 60 days was not available in a study, we selected the 30-days risk period. The secondary outcome was AD/AR.

Studies that met inclusion criteria were not excluded a priori on the basis of weakness of design, data quality or linguistic criteria.

Search Process

The bibliographic databases MEDLINE, Web of Science Core Colection and CENTRAL were comprehensively searched from their inception to March 2019 for studies fulfilling the inclusion criteria. The search strategy, including free-text words and MeSH terms without language restrictions, is detailed in Supplementary Figure 1. Handsearch was also undertaken among the references of the included articles.

Data Extraction and Evaluation

NV and DC worked independently at articles screening and full-text assessment. All discrepancies were solved by consensus after analysis of the source papers. The data extraction was done into a prepiloted form, including: study year, study design, location of the study, sample size, drug exposure, specific FLQ used, duration of follow-up, the outcomes evaluated (AA/AD/AR) and participants characteristics such as mean age, sex, comorbidities (diabetes, hypertension, hyperlipidemia, personal history of any vascular disease, smoking and chronic pulmonary obstructive disorder). The results of the outcomes of interest were extracted, as well as data on adjustment techniques applied (design, comparator, and adjusted variables) and whenever possible adjusted relative risk measures were retrieved, giving preference for those adjusted to most of the referred clinical characteristics.

Data Synthesis

We used RevMan software (version 5.3.5) for statistical analysis and to derive the forest plots.

Firstly were evaluated the risk of FLQ against a non-FLQ control group using random-effects meta-analysis weighted by the inverse-variance method to estimate pooled odds ratios

(ORs) and 95% confidence intervals (CIs). Heterogeneity was assessed with the I^2 statistic, that measures the percentage of total variation between studies due to heterogeneity.[16] 95% CIs for I^2 were also determined, through application of the formulas provided by Borenstein et al (Supplementary Table 5).[17] We used a random-effects model independently of the existence ($I^2 \geq 50\%$) or not of substantial heterogeneity between trials' results because we pooled results of studies with different designs and patients´ characteristics.[18] The effect measurement estimate chosen was OR because relative estimates are more similar across studies with different designs, populations and lengths of follow-up than absolute effects.[19] When outcomes were adjusted for different variables, we used the one reflecting a higher degree of adjustments.[20] If single studies provided estimates for different FLQ we pooled all the estimates through random-effects meta-analysis to derive the class effect.

We also performed an analysis of FLQ' risk against a negative active control - beta-lactam antibiotics - which at least controls the analysis for the infection status. When no direct comparison between FLQ and beta-lactams was available, we performed adjusted indirect comparisons between the pooled estimate of FLQ (vs control) and beta-lactams (vs control) using the Bucher frequentist method.[21] This method is believed to be valid assuming that the relative effect of interventions is consistent across different studies.[22] We used by default the random-effects model because adjusted indirect comparisons that used the fixed-effects model tends to underestimate the standard errors of pooled estimates.[22]

The indirect estimates were then pooled with direct estimates through a random-effects model meta-analysis in order to derive more precise estimates.[23]

Sensitivity analyses were performed according to study design, with exclusion of studies with higher risk of bias and exclusion of studies with a disproportionately high statistical weight.

To estimate an absolute measure of effect we calculated the number needed to harm (NNH) and the corresponding CI, per pooled comparison.[24] We used the pooled ORs to calculate the NNH through the formulas provided by Smeeth et al.[25] The baseline risks were acquired from population-based studies.

Risk of bias was independently evaluated by 2 authors (NV and DC). The risk of bias in nonrandomized studies - of interventions (ROBINS-I) tool was used, assessing the following domains: confounding, selection of participants, classification of intervention, deviations from intervention, missing data, measurement of outcome and selection of reported results.[26] These domains were qualitatively classified as at critical, serious, moderate or low risk of bias. The overall risk of bias for each observational study received the same classifications, performed per main outcome and comparison of interest.

The Grading of Recommendations, Assessment, and Evaluation framework was used to report the overall quality of evidence.[27] The certainty in the evidence for each outcome was graded as high, moderate, low or very low.[28]

Reporting and/or publication bias tests for funnel plot asymmetry were planned for use if a minimum of 10 studies were included in the meta-analysis (since below this 10 studies threshold the power of these tests is too low, and therefore cannot adequately distinguish chance findings from real asymmetry in the funnel plots).[29]

RESULTS

Search Result and Study Selection

The search strategy yielded a total of 362 published references. Following our inclusion and exclusion criteria, we were able to include 7 studies for analysis, all of them observational (Fig. 1). There were no randomized controlled trial studying this topic.

Characteristics of the Included Studies

The 7 studies included were all observational, with heterogeneous designs: 2 cohort studies (Daneman et al — "Daneman" - and Pasternak et al — "Pasternak"),[15,30] 1 nested case-control study (Lee 2015 et al — "Lee 2015"),[31] 1 case-crossover study (Lee 2018 et al — "Lee 2018"),[14] 1 case-time-control study (Maumus-Robert et al — "Maumus-Robert"),[32] and 2 DAAERs (Sommet et al — "Sommet" - and Meng et al — "Meng").[33,34] Only the 2 cohort studies were prospective. The comparator in 5 was an active comparator (beta-lactams, namely amoxicillin[15,30,32,33] or cefuroxime[34]). The remaining 2[14,31] used only a control comparator (nontreatment). In 2 of the studies (Daneman and Meng) the data were compared indirectly as there were different estimates evaluating the risk of FLQ and beta-lactams independently.[30,34]

The total number of cases and controls (Table 1 and Supplementary Table 6 for details and differences according with study design) was, respectively, 1,026,115 and 1,825,652 (including also at least 217,088 cases and controls from DAAERs). The number of aortic disease patients was 26,607.

The mean age of participants averaged across studies was 70.2 years and the average proportion of male individuals was 61%. Tables 1 and 2 and Supplementary Table 2 show the general characteristics of the included studies and Supplementary Table 1 shows the prevalence of risk factors for aortic diseases reported in each individual study.

In general, the outcomes chosen comprised all types and locations of AA/AD/AR (Supplementary Table 2).

Reporting Quality of the Included Studies

The risk of bias of the included studies assessed through ROBINS-I tool[26] was moderate in 5 studies (Daneman, Pasternak, Lee 2015, Lee 2018 and Maumus-Robert studies),[14,30–32] serious in one (Sommet),[33] and critical in another (Meng)[34] (Table 3 and Supplementary Table 3).

Some criteria for prevention of bias were, overall, successfully met by the 5 studies classified as having a moderate risk of bias, namely, the "selection of participants," "missing data"

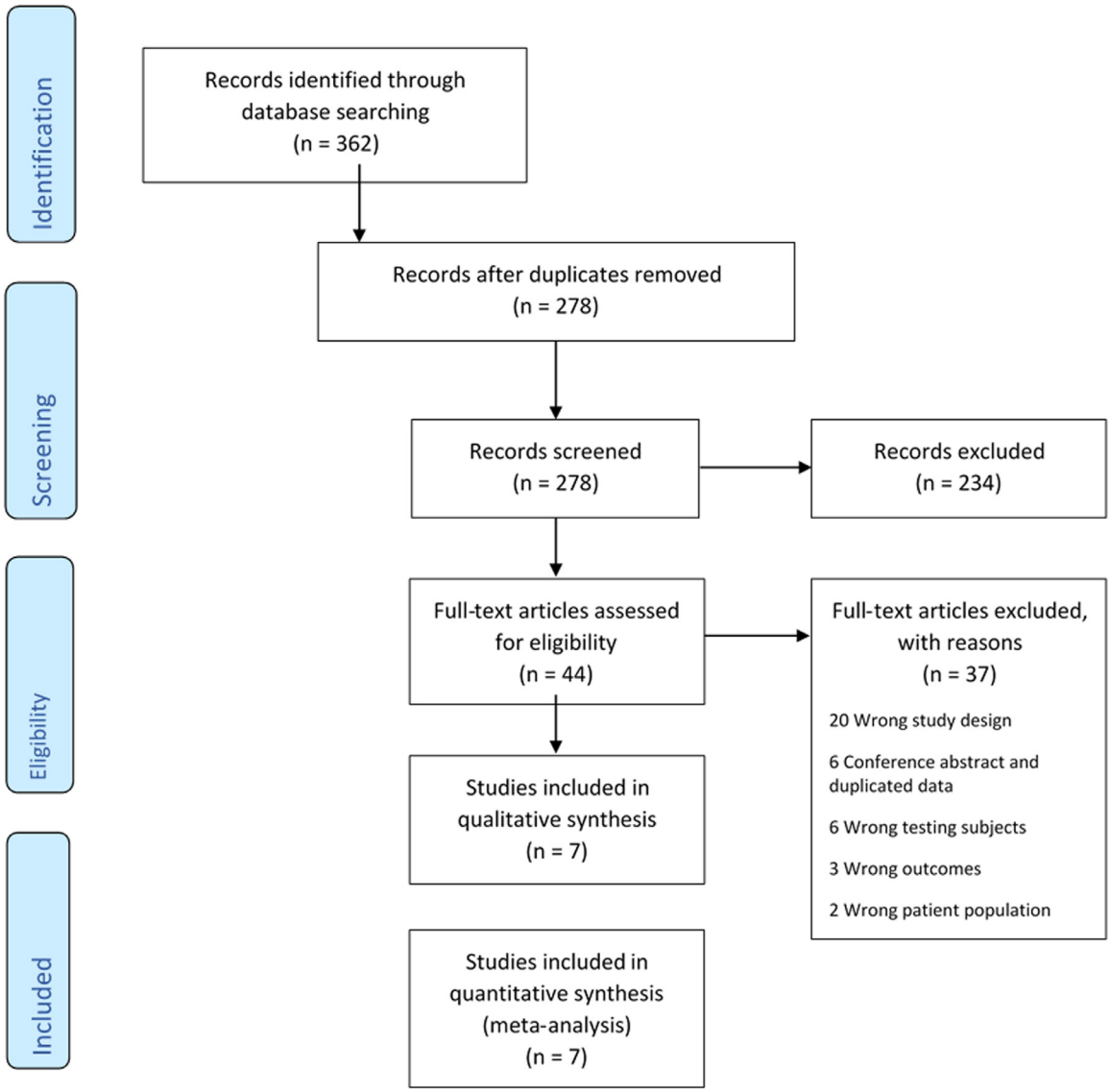

Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2009 flow diagram, mapping out the number of records identified, included and excluded, and the reasons for exclusions.

handling, "measurement of outcomes," and "selection of the reported result" criteria.

However, some bias sources persisted unresolved. Firstly, and mostly due to their observational nature, these studies had some difficulty on guaranteeing an unbiased application of the intended intervention and of a classification of those interventions.

Secondly, and most critical in differentiating the quality of these studies, was their performance on addressing confounding factors. Pasternak and Daneman, being cohort studies, in spite of applying extensive adjustment techniques and using an active comparator (amoxicillin use) were considered to have an overall moderate risk of bias in this domain. Lee 2015, having used a case-control design with propensity score matching, and having considered a broader range of covariates than the 2 studies previously mentioned, was considered to have a lower confounding risk. Lee 2018 and Maumus-Robert, having used within-subject designs (case-crossover and case-time-control, respectively), and adding to that control matching, were more likely the studies that better mitigated this risk, yet, still considered to have a moderate one.

Regarding Meng and Sommet, it was considered that, owing to the limitation of the results obtained from an adverse event reports database, no reliable control of confounding factors was achieved. Meng and Sommet were then classified as having a general "critical" and "serious" risk of bias, respectively.

The Grading of Recommendations, Assessment, and Evaluation confidence in all the main pooled estimates was considered to be very low (Table 4).

Table 1. General Characteristics of the Included Studies

Study (1st Author)/ Year	Study Design	Population Location; Study N[#]	Case[‡‡] Group (N)[**]	Control Group[§§] (N)[††]	Follow-up (Years)/ Setting	Age (Years)/ Male%	FLQ Exposure Assessment (and Dose and Duration)[‖]	Comparator/ Reference Category	Outcomes Evaluated	Outcomes Assessment	Risk Period Before Outcome Considered
DANEMAN 2015	Longitudinal inception cohort	Ontario, Canada; 1,744,360	657,950	1,086,410	Between 2 and 17; from 1997 to 2014	65−82/49%	Prescribed medications records[*] Cipro, nor, levo, moxi, oflo	AMX use or nontreatment	AA[‡]; Aortic rupture or AD	ICD-9 and ICD-10 codes	30 days
LEE 2015	Nested case-control	Taiwan; 741,652	1477	147,700	9.9 (mean); from 2000 to index date[†]	70.6 (mean)/ 72.8% (mean)	Reimbursement order of oral FLQ[§] Cipro, nor, levo, moxi, oflo, eno, lome, spar, gemi, peflo	Nontreatment	First occurrence of AA or AD requiring hospitalization	ICD-9 codes and use of advancing imaging studies	60 days[¶]
LEE 2018	Case-crossover and case-time-control	Taiwan; approx. 1,000,000	1213	1213 (matched)	From 2002 to 2011	70.58 ± 13.77/ 72.46%	Reimbursement order of oral FLQ[§] Cipro, nor, levo, moxi, oflo, eno, lome, spar, gemi, peflo	Period with no exposure to FLQ	AA or AD	ICD-9 codes and use of advancing imaging studies	60 days[¶]
PASTERNAK 2018	Cohort	Sweden; 2,195,755 (treatment episodes)	360,088 (FLQ treatment episodes, propensity score matched)	360,088 (AMX treatment episodes, propensity score matched)	52 ± 17 days (mean; FLQ group) and 55 ± 14 days (mean; AMX group); from 2006 to 2013	68 (mean)/45%	Prescribed medications records Cipro (78%), nor (20%), other F LQ (2%)	AMX use	First diagnosis of AA or AD	ICD-10 codes[†]	60 days[¶]
MAUMUS-ROBERT 2019	Case-crossover and case-time-control	France; 5946 (with AA or AD)	1545 patients with AA/ AD/AR exposed to FLQ or AMX	16,995 nonaortic disease patients exposed to FLQ or AMX	Up to 180 days before outcome; from 2010 to 2015	68.5 (mean))/70%	Out-hospital reimbursements Types of FLQ nonspecified	AMX use or nontreatment	Aortoiliac ruptured aneurysm or AD	ICD-10 codes and medical procedures	60 days[¶]
SOMMET 2018	Case/noncase (DAAER)	Worldwide (130 countries); 172,588 ICSRs with FLQ and 40,658 with AMX	121 AA or AD associated with FLQ or AMX ICSRs	213,246 nonaortic disease patients associated with FLQ or AMX ICSRs	No follow-up; setting from 1972 to 2017	≥50/no data	ICSRs (Only FLQ reported with outcome) Cipro, levo, moxi, oflo, gati, tosu	AMX use	ICSRs containing terms AA or AD	Preferred terms in the MedDRA	Nonapplicable
MENG 2019	Case/noncase (DAAER)	USA; 7,153,801 AERs	3721 AA/AD AERs FLQ and CFX related	Nonaortic disease patients associated with FLQ or CFX ICSRs nonreported	No follow-up; setting from 2004 to 2016	≥18/56% (AA or AD FLQ related)	AERs Cipro, levo, moxi	Cefuroxime use or nontreatment	AA or AD according with AER	Preferred terms in the MedDRA	Nonapplicable

AA, aortic aneurysm; AD, aortic dissection; AER, adverse event reports; AMX, amoxicillin; CFX, cefuroxime; DAAER, disproportionality analysis of adverse event reports; FLQ, fluoroquinolones; ICD, International Statistical Classification of Diseases and Related Health Problems; ICSRs, Individual Case Safety Reports; MedRA, Medical Dictionary for Regulatory Activities.

*With more than 99% concordance with pharmacy chart review.

[†]"Index date" meaning: outcome diagnosis, termination of health insurance coverage, death or end of study period.

[‡]Normal, complicated by rupture or dissection, or labelled has primary diagnosis.

[§]Doses for a minimum period of 3 days.

[‖]Only the prefixes of the FLQ used are presented, since practically all the FLQ end with "-floxacin."

[¶]Other periods in sensitivity analyses.

[#]Refers to the original pool of individuals, from which the cases and controls were retrieved, unless otherwise specified in the table cells.

[**]"Case" concept in accordance with the respective study design.

[††]"Control" concept in accordance with the respective study design.

[‡‡]"Exposed to FLQ group," in studies with cohort design.

[§§]"Nonexposed to FLQ group," in studies with cohort design.

Table 2. Outcome Adjustments, Per Study

Study (1st Author)/Year	Outcome Adjustments
DANEMAN 2015	Covariates adjustment: demographic factors (sex, income quintile), prior healthcare utilization (total hospital admissions, physician visits in prior year), several comorbidities prior or current; Amoxicillin comparator as confounding by indication control.
LEE 2015	Ninety-six covariates adjustment: demographics; intensity of healthcare utilization; cardiovascular comorbidities, risk factors for AA and AD, use of specific medications, several infectious diseases; Adjustment for individual confounders, by propensity score matching.
LEE 2018	Crossover design: adjustment for within-person time-invariant confounding; Control-crossover design: adjustment for exposure trend bias (case to control matching including covariates on demography, insurance premiums, comorbidities, healthcare utilization and use of medications); Adjustment to some T-VC: use of several medications and several types of infectious complications;
PASTERNAK 2018	Propensity score matching for 47 baseline factors control (demography, medical history, concomitant use of other medical drugs, measures of healthcare use); Amoxicillin comparator as confounding by indication control;
MAUMUS-ROBERT 2019	Case-crossover design: adjustment for within-person time-invariant confounding; Adjustment for exposure trend bias: 10 controls matched with cases on several medications (use of other antibiotics, corticosteroids, anticoagulant agents, antiplatelet agents, and antihypertensive drugs); Amoxicillin comparator as confounding by indication bias control (expressed has "[Ratio]"[1]).
SOMMET 2018	Adjusted for age, sex, year of report, continent of report, notifier type and number of drugs prescribed; Amoxicillin comparator as confounding by indication control.
MENG 2019[2]	No specific adjustments reported. Cefuroxime comparator as confounding by indication control.

AA, aortic aneurysm; AD, aortic dissection; AMX, amoxicillin; FLQ, fluoroquinolones; T-VC, time-varying confounders.
Table 2 notes:
[1]"Ratio" between a Case-time-control estimate for FLQ use and another for AMX use;
[2]regarding this study, the results presented were statiscally compiled, since they were reported only for individual FLQ.

Table 3. ROBINS-I Assessment of Risk of Bias, Per Study and ROBINS-I Area of Bias

Study/Overall Risk of Bias Per Outcome	FLQ Vs Control (AA OR AD/AR)	FLQ Vs Control (AD/AR)	FLQ Vs B-L (AA OR AD)	FLQ Vs B-L (AD/AR)
PASTERNAK 2018	Serious	Serious	Moderate	Moderate
DANEMAN 2015	Serious	Serious	Moderate	Moderate
LEE 2015	Serious	Serious	Moderate	Moderate
LEE 2018	Serious	Serious	Moderate	Moderate
MAUMUS 2019	Serious	Serious	Moderate	Moderate
SOMMET 2018	Critical	Critical	Serious	Serious
MENG 2019	Critical	Critical	Critical	Critical

Risk of AA/AD/AR

There was, compared with a nontreatment control, a statistically significant association between FLQ use and the incidence of AA/AD/AR (OR 2.26; 95%CI 1.93−2.65; $I^2 = 30\%$ [0−73]; 5 studies) (Fig. 2, Supplementary Table 5). For the risk of aortic complications (AD/AR only), there was also a statistically significant association (OR 2.76; 95%CI 2.32−3.27; $I^2 = 0\%$ [0−64]; 4 studies) (Fig. 2, Supplementary Table 5).

The risk of AA/AD/AR of fluroquinolones against beta-lactams as an active comparator yielded also a positive association, but with a smaller magnitude, both for risk of AA/AD (OR 1.56 95%CI 1.37−1.79; $I^2 = 0\%$ [0−53]; 5 studies) and AD/AR only (OR 1.88 95%CI 1.25−2.83; $I^2 = 4\%$ [0−97]; 3 studies) (Fig. 3, Supplementary Table 5).

The NNH for AA/AD/AR

The NNH for AA/AD/AR within 60 days after FLQ use was 612 (95%CI 468−829) treatment courses of FLQ, for the nontreatment comparison. For the beta-lactam comparison the NNH for AA/AD was 2554 (95%CI 1811−3865). We have used the respective effect estimates from our meta-analysis (OR = 2.26 and OR = 1.56) and the respective control event

Table 4. Summary of Findings According to the GRADE Criteria, Depicting the Primary and the Secondary Outcomes

Outcomes	Relative Effect (95%CI)	№ of Participants (Studies)	Certainty of the Evidence (GRADE)	Comments
Aortic aneurysm or dissection/rupture (FLQ vs Control)	**OR 2.26** (1.93−2.65)	660,725 cases 1,239,360 controls (5 observational studies)[§]	⊕○○○ VERY LOW*,†	Fluoroquinolones may increase the risk of aortic aneurysm or dissection/rupture but the evidence is very uncertain.
Aortic aneurysm or dissection (FLQ vs B-L)	**OR 1.56** (1.37−1.79)	1,194,433 cases 1,491,193 controls (5 observational studies)[§,‖,¶]	⊕○○○ VERY LOW*,†,‡	Fluoroquinolones may increase risk of aortic aneurysm or dissection but the evidence is very uncertain.
Aortic dissection/ rupture (FLQ vs Control)	**OR 2.76** (2.32−3.27)	663,234 cases 1,238,147 controls (4 observational studies)[§]	⊕○○○ VERY LOW*,†	Fluoroquinolones may increase the risk of aortic dissection/rupture but the evidence is very uncertain.
Aortic dissection/ rupture (FLQ vs B-L)	**OR 1.88** (1.25−2.83)	363,895 cases 364,125 controls (3 observational studies)[§,‖]	⊕○○○ VERY LOW*,†,‡	Fluoroquinolones may increase the risk of aortic dissection/rupture but the evidence is very uncertain.

*Residual confounding.
†Retrospective observational studies.
‡Broad confidence intervals.
§Includes Meng (one AER counted as 1 subject).
‖Includes Pasternak (Each "treatment episode" assumed conservatively to correspond to 1 subject).
¶Includes Sommet (one AER counted as 1 subject).

rates were obtained from the population-based studies by Daneman et al (0.13%) and Pasternak et al (0.07%, from the group exposed to amoxicillin) (Fig. 4).

Sensitivity Analyses

Sensitivity analyses excluding Meng (for having a "critical risk" of general bias and being the single study reporting only unadjusted risk estimates) showed practically the same results (Supplementary Figures 2 and 3).

Analyses were also performed grouping studies with the same design, still comparing between the same types of intervention groups and outcomes, to assess potential differences of results between designs (Supplementary Figures 4−7). Among studies with the same design, all associations of FLQ use with the outcomes remained significantly positive. The analysis with exclusion of studies with a disproportionately high statistical weight (the study by Daneman et al) has yielded identical results as without such exclusion (Supplementary Figures 8 and 9).

Although planned, a publication bias analysis was not performed, since only 7 studies were included in our review.

DISCUSSION

The main finding of this systematic review is that the best and most up-to-date observational evidence available supports the hypothesis that FLQ use is positively associated, within the following 60 days after use, with aortic disease, namely AD/AR, and also AA in a slightly lesser extent.

Regarding the diagnosis and register of the outcomes on medical databases, most studies in this review seem to have tackled well the issues concerning it (Table 1), having used broad and accurate disease classification codes, oftentimes complemented with records of diagnostic imaging evidence. The exposure assessment — since all the studies are retrospective and observational — was performed indirectly (Table 1), but a high concordance between records and effective use can to a certain extent be assumed.[35]

Control for risk factors was achieved with variable success across studies (Table 2), yet some important ones were not

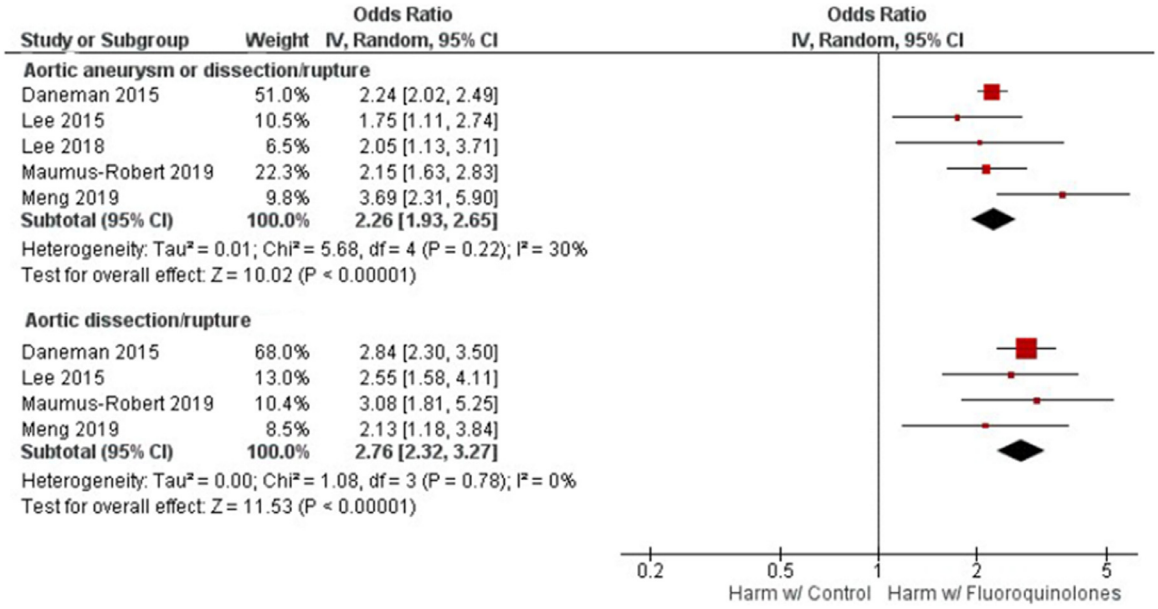

Figure 2. Upper plot: Forest plot comparing risk of aortic aneurysm, aortic dissection or aortic rupture between fluoroquinolones users and nontreatment controls. Lower Plot: Forest plot comparing risk of aortic dissection or rupture between fluoroquinolones users and nontreatment controls. For both outcomes, a significantly higher harm effect is seen in fluoroquinolone users, in comparison with nontreatment controls.

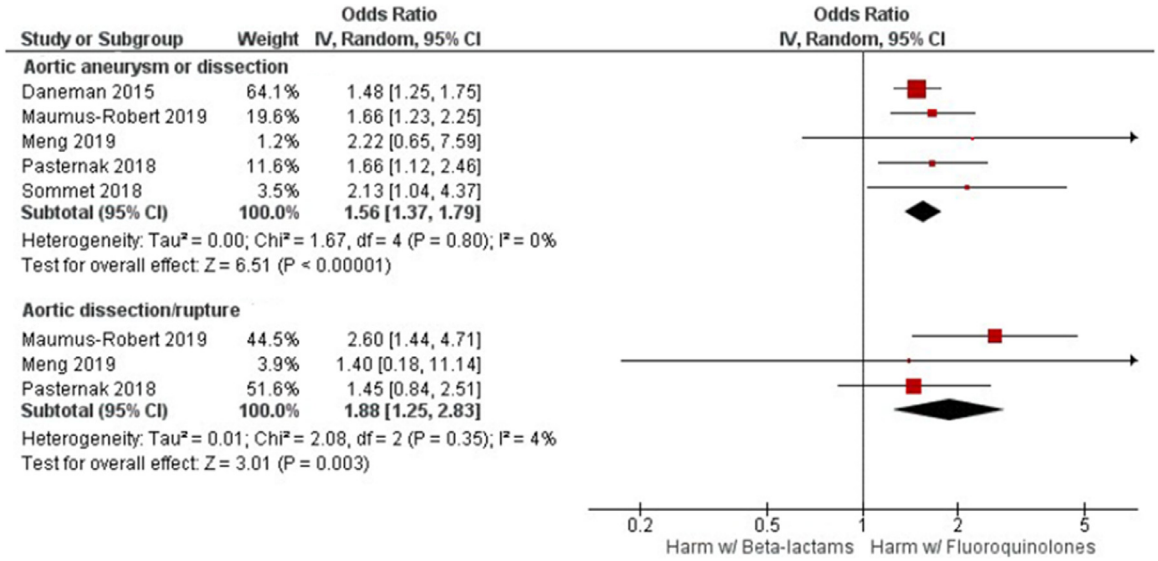

Figure 3. Upper plot: Forest plot comparing risk of aortic aneurysm or dissection between fluoroquinolones users vs beta-lactam users. Lower plot: Forest plot comparing risk of aortic dissection or rupture between fluoroquinolones users vs beta-lactam users. For both outcomes, a significantly higher harm effect is seen in fluoroquinolone users, in comparison with beta-lactam users.

accounted by most studies with between-subject designs, namely tobacco use and congenital collagen disorders, and none accounted for family history of aortic disease. However, probably the most challenging confounding factor remains being the "infection state". No study included only patients presumably without an ongoing infectious process at the time of the intervention. In addition, and although it is known mycotic aneurysms represent only around 0.7–1% of all surgically treated AAs,[36] the primary studies have not indicated the prevalence of this entity across its sample, while generally presenting a sample with a higher prevalence of comorbidities that increase its risk (such as cardiovascular and immunosuppressive disorders).[37] Therefore, the risks of protopathic bias — symptoms preceding diagnosis of outcome and leading to intervention — and indication bias from infections to which FLQ are indicated but that can also extend to originate mycotic aneurysms cannot be excluded.

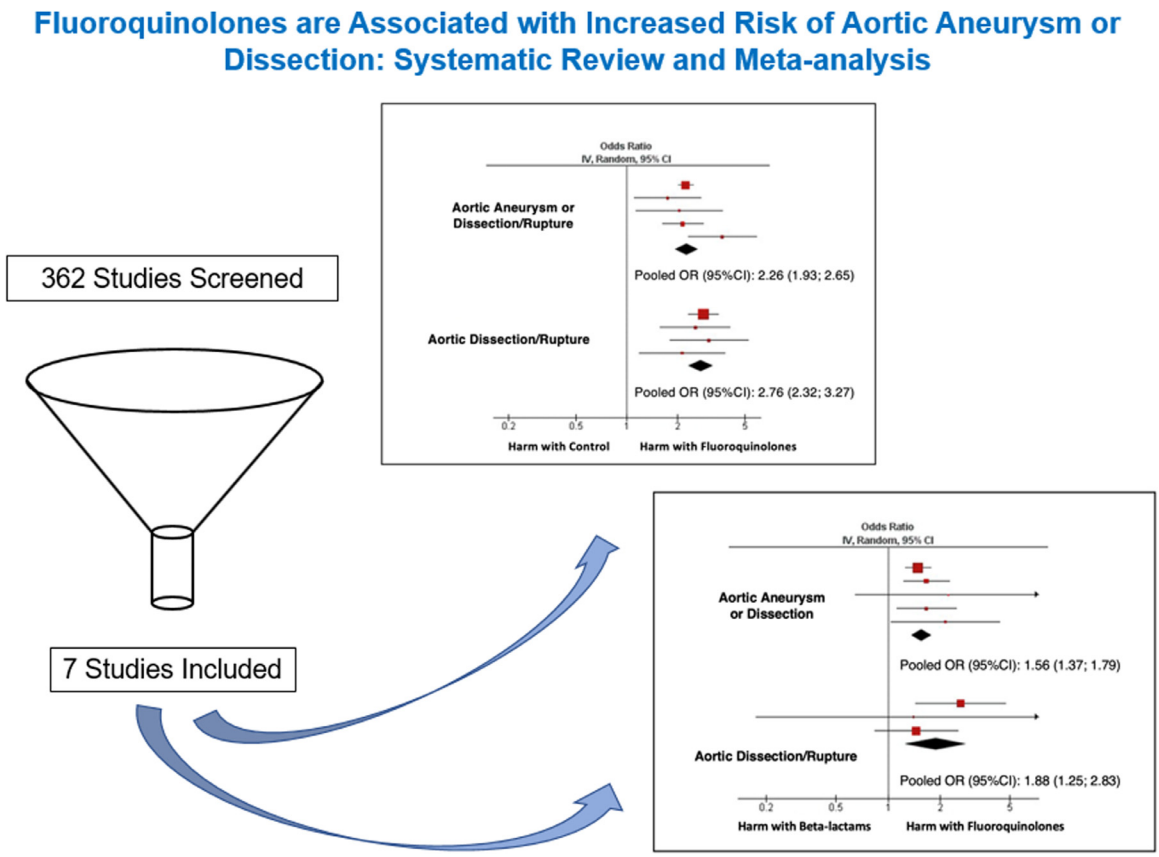

Figure 4. (Graphical abstract) - We sought out to perform a new and updated meta-analysis to assess for an harm effect of fluoroquinolone use on aortic disease. Seven studies were included, and pooling of risk estimates per comparison used in the primary studies was performed. A statistically significant harm effect was found for all assessed outcomes of aortic disease, yet relatively attenuated for the "beta-lactam" comparator pooling. This likely represents an effective control for the "infectious process" variable, a plausibly important confounding factor in this risk association.

Additionally, the risks from detection bias - imaging done after acute infection, incidentally finding the outcome - or potential co-interventions, of concomitant medication in general or additional antibiotics received upon intervention, although respectively addressed through improved diagnostic certainty across studies (imaging for outcome ascertainment, or consideration of primary diagnosis only, or emergencies admissions only, or the outcomes of AD/AR themselves — all persistently reporting a FLQ harm effect) and sample balancing on use of other drugs (Table 2), or exclusion of multiple antibiotic administration on intervention (Pasternak), could also not be fully eliminated.

Still, 5 out of 7 of the included studies were able to incorporate a group with an active comparator, which plausibly should mitigate, at least partially, the aforementioned risk of indication bias, and others, even if the indications for FLQ and beta-lactams do not wholly overlap, and a protective effect of the latter on aortic disease cannot be entirely ruled out (future studies are recommended). Also, the studies using either a within-subjects crossover design, or a disease (even infectious) propensity score matching should have positively contributed to this confounding mitigation, and for other residual one.

Regarding risk differences between AA and AD/AR, our review has found mixed results: Daneman, Pasternak and Meng showed less risk for AD/AR comparing with AA, while Lee 2015 and Maumus-Robert showed increasing risk for AD/AR comparing with AA. It is therefore plausible that this mixture could be explained by differences in participants comorbidity profiles and by variable control methodology across studies.

Considering previous findings, evidence from in vitro studies and studies in animals has been pointing to an adverse effect of FLQ in collagenous structures, being in its synthesis[8] or degradation, through the upregulation of matrix metalloproteinases.[9] Epidemiological evidence supporting this process also has been accumulating,[38] to which the observational studies included in this review were added, as well as previous reviews comprising them.[39–43] It should be referred that the latter have also reported an harm effect of FLQ. Nevertheless, our review has included 2 more studies and a larger sample size than the most recent one, a more exhaustive risk of bias evaluation (through ROBINS-I), separate pooling on types of comparator used, planed sensitivity analyses grouping studies with same design, exclusion of studies with higher risk of bias and

excluding studies with a disproportionately high statistical weight, and several tables presenting a more in-depth view of the characteristics of the primary studies and risk of bias assessment. A compared synthesis of these reviews is presented on Supplementary Table 4.

Limitations on this review should come mainly from limitations of the underlying data. Only observational studies were found, which inherently are more prone to residual confounding and issues concerning the accurate assessment of exposure and outcomes, which was done indirectly. More detailed effect analyses were not able to be performed, due to general lack or insufficiency of individual level data, for example on dose of the intervention, on its administration route (only assessed by Meng), on its duration of use (only assessed by Lee 2015 and 2018) and on the types of FLQ used (only assessed by Meng, Sommet, and Daneman). Additionally, the outcome division generally adopted by the studies - between AA of all types and locations and AD - does not reflect the most accurate pathophysiological division: going already beyond the fact that aortic thoracic aneurysms, abdominal AA, AD, and AA rupture are all distinct disease entities, abdominal AAs are mainly caused by atherosclerotic degeneration, while thoracic AAs and AD are mainly caused by collagen or inflammatory disorders. Therefore, and however plausible that FLQ can have a negative influence on each of these disease processes, this chosen outcome division can have implications on the accurate assessment of the FLQ effect.[44] In addition, and for the reasons explained above, some sources of bias remain fully unresolved, namely the "infectious process" confounding factor and detection bias.

Although our meta-analysis has pooled studies with a diversity of methodological designs, no significant differences in the results were found when grouping studies with the same design and performing comparisons (Supplementary Figures 4–7); furthermore, the statistical heterogeneity was generally very low (Figs. 2 and 3), even more when Meng - the 1 study considered to have a "critical" risk of bias — was excluded (Supplementary Figure 2 and 3).

It remains to be answered whether this risk association is a "FLQ class" effect. Previous experimental studies have obtained similar risk associations with different FLQ[8]; however, observational studies have generally not performed specific analyses directed at this issue, or have but with limited validity (Meng and Sommet).

Also unknown is how long it takes for FLQ to exert its effects on aortic disease. Previous studies, on other collagen effects of FLQ, have served as basis for an estimation of what interval of hazard period should be considered when studying aortic disease: for tendinopathies, a highest hazard period of 15-30 days has been determined[38]; for retinal detachment, 10 days.[45] According to this, the studies included in our review have generally found significantly reduced risk associations when considering a hazard period beyond 60 days. However, within these 60 days, it seems that this risk effect might not be equally distributed: both Pasternak and Lee 2018 have found a more pronounced effect on the first 10 days after the beginning of the intervention (not reported in this review); in addition, a second "risk peak" seems plausible, between 30 and 50 days after the beginning of the intervention. Also, by looking at Maumus-Robert, we can see a difference in the risk effect between the "30-day hazard period" estimate and the "60-day hazard period" one, being the later slightly higher, a difference consistent for both the AA/AD/AR and the AD/AR outcomes. All this could point to a possible bi-modal distribution of the risk effect. If the first "peak" can presumably be explained by the effect of an ongoing exposure (FLQ treatment courses last usually 7–14 days), for the second one an explanation seems more challenging. However, since for both hypothetical peaks the influence of an ongoing or recovery disease status can still be present, further studies are recommended to address this question.

More studies should also be conducted on various doses, duration of use and administration route of FLQ.

CONCLUSION

Our systematic review with meta-analysis showed that FLQ use was associated with aortic disease, for both AA/AD and AD/AR, even in comparison with groups using beta-lactams antibiotics, which addresses the "infectious process" confounding factor. Therefore, in acknowledging this potential risk it is recommended that physicians should be conservative in the prescription of these FLQ, particularly in patients potentially susceptible to aortic disease, or opt for safer antibiotic alternatives. More studies are needed in order to clarify the risk mechanism involved in this association.

SUPPLEMENTARY MATERIAL

Scanning this QR code will take you to the article title page to access supplementary information.

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