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SYSTEMATIC REVIEW ARTICLE

Fluoroquinolones and the Risk of Aortic Aneurysm or Aortic Dissection: A Systematic Review and Meta-Analysis

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Abstract: ***Objectives*:** We performed a systematic review and meta-analysis to explore the risk of an aortic aneurysm or aortic dissection following fluoroquinolone administration.

***Methods*:** PubMed, Cochrane library, ClinicalTrials.gov, Embase and Google Scholar were systematically reviewed for controlled studies including adult patients exposed to fluoroquinolones with a primary outcome of aortic aneurysm or aortic dissection.

***Results*:** The meta-analysis was conducted by pooling the effect estimates of four controlled observational studies (one case-control, one case-crossover and two cohort studies). Fluoroquinolone administration more than doubled the risk to develop aortic aneurysm or aortic dissection within 60 days following fluoroquinolone exposure (adjusted Relative Risk [RR] (95% confidence interval [CI]) = 2.14 (1.93 - 2.36); I2 = 15.8%). The quality of the finding was rated as moderate.

The risk increase for aortic aneurysm alone was found to be significant (adjusted RR (95% CI) = 2.23 (2.01 - 2.45); I2 = 0%) while the risk increase for aortic dissection alone was not found to be significant (adjusted RR = 1.88 (0.11 - 3.65); I2 = 74%).

In subgroup analysis, the risk increase for aortic aneurysm or aortic dissection appeared to be higher in females compared to males (RR = 1.87 (1.24 - 2.51); I2 = 0% *versus* RR = 1.58 (1.25 - 1.92); I2 = 0%, respectively) and higher in older patients compared to younger patients (RR = 1.72 (1.37 - 2.07); I2 = 0% versus RR = 1.47 (0.91 - 2.04); I2 = 0%, respectively).

Subgroup analysis of two studies which measured the duration-response analysis found that as the duration of fluoroquinolone therapy increased from 3 to 14 days to greater than 14 days, there was an increased risk of aortic aneurysm or dissection.

***Conclusion*:** The findings of this meta-analysis confirm the positive association between fluoroquinolones and the development of aortic aneurysm or dissection. The data tend to show that this association may be majorly driven by aortic aneurysm. Additionally, some risk factors appear to prevail including prolonged fluoroquinolone treatment and older age.

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1. INTRODUCTION

The fluoroquinolones class of antibiotics (*e.g.*, ciprofloxacin, levofloxacin, moxifloxacin) has been used to treat a broad range of infections ranging from urinary tract infections to respiratory infections. Fluoroquinolones were found to be the third most prescribed class of antibiotics in the United States [1]. Several observational trials have shown an association between the use of fluoroquinolones and the development of collagen-related adverse events including tendon rupture, retinal detachment, aortic aneurysm or aortic dissection [2-4]. This was thought to be linked, in part to fluoroquinolone-related oxidative stress resulting in degenerative changes to the extracellular matrix components [5, 6].

Aortic aneurysm and aortic dissection are rare events. The reported incidence for aortic dissection is 2.9/100,000 case/patient/year [7]. The prevalence of abdominal aortic aneurysms is reported to be up to 8% in men older than 65 years [8]. Despite their low occurrence, aortic aneurysm and aortic dissection count as the most severe collagen-related adverse events because they can lead to life-threatening conditions like rupture of an aortic aneurysm or acute aortic dissection [9].

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Aortic aneurysm is defined as a permanent localized dilation of the aorta resulting in at least a 50% increase in the aortic diameter [10]. Most patients are asymptomatic until they experience a complication (aortic aneurysm rupture). Unless treated immediately, aortic aneurysm rupture leads to massive internal bleeding and results, in shock and death [11]. Aortic aneurysm rupture is reportedly fatal in 50 to 80% of the cases [9].

Aortic dissection is the development of a tear in the aortic intima that creates a false lumen through the aortic media. Acute aortic dissection has an early (<24 h) reported a mortality rate that reaches 50% when associated with delayed or missed diagnosis [12]. Acute Stanford type A (involving of the ascending aorta) aortic dissection has a reported higher mortality rate than acute Stanford type B (not involving the ascending aorta) [9].

Given the high risk of a fatal outcome from aortic aneurysm or dissection and the widespread use of fluoroquinolones, exploring the association between fluoroquinolones and aortic aneurysm or dissection is of particular clinical interest. A systematic review and meta-analysis paper studying this association has been published in 2017. It was performed on a small number of observational studies (n = 2) and concluded a small but significant increase in the risk aortic aneurysm and aortic dissection following exposure to fluoroquinolones [3]. Since then, newer studies were published on the subject. Hence, conducting a new systematic review and meta-analysis will allow us to strengthen the evidence of the suspected risk between fluoroquinolones and the development of aortic aneurysm or dissection and measure this risk for each event alone. Furthermore, performing subgroup analysis with additional published data may enable us to characterize better the association in terms of timing and risk factors. This is of great importance to understand the underlying pathophysiology, improve clinical judgment during fluoroquinolone prescription and direct future studies.

2. OBJECTIVES

The primary objective of this systematic review is to confirm the positive association between fluoroquinolone antibiotics and the development of aortic aneurysm or aortic dissection and determine for each outcome alone (aortic aneurysm and aortic dissection) the magnitude of its association with fluoroquinolone exposure. The secondary objective is to determine other parameters that may potentiate this association (age, sex, timing and duration of drug exposure, *etc*.).

3. MATERIALS AND METHOD

3.1. Ethical Approval

Ethical approval was not obtained because the study is a systematic review and meta-analysis of published studies.

3.2. Registration

This systematic review and meta-analysis study was carried out according to a protocol that was registered on PROSPERO under the reference number CRD42018096486 (cf. Appendix No. 1). Reporting and writing this systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13].

3.3. Selection Mode

The selected publications were controlled studies performed in the adult population treated by any of the following fluoroquinolones: besifloxacin, ciprofloxacin, enoxacin, gatifloxacin, levofloxacin, moxifloxacin, norfloxacin, ofloxacin or pefloxacin. The basic structure of the fluoroquinolone antibiotics is provided in Fig. (**1**). The control group consisted of patients not treated with fluoroquinolones: either taking other antibiotics or not taking any antibiotic. The primary outcome of eligible studies was any of the following events: aortic aneurysm (including thoracic or abdominal aortic aneurysm rupture) or aortic dissection (including acute aortic dissection). Systematic review articles were excluded.

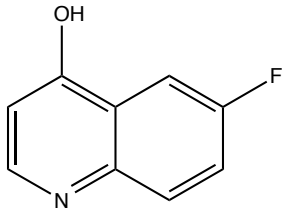

Fig. (1). Basic fluoroquinolone structure.

3.4. Search Strategy

The following databases were systematically reviewed from inception through 23-Nov-2018: PubMed, Cochrane library, ClinicalTrials.gov, Embase and Google Scholar. The keywords used in the search strategy were: fluoroquinolone (1), besifloxacin (2), ciprofloxacin (3), enoxacin (4), gatifloxacin (5), levofloxacin (6), moxifloxacin (7), norfloxacin (8), ofloxacin (9), pefloxacin (11), aortic aneurysm (12), aortic dissection (13). The following keywords combination was used in each database: ((1) OR (2) OR (3) OR (4) OR (5) OR (6) OR (7) OR (8) OR (9) OR (10) OR (11)) AND ((12) OR (13)). There was no language restriction. All articles published before 1995 were not considered for this review.

3.5. Articles Review and Selection

Articles review and selection were performed independently by three reviewers (PR, ME and AV). All the articles (titles and abstract or full text if abstract was not available) found in the databases using the search strategy previously described were screened in order to preselect the studies that met the eligibility criteria.

3.6. Data Extraction

The three reviewers (PR, ME and AV) independently extracted the data from the selected studies using a spreadsheet template that included information about the study design, exposure, outcomes, participants' characteristics, results and risk of bias. The three extraction sheets were compared for differences. Discrepancies were resolved after checking the source document and following a discussion between the three reviewers [14].

3.7. Risk of Bias in Individual Studies

The risk of bias was assessed using the Modified Newcastle Ottawa Quality Assessment Scale for case-control studies and cohort studies.

3.8. Data Analysis

Qualitative and quantitative analyses were conducted. A meta-analysis was planned when at least two studies could be pooled together. The selected studies were assessed for clinical homogeneity by comparing the population characteristics, the interventional groups, the control groups, and the outcomes. They were evaluated afterward for statistical heterogeneity calculating the I2 index.

The fixed-effect model was used for conducting meta-analysis when statistical heterogeneity was low (I2 < 50%); the random-effects model was used when statistical heterogeneity was moderate (I2 between 50% and 75%) or high (I2 > 75%). All meta-analyses were conducted in a spreadsheet using the method developed by Neyeloff and colleagues [15].

It was assumed that Relative Risk (RR) and Hazard Ratio (HR) were similar because of the low incidence rates of aortic dissection and aortic aneurysm. Consequently, the pooled results are reported as RR. Finally, sensitivity analysis and subgroup analysis were performed.

3.9. Confidence in Cumulative Evidence

The quality of the evidence was assessed using the Cochrane GRADE criteria [16].

4. RESULTS

4.1. Study Selection

The electronic database's search yielded 88 studies. After excluding duplicates and studies not meeting eligibility criteria, four studies were selected for qualitative and quantitative analysis. The flow diagram describing the study selection process is presented in Fig. (**2**).

4.2. Study Characteristics

The main characteristics of the selected studies (n = 4) are presented in Table **1**. All the selected studies were observational: one case-control, one case-crossover, and two cohort studies. No randomized controlled trials were found to meet the eligibility criteria.

All the selected studies mentioned the risk of aortic aneurysm or dissection in fluoroquinolone users in their primary objective. Daneman's population-based longitudinal cohort study in Ontario, Canada aimed to evaluate the fluoroquinolone-associated risk of collagen adverse events (tendon rupture, aortic aneurysm diagnosed in a hospital or emergency department or retinal detachment) [17]. Pasternak's nationwide historical cohort study in Sweden and Lee's nested-case-control and case-crossover studies in Taiwan aimed to assess the fluoroquinolone-associated risk of aortic aneurysm or aortic dissection [18-20].

All four studies included mainly elderly patients. The mean age at inclusion was 65 years for Daneman's cohort, 68 for Pasternak's cohort, 71 for Lee's case-control study and 71 for Lee's case-crossover study.

4.3. Exposure

Exposure to fluoroquinolones was defined using prescription data. Current exposure to fluoroquinolone was defined as up to 30 days following antibiotic course in the study of Daneman *et al*. It was defined as up to 60 days following antibiotic course in the three other studies: Pasternak *et al*. (n = 1) and Lee *et al*. (n = 2).

Two studies (Daneman *et al*. and Pasternak *et al*.) reported the most commonly prescribed fluoroquinolones. The prescription patterns were similar in the two studies with ciprofloxacin being the most prescribed fluoroquinolone followed by norfloxacin.

4.4. Outcomes

In Pasternak's cohort, Lee's case-control and Lee's case-crossover studies, the primary outcome was defined as aortic aneurysm or aortic dissection. However, in Daneman's cohort, only aortic aneurysm was mentioned as the primary endpoint. In all the selected studies, the primary outcome was measured through the identification of International Classification of Disease (ICD) codes pertaining to aortic aneurysm or aortic dissection in patients' databases.

4.5. Risk of Bias for Individual Studies

The risk of bias for individual studies was found to be small for case-control and cohort studies. The scores for the risk of bias are presented in the last three columns of Table **1**.

4.6. Risk for Aortic Aneurysm or Aortic Dissection

In the fixed-effect meta-analysis of the four selected studies, adults currently exposed to fluoroquinolone were found to have a significantly higher risk to develop aortic aneurysm or aortic dissection compared to unexposed adults (adjusted RR (95% confidence interval [CI]) = 2.14 (1.93 - 2.36); I2 = 15.8%) Fig. (**3**).

Three studies reported the risk for aortic aneurysm alone (Pasternak *et al*., Daneman *et al*. and Lee's case-control study). In the fixed-effect meta-analysis of the three studies, the risk of aortic aneurysm alone in current fluoroquinolone users versus nonusers was also significantly increased (adjusted RR (95% CI) = 2.23 (2.01 - 2.45); I2 = 0%).

Two studies reported the risk for aortic dissection alone (Pasternak *et al*. and Lee's case-control study). Given the moderate statistical heterogeneity (I2 = 75%), the random-effects model was used to calculate the risk of aortic dissection alone. This risk was also found to be higher in current fluoroquinolone users versus nonusers, but it was not statistically significant (adjusted RR = 1.88 (0.11 - 3.66); I2 = 75%).

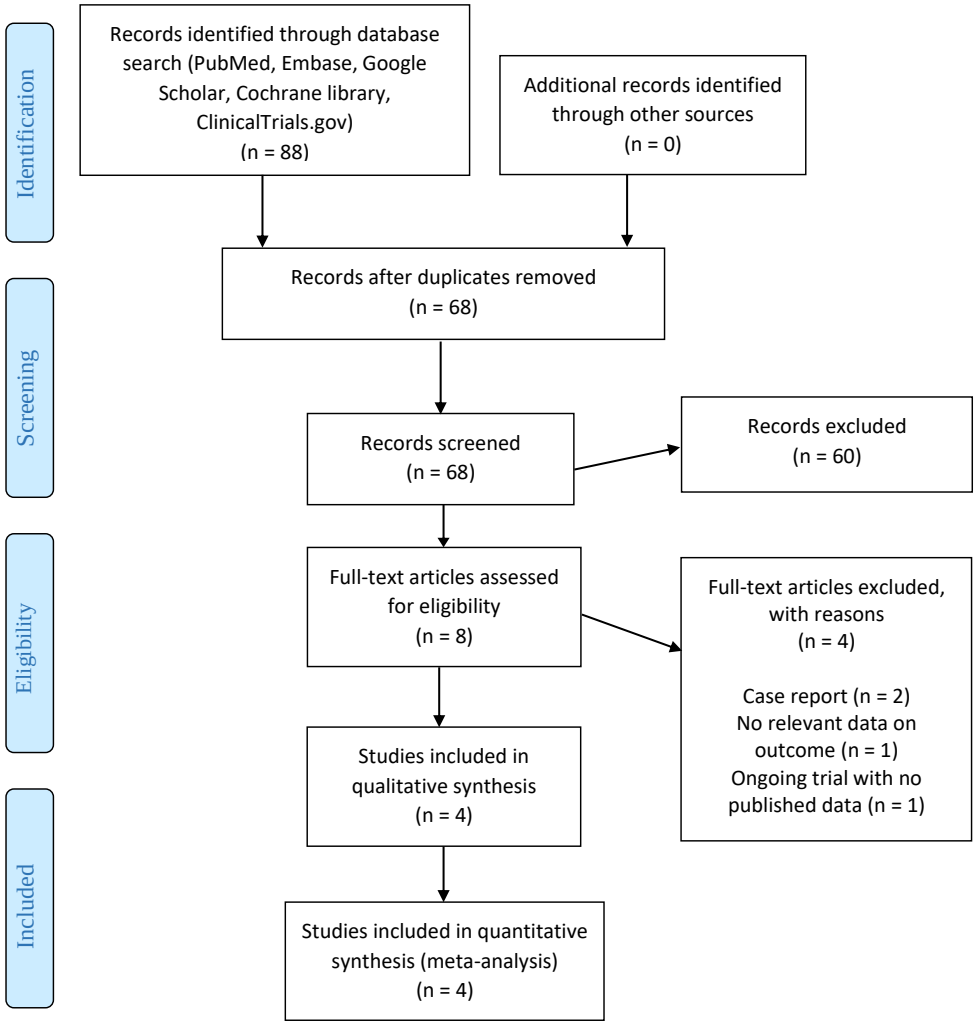

Fig. (2). Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 flow diagram.

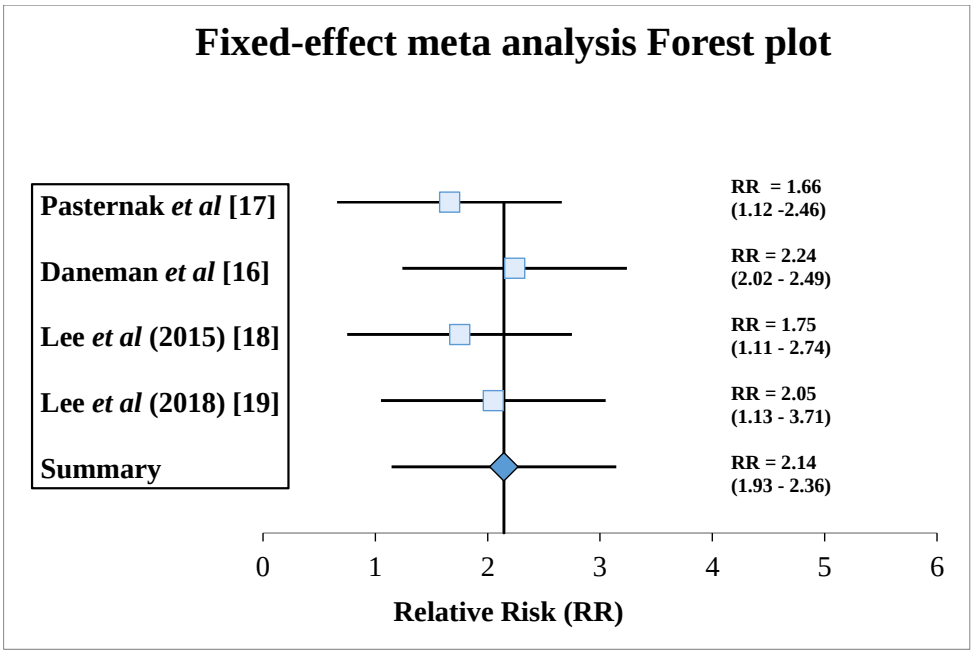

Fig. (3). Fixed-effects meta-analysis of fluoroquinolone current use and the risk of aortic aneurysm or aortic dissection.

Table 1. Design, characteristics, primary outcome and effect size of selected studies.

Study Authors (Year of Publication)	Study Design	Study Period	Study Location	Follow-up Duration	Inclusion Criteria	Intervention	Current FQ Exposure	Control	Age (mean)	Males (%)	Sample Size	Primary Outcome	ES for AA or AD	ES for AA	ES for AD	Risk of Bias for Individual Study (Modified Newcastle Ottawa Quality Assessment Scale)#		
																Selection	Comparability	Outcome
Pasternak *et al.* (2018) [18]	PSM cohort study with active comparator	07/2006 to 12/2013	Sweden	120 days	≥ 50 years	FQ	In 60 days prior to the event	Amoxicillin	68	45%	720 176	AA or AD	PSM HR (95% CI) = 1.66 (1.12 to 2.46)	PSM HR (95% CI) = 1.90 (1.22 to 2.96)	PSM HR (95% CI) = 0.93 (0.38 - 2.29)	****	**	***
Daneman *et al.* (2015) [16]	Population-based longitudinal cohort study	03/1997 to 03/2014	Ontario, Canada	Min 2 years Max 17 years	Turning 65	Ciprofloxacin, norfloxacin, levofloxacin, moxifloxacin, ofloxacin	In 30 days prior to the event	Unexposed to FQ	65	49%	1 744 360	AA	Adjusted HR (95% CI) = 2.24 (2.02 - 2.49)	Adjusted HR (95% CI) = 2.24 (2.02 - 2.49)	NR	****	**	***
Lee *et al.* (2015) [19]	Nested case-control study	01/2000 to 12/2011	Taiwan	Mean duration = 3613.3days	Adults	Ciprofloxacin, levofloxacin, ofloxacin, sparfloxacin, norfloxacin, lomefloxacin, moxifloxacin, gemifloxacin, enoxacin, pefloxacin	In 60 days prior to the event	Controls = patients not hospitalized for aortic aneurysm or dissection	71	73%	149 177	AA or AD	Current use: PSM RR (95% CI) = 1.75 (1.11-2.74)	PSA RR (95% CI) = 2.36 (1.66 - 3.36)	PSA RR (95% CI) = 2.55 (1.58 - 4.11)	****	**	**
Lee *et al.* (2018) [20]	Case crossover study	01/2000 to 12/2011	Taiwan	300 days	Adults	Ciprofloxacin, levofloxacin, ofloxacin, sparfloxacin, norfloxacin, lomefloxacin, moxifloxacin, gemifloxacin, enoxacin, pefloxacin	In 60 days prior to the event	Controls = participants act as their own control during the referent period (60 to 180 days before the event)	71	72%	1213	AA or AD	Adjusted OR (95% CI) = 2.05 (1.13 - 3.71)	NR	NR	NA	NA	NA

= the higher the number of stars the lower the risk of bias, each study can be allocated a total of 9 stars, AA = Aortic Aneurysm, AD = Aortic Dissection, CI = Confidence Interval, ES = Effect Size, FQ = Fluoroquinolone, HR = Hazard Ratio, NA = Not Applicable, NR = Not Reported, RR = Relative Risk, PSA = Propensity Score Adjusted, PSM = Propensity Score Match

4.7. Sensitivity Analysis

On the one hand, sensitivity analyses were performed by using the reported crude effect size results and on the other hand by excluding each study of the effect summary calculations. In the different sensitivity analyses, the results were similar in pattern to those found in the initial analyses presented above.

4.8. Subgroups Analysis and Duration-Response Analysis

Two studies (Pasternak *et al*. and Lee's case-control) reported the risk of aortic aneurysm or dissection in current fluoroquinolones users versus nonusers for the female and the male subgroups. The fixed-effect meta-analysis for each subgroup was similar in pattern to the results in the whole population, with females showing a more pronounced risk to develop aortic aneurysm or dissection under current fluoroquinolone exposure than males (RR = 1.87 (1.24 - 2.51); I2 = 0% for females versus RR = 1.58 (1.25 - 1.92); I2 = 0% for males).

The same two studies reported the effect size for the subgroup of older patients (aged ≥ 65 according to Pasternak *et al*.; aged ≥ 70 according to Lee *et al*.) and the subgroup of younger patients (aged < 65 according to Pasternak; aged < 70 according to Lee *et al*.). In the fixed-effect meta-analysis, the risk increase of aortic aneurysm or dissection under current fluoroquinolone exposure was more considerable in older patients than in younger patients (RR = 1.72 (1.37 - 2.07); I2 = 0% for older patients versus RR = 1.47 (0.91 - 2.04); I2 = 0% for younger patients).

Lee's case-control and Lee's case-crossover studies performed duration-response analysis to explore the association between the duration of fluoroquinolone therapy and the risk of aortic aneurysm or dissection. In both studies, as the duration of fluoroquinolone therapy increased from 3 to 14 days to greater than 14 days, there was an increased risk of aortic aneurysm or dissection. In both studies, the reference group had a fluoroquinolone therapy shorter than three days. In the fixed-effect meta-analysis, the pooled RR for aortic aneurysm or dissection was 1.72 (1.07 - 2.38); I2 = 0% following a 3 to 14-day exposure to fluoroquinolones while the pooled RR was 1.92 (0.85 - 2.99); I2 = 0% following an exposure longer than 14 days.

4.9. Confidence in Cumulative Evidence

Using the Cochrane GRADE criteria, the quality of evidence of the risk of aortic aneurysm or dissection in current fluoroquinolone users was rated as moderate. Similarly, the quality of evidence for the risk of aortic aneurysm alone was graded as moderate. However, the quality of evidence for the risk of aortic dissection alone was rated as low. This was mainly due to a small combined effect estimate (RR = 1.88 for dissection alone *versus* RR = 2.23 for aortic aneurysm alone).

5. DISCUSSION

This meta-analysis shows that the use of fluoroquinolones in adults more than doubles the risk of aortic aneurysm or aortic dissection within 60 days following fluoroquinolone exposure (adjusted RR (95% CI) = 2.14 (1.93 - 2.36); I2 = 15.8%). The quality of the evidence was rated as moderate for this outcome. This result was expected and strengthens the conclusion of the previous meta-analysis [3].

Proper to our study, is the characterization of the association in terms of individual outcomes and contributing factors. Indeed, our data suggest the association may be majorly driven by aortic aneurysm rather than by aortic dissection. The risk increase for aortic aneurysm alone was found to be significant (adjusted RR (95% CI) = 2.23 (2.01 - 2.45); I2 = 0%), while the risk increase for aortic dissection alone was not found to be significant (adjusted RR = 1.88 (0.11 - 3.66); I2 = 75%). The quality of the evidence was rated as moderate for the risk of aortic aneurysm alone, and it was rated as low for the risk of aortic dissection alone. The observed differences in the risk of individual outcomes are possibly linked to the fact that aortic aneurysm is more frequent than aortic dissection in the general population [7, 8]. Additionally, subgroup analysis shows that female and older patients are more susceptible to fluoroquinolone-associated aortic aneurysm or dissection than males and younger patients, respectively. Finally, according to the pooled duration-response analysis, as the duration of fluoroquinolone therapy increased from 3 to 14 days to greater than 14 days, there was an increased risk of aortic aneurysm or dissection.

Furthermore, three of the four selected studies clearly showed that the risk of aortic aneurysm or dissection was highest during the first 60 days after exposure to fluoroquinolones. Lee's case-control study showed an increased risk of aortic aneurysm or dissection during the first 60 days after fluoroquinolone exposure compared to the period between 61 to 365 days after exposure (PSM RR = 1.75 *versus* 1.19, respectively). Lee's case-crossover study showed higher odds of developing aortic aneurysm or dissection during the first 60 days after fluoroquinolone exposure than during the first 180 days (OR = 2.70 *versus* 1.28, respectively). Pasternak's cohort study showed no increased risk of aortic aneurysm or dissection associated with fluoroquinolone exposure in the period of 61-120 days from start of treatment. These converging data suggest that the underlying mechanism is relatively acute in onset and mostly waning after treatment cessation. This appears to be consistent with the pathophysiology of aortic dissection as the latter tends to be a rapidly developing event that assumes the pre-existence of a medial weakness [21]. Contrastingly, aortic aneurysm tends to be a progressively developing condition, whereby at least a 50% increase in the diameter of the aorta is required for diagnosis [22]. Hence, fluoroquinolone-associated aortic aneurysm may be explained by a possible accelerated increase in the diameter of the aorta. Further studies are needed to support this hypothesis.

Fluoroquinolones are known to cause collagen-related adverse effects, most notably tendon rupture which has been extensively studied. One of the mechanisms behind fluoroquinolone-associated tendinopathies is thought to be oxidative damage due to structural and functional changes of the catalase enzyme [23]. Other suggested mechanisms include up-regulation of matrix metalloproteinases (MMP)2 in tendon leading to the degradation of type I collagen; iron chelation leading to inhibition of iron-dependent enzymes like the propyl 4-hydroxylase responsible for collagen propyl hydroxylation [24, 25].

The possible mechanisms behind fluoroquinolone-associated aortic aneurysm and aortic dissection appear to be close to those involved in tendon rupture. Animal studies have revealed that MMP2 plays a role in the development of aortic aneurysm and that endothelial cell-specific reactive oxygen species can increase susceptibility to aortic dissection [26, 27]. A study in a mouse model of moderate, sporadic aortic aneurysm and dissection exposed to ciprofloxacin showed increased susceptibility to aortic dissection and rupture with parallel decreased expression and activity of lysyl oxidase, increased levels and activity of MMP, and increased elastic fiber fragmentation and cell injury [28]. A recent study showed that cultured human aortic myofibroblasts exposed to ciprofloxacin for 24 hours had significantly decreased Tissue Inhibitor Metalloproteinases (TIMP)1 and TIMP2 protein expression and increased MMP9 to TIMP2 ratio paralleled with significantly attenuated collagen-1 expression compared to unexposed cells. Cell apoptosis, necrosis, and metabolic viability were not significantly affected by ciprofloxacin exposure. These findings suggest rapid extracellular matrix degradation as the main underlying mechanism behind fluoroquinolone-associated aortic event, which is consistent with the observed early-onset characteristic of the association with respect to the exposure to fluoroquinolones [29]. Further studies are needed to strengthen this observation.

5.1. Study Strength and Limitations

Our study has several strengths. We searched multiple databases according to a written and registered protocol; we analyzed both composite and individual outcomes, performed sensitivity analysis, and subgroup analysis. Although the selected studies were all observational, the risk of bias for the individual study was found to be low. In addition, all the selected studies adjusted for confounders by using either propensity score matching (Pasternak *et al*.), propensity score adjustment (Lee's case-control), adjustment for time-varying confounders (Lee's case-crossover) or adjustment for baseline characteristics (Daneman *et al*.).

There are some limitations to our meta-analysis. First, the number of included studies remains low (n = 4), although greater than the previous meta-analysis performed on the same subject (n =2). Second, no randomized controlled trials

were found. Indeed, since the incidence rates of aortic aneurysm and aortic dissection are low, randomized controlled trials are usually inadequately powered to evaluate these outcomes. Third, only two studies (Pasternak *et al*. and Lee's case-control study) reported the risk for aortic dissection alone. Consequently, the cumulative effect size for aortic dissection alone was pooled from two studies and the statistical heterogeneity was moderate (I2 = 75%). Fourth, the possible role of infectious pathogens in the development aortic structural abnormalities including aortic aneurysm and aortic aneurysm rupture has been reported in the literature, especially with *Borrelia burgdorferi sensu lato*, *Salmonella* and *Staphylococcus* species [30-33]. Consequently, an underlying infection in the fluoroquinolone-exposed group may be a confounding factor. It should be noted however that one study (Pasternak *et al*.) out of the four selected studies accounted for this confounding factor by choosing a control group exposed to an active comparator (amoxicillin). Finally, the dose-effect relationship, which has important clinical implications, was not explored in any of the selected studies.

CONCLUSION

Considering the results of our meta-analysis, caution must be taken in prescribing fluoroquinolones to patients with aortic dilatation, patients at risk for aortic aneurysm and dissection and elderly patients. In those patients, fluoroquinolone treatment must be prescribed only when no other treatment options are available. If this is the case, a shorter treatment course (less than 14 days) must be favored.

The contributing factors to fluoroquinolone-associated aortic aneurysm or dissection that were highlighted in our study (early exposure to fluoroquinolones, female gender and elderly patients) were also reported with fluoroquinolone-associated tendon rupture [34, 35]. Consequently, it may be interesting to study whether other reported risk factors for fluoroquinolone-associated tendon rupture like concomitant corticosteroid intake, renal failure and diabetes may also contribute to the occurrence of fluoroquinolone-associated aortic events [34-38].

LIST OF ABBREVIATIONS

ICD	=	International Classification of Disease
MMP	=	Matrix Metalloproteinases
PRISMA	=	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
TIMP	=	Tissue Inhibitor Metalloproteinases

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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Declared none.

SUPPLEMENTARY MATERIAL

Appendix 1: Prospero Registration

Prisma Checklist

Supplementary material is available on the publisher's web site along with the published article.

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