Fluoroquinolones and the Risk of Aortopathy: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: Recent studies have raised concerns that fluoroquinolone use is associated with an increased risk of aortopathy, including aortic aneurysm with and without dissection.

Objective: We performed a meta-analysis with a comprehensive literature review to further investigate this association.

Methods: This analysis was conducted per PRISMA guidelines. PubMed, Cochrane Library, ClinicalTrials.gov, Embase, Web of Science, and Google Scholar were searched for studies that included adult patients (age >18 years) exposed to fluoroquinolones or control antibiotics (amoxicillin/any other antibiotic) for urinary tract infection or pneumonia with a primary outcome of aortic aneurysm or dissection. Heterogeneity was calculated using Q statistic I^2.

Results: A total of 6 studies—comprised of 59% males—were included in our analysis, which showed an increased combined risk of development of aortic aneurysm and aortic dissection with quinolone exposure when compared with controls (relative risk [RR] = 2.11; 95% CI, 1.62 - 2.75; I^2 = 83.700). Individual relative risk for aortic aneurysm (RR = 2.83; 95% CI, 2.02 - 3.95, I^2 = 89.150) and aortic dissection (RR = 1.99; 95% CI, 1.23 - 3.06; I^2 = 71.33) also were significantly increased.

Conclusion: Compared to other antibiotics, the use of fluoroquinolones was associated with a significantly higher risk of aortic aneurysm and dissection combined.

INTRODUCTION

Among the antibiotics prescribed for treatment of urinary tract and respiratory infections, fluoroquinolones are the most widely used—both in outpatient and inpatient settings. Fluoroquinolone use has increased dramatically over the past few decades, and they are now the third most-prescribed class of antibiotics in the United States.[1-3] However, recent studies have shown that widespread use of fluoroquinolones is associated with an increased risk of collagen-related adverse effects, including tendinopathy, retinal detachment, and aortopathy—aortic aneurysm (AA) and aortic dissection (AD). AA and AD are the life-threatening cardiovascular diseases that need prompt intervention and often involve surgery without treatment. AD is the development of a tear in the aortic intima that creates a false lumen through the aortic media. AA is a permanent localized dilation of the aorta resulting in at least a 50% increase in the aortic diameter.[4] The mortality rate is 1% to 3% per hour during the first 24 hours, 30% at 1 week, 80% at 2 weeks, and 90% at 1 year.[5]

There is limited but increasing data in the literature on the association of aortic disease with fluoroquinolones. Two 2 meta-analyses on the topic also have been published.[6,7] The most recent one—published in January 2019—was performed on a small number of studies (n=4);[6] since then, newer research has been published.

Given the frequent use of fluoroquinolones and the significant risk of fatal outcomes from AA and AD, we performed a meta-analysis with a comprehensive literature review to investigate this association further. The primary objective of our analysis was to confirm the association between fluoroquinolones and the development of aortopathy and to measure the risk for each event separately.

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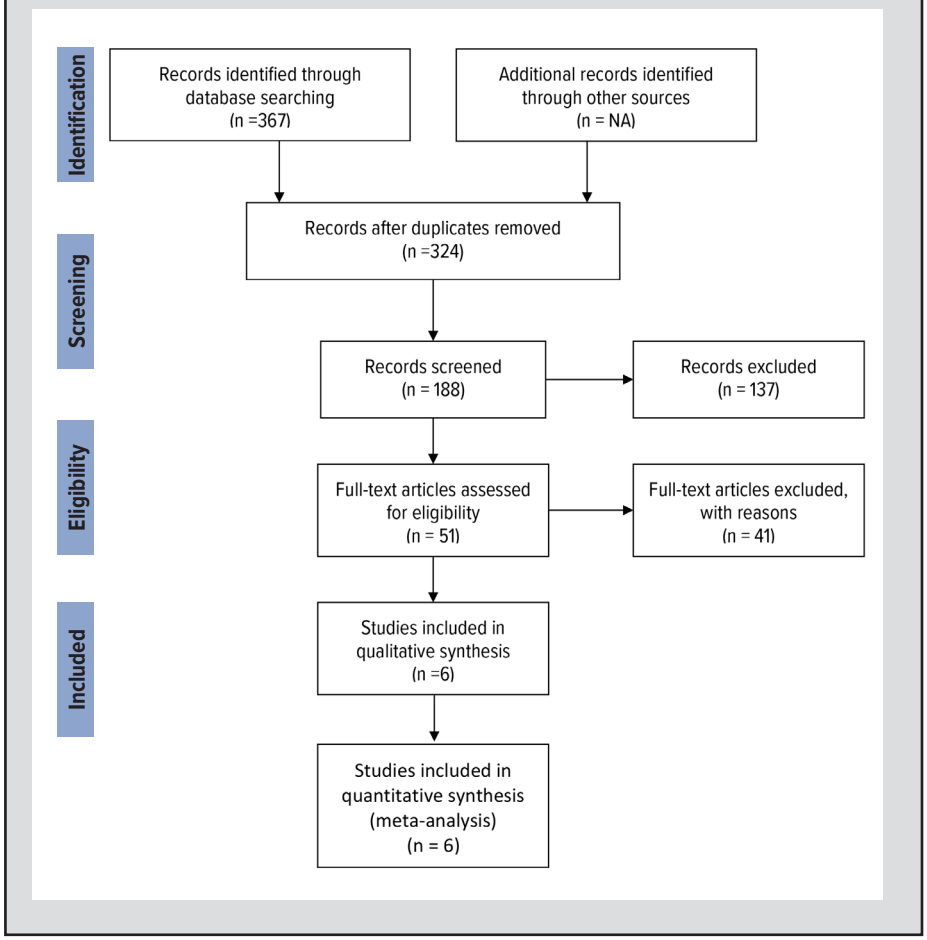
Figure 1. PRISMA Flow



METHODS

We conducted a systematic review and meta-analysis following PRISMA guidelines (Figure 1).

Search Strategy

We searched the PubMed, Cochrane Library, Embase, Web of Science, and Google Scholar databases from inception through November 2019 using the following keywords: "quinolones" AND "fluoroquinolones" AND "aortic aneurysm" AND "aortic rupture" AND "aortic dissection." Additionally, unpublished trials were identified from the clinicaltrials.gov website and references for retrieved articles were reviewed for relevant articles. After removing 43 duplicates, titles and abstracts of 367 articles were screened for relevance by 3 independent reviewers (AL, MA, VK); conflict was settled by discussion. A total of 6 articles were deemed relevant, and their abstracts and full texts were screened for eligibility (Figure 1).

Articles selected reported on studies performed in adult populations treated by any fluoroquinolone antibiotics, with control groups comprised of patients who were not treated with fluoroquinolones. The primary patient outcome in eligible studies was the development of either AA or AD.

Study Selection

Only original studies that reported the use of fluoroquinolones with a primary outcome of development of AA and/or AD met the inclusion criteria. Included studies also provided odds ratios and confidence intervals, or the odds ratio could be calculated from data provided. There was no language restriction.

Only 6 articles qualified for this strict selection criteria and were included in the meta-analysis: 2 cohort studies, 2 case-control studies, 1 case crossover study, and 1 Food and Drug Administration (FDA) database study. The reasons for excluding the other 9 articles were as follows: irrelevant (n = 2), meta-analysis (n = 3), reviews (n = 2), and poor data reporting (n = 2). Exclusion criteria were AA/AD patients who used other antibiotics, studies showing no subjective data, preclinical studies, interim reports for studies other than the most recent one, and studies not reporting a comparative outcome with normal controls.

Data Extraction and Quality Assessment

The 3 reviewers independently extracted the data from the selected studies using a Microsoft Excel spreadsheet template that included information about study design, exposure, outcomes, participants' characteristics, results, and risk of bias. The extraction sheets were compared for differences and discrepancies were resolved after checking the source document and following a discussion between the 3 reviewers. The Newcastle–Ottawa quality assessment scale was used to evaluate the quality of the included observational studies (see Appendix).

Analysis

The meta-analysis was performed with STATA software using a random effect model. A 2-sided 95% confidence interval was considered statistically significant. Heterogeneity was calculated using the Q statistic and I^2. Heterogeneity of individual outcomes for included studies was reported using a log-rank test. The main summary estimate was relative risk with 95% con-fidence intervals.

RESULTS

The 6 studies in the meta-analysis included 1 longitudinal cohort study, 1 nested case-control study, 1 nationwide cohort study, 1 case time control study, 1 case crossover study, and 1 FDA database study. The primary outcome in all of these studies was the

occurrence of AD or AD—according to International Classification of Diseases, Clinical Modification (ICD-9-CM) codes— during the follow-up period.

The nested case-control study (N = 149,212) was conducted by Lee et al (2015) using the national health insurance database of Taiwan from January 1998 through December 2011.[8] The authors matched 1477 cases (patients hospitalized for AD or AA; 1103 males, 374 females) with 147,700 untreated controls (107,600 males, 40,100 females) based on age and sex and found an increased risk of AA or AD with the current use of fluoroquinolones (RR = 2.43).

Daneman et al conducted the population-based longitudinal cohort study in Ontario, Canada from April 1997 to March 2012 (N = 1,744,360).[9] Patients who received fluoroquinolone prescriptions (cases: n = 657,950; 319,485 males, 338,465 females) were compared with patients who did not receive fluoroquinolone prescriptions during follow-up (n = 1,086,410 controls; 225,652 males, 860,758 females). Their results demonstrated a 2- to 3-fold increase in AA (hazard ratio [HR] 2.24).

Lee et al conducted another case-crossover study on a large national administrative database in Taiwan, where they identified 1213 patients with a mean age of 72.46 who were hospitalized between 2001 and 2011 with AA/AD.[10] There were 879 males and 334 females included in the study, respectively. Cases were patients diagnosed with AD or AA, and study participants acted as their own controls. The study showed an increased risk of AA/AD with prolonged exposure to fluoroquinolones, with odds ratio (OR) of 2.41 for 3 to 14 days and OR of 2.83 for >14 days.

Pasternak et al conducted the nationwide cohort study in Sweden on patients older than 50 years who received a fluoroquinolone prescription during July 2006 to December 2013 study period.[11] They compared fluoroquinolone-treated patients (cases: n = 360,088; 162,807 males, 197,185 females) with patients the same age treated with amoxicillin (controls: n = 360,088; 162,641 males, 197,447 females). The use of fluoroquinolones was associated with an increased risk of AA or AD, with HR of 1.66 within 60 days from the start of treatment.

Maumas-Robert et al 2018 conducted the case-time control and nested case-control study (N = 5,946) using a French health insurance database.[12] Cases were patients age >18 years with incident AA or AD (n = 86) who were exposed to fluoroquinolones and diagnosed between July 2010 and December 2015; controls were patients age >18 years (n = 316) who had been exposed to amoxicillin. The study assessed the exposure to fluoroquinolones

Figure 2. Forest Plot Showing Risk of Aortic Aneurysm and Aortic Dissection With Flouroquinolone Use

Study	Year	RR	Lower Limit	Upper Limit	Z value	*P* value
Daneman et al [9]	2015	2.72	2.528	2.927	26.722	0.000
Lee et al [8]	2015	2.93	2.166	3.963	6.976	0.000
Pasternak et al [11]	2018	1.66	1.120	2.460	2.525	0.012
Robert et al [12]	2018	1.80	1.404	2.307	4.641	0.000
CC Lee et al [10]	2018	2.71	1.138	6.451	2.253	0.024
		2.30	1.803	2.927	6.727	0.000

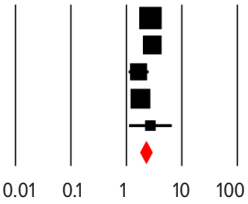


Figure 3. Forest Plot Showing Risk of Aortic Aneurysm With Flouroquinolone Use

Study	Year	RR	Lower Limit	Upper Limit	Z value	*P* value
Daneman et al [9]	2015	2.24	2.018	2.487	15.113	0.000
Lee et al [8]	2015	2.36	1.659	3.358	4.773	0.000
Pasternak et al [11]	2018	1.90	1.220	2.960	2.839	0.005
Meng et al [13]	2019	2.31	1.621	3.292	4.633	0.000
Meng et al 1 [13]	2019	5.03	3.968	6.377	13.348	0.000
Meng et al 2 [13]	2019	4.18	2.860	6.110	7.386	0.000
		2.83	2.024	3.948	6.094	0.000

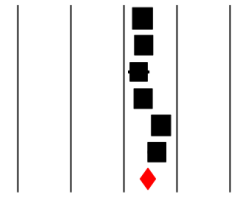
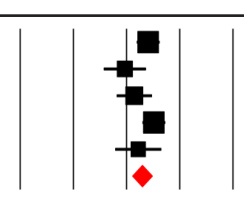


Figure 4. Forest Plot Showing Risk of Aortic Dissection With Flouroquinolone Use

Study	Year	RR	Lower Limit	Upper Limit	Z value	*P* value
Lee et al [8]	2015	2.55	1.581	4.113	3.838	0.000
Pasternak et al [11]	2018	0.93	0.379	2.283	-0.158	0874
Meng et al [13]	2019	1.40	0.663	2.955	0.883	0.377
Meng et al 1 [13]	2019	3.26	2.020	5.261	4.840	0.000
Meng et al 2 [13]	2019	1.66	0.622	4.432	1.011	0.312
		1.99	1.299	3.060	3.159	0.002



within the first 365 days of reported AA or AD; risk of AA/AD was found to be significant, with OR of 1.6 in the first 60 days.

Meng et al assessed fluoroquinolone-associated AA/AD through data mining the FDA Adverse Event Reporting System from January 2004 to December 2016.[13] Ciprofloxacin, moxi-floxacin, and levofloxacin were used as study drugs, while cefuroxime was used as negative exposure control. The adverse events were AA and AD. A total of 3721 events were reported in patients aged 18 years and older; 153 events were in association with fluoroquinolones. Sex was reported in only 139 events: 86 males and 53 females, respectively. Although all 3 antibiotics were found to be associated with AA, only levofloxacin was noted to have an association with AD. The authors also noticed that oral versus intravenous use of these antibiotics was more likely to produce fatal side effects.

Meta-Analysis

The risk of AA rupture and AD was doubled following quinolone exposure when compared with controls (RR = 2.11; 95% CI, 1.62 - 2.75). The relative risk for the rupture of aortic aneurysm alone was found to be significantly elevated (RR = 2.83; 95% CI, 2.02 - 3.95). Likewise, the relative risk for AD alone also doubled (RR = 1.99; 95% CI, 1.23 - 3.06). See Figures 2, 3, and 4.

DISCUSSION

Our analysis showed that the use of fluoroquinolones doubles the risk of AA or AD within the first 60 days of exposure (RR = 2.11; 95% CI, 1.62 - 2.75). These results further strengthen the conclusion of the previous meta-analysis that included 4 studies.[6]

Our data suggest that fluoroquinolone use has a higher degree of correlation with AA versus AD. The relative risk for rupture of AA alone was found to be significantly elevated (2.83; 95% CI, 2.02 - 3.95), while the relative risk for AD alone was 1.99 (95% CI, 1.23 - 3.06). This difference can be explained by the fact that AA is more frequently seen in the general population than AD.[14,15]

The FAERS database study was the only one that compared the 3 different fluoroquinolones (levofloxacin, moxifloxacin, and ciprofloxacin). Their results highlight that the use of levofloxacin is associated with greatest risk, followed by moxifloxacin and ciprofloxacin, when compared to the control antibiotic (cefuroxime): AD (OR 3.26) and AA (OR 5.03). They also assessed the influence of the route of administration. Oral administration is far more common in outpatient settings with community-acquired pneumonia and more likely to produce these fatal adverse effects versus intravenous (IV) administration, which might be due to lesser dura-tion of IV administration. Studies conducted by Daneman et al[9] and Lee et al[8,10] didn't have an active comparator and older patient population (age >50 years), which might have led to an overestimation of the risk.

Higher risk during the first 60 days after the start of treatment with fluoroquinolones indicates the process is acute to subacute in onset, and risk is largely waned after treatment cessation. According to Lee et al,[8] risk is also associated with the treatment duration. When prescribed for more than 14 days, risk is significantly elevated compared to the usual prescription of 3 to 14 days. Studies also have noted that the risk of fluoroquinolone-associated tendinopathy (eg, Achilles tendon rupture) is also high in the first 15 to 30 days.[16] Therefore, AA associated with the fluoroquinolone use might be explained by the accelerated increase in the diameter of the aorta.

The exact biological mechanism of quinolone-induced aortopathy remains unknown. So far, few plausible mechanisms have been proposed—one being oxidative damage from functional and structural changes of catalase enzymes by quinolone antibiotics. Another is the upregulation of matrix metalloproteinases (MMP) in the tendons, which leads to degeneration of type 1 collagen. Also, fluoroquinolones have chelating properties against metal ions, which are essential for type 1 collagen synthesis. The aorta wall is rich in type 1 and type III collagens, which might be affected by these proposed mechanisms.

Animal studies have shown the role of MMP enzyme[2,9] in the development of AA.[17,18] A study on mouse models with AD and AA by LeMaire et al in 2018 showed that mice exposed to ciprofloxacin had increased MMP activity, with increased elastic fiber fragmentation and cellular injury.[15] Likewise, these MMP have been shown to induce the development of AA in humans. One study showed that cultured human aortic myofibroblasts exposed to ciprofloxacin for 24 hours had significantly decreased tissue inhibitor metalloproteinase 1 and 2 protein expression and increased MMP9 to tissue inhibitors of matrix metalloproteinases (TIMP2) ratio paralleled with significantly attenuated collagen 1 expression compared to unexposed cells.[19] Despite these initial epidemiology findings, further indepth studies are needed to strengthen this association.

Limitations

There are some limitations to our analysis. First, the number of studies included is small (n = 6), although greater than the previous meta-analysis on the same subject (n = 4). Additionally, no randomized control trials were found on the subject. One out of 6 studies included another antibiotic as an active comparator,[11] which is why infection as a confounding factor was not ruled out.

CONCLUSION

The risk of AA rupture and AD may be overestimated by a few previous studies, but our meta-analysis demonstrates that exposure to quinolone antibiotics for the management of common upper/lower respiratory tract and urinary tract infections is still substantially associated with AA/AD. Reducing unnecessary prescriptions or decreasing the number of days of fluoroquinolone use might be a simple way to reduce this risk. Given the global burden of AA/AD and the growing use of quinolone antibiotics, more randomized control trials should be conducted to validate this association.

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