



Fluoroquinolones and the risk of aortopathy: A systematic review and meta-analysis

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ABSTRACT

Objective: To investigate the association between fluoroquinolones use and development of aortopathy.

Methods: A systematic review and meta-analysis was conducted following PRISMA and MOOSE guidelines for reporting systematic reviews of observational studies. Multiple databases were searched and two authors independently screened studies for eligibility. Newcastle Ottawa scale was used to assess the quality of included studies. Primary outcome of interest was development of aortic aneurysm or dissection among fluoroquinolones users in comparison to non-users. An inverse variance model meta-analysis was used to pool odds ratio or hazards ratio from included studies to calculate the overall effect estimate. Pre specified subgroups analyses were also conducted to explore sources of heterogeneity.

Results: Three observational studies that enrolled 941,639 subjects met the inclusion criteria and were included in the final analysis. All studies were of a good methodological quality. Current use of fluoroquinolones, defined as within 60 days from development of the primary outcome, was associated with significantly elevated risk of developing aortic aneurysm and/or dissection in comparison to controls, (OR = 2.04; 95% CI [1.67, 2.48]). There was only a mild degree of between study heterogeneity, $I^2 = 33\%$. The association remains robust among all subgroups analyses.

Conclusion: Our findings indicate that current fluoroquinolone use was significantly associated with increased risk of aortic aneurysm and dissection. Health care providers need to be aware of this serious association and use fluoroquinolones judiciously in order to minimize the risk of the serious sequela of aortopathy.

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1. Introduction

Fluoroquinolones are one of the most frequently prescribed antibiotics used to treat common infections like pneumonia and urinary tract infections. It is estimated that ~30 million fluoroquinolone prescriptions were written in the United States in the year 2010 in the outpatient setting [1]. Moreover, fluoroquinolone use has dramatically increased over the past few decades and is associated with significant health care expenditure [2]. It is estimated that in the period between 1991 and 2015, Medicare spending on fluoroquinolones has risen by 245.5% from US \$ 11.8 million to US \$ 40.8 million [2].

Fluoroquinolone antibiotics have been associated with an increased risk of tendinopathy and retinal detachment [3,4]. More recently, few

studies have linked the use of fluoroquinolones to the development of aortopathy, including aortic aneurysm and dissection [5–7]. Aortic aneurysm and dissection are life threatening conditions that need urgent intervention to prevent death and serious consequences like myocardial infarction, cardiac tamponade, stroke, life-threatening bleeding, and limb ischemia.

Owing to the widespread use of fluoroquinolones and serious adverse outcomes associated with aortopathy including death, we sought to systematically review the literature and perform a meta-analysis to investigate the association between fluoroquinolone use and the risk of aortic aneurysm and dissection.

2. Methods

We carried out a systematic review and meta-analysis according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [8] and Meta-Analysis of Observational Studies in Epidemiology guidelines for reporting systematic review and meta-analysis of observational studies guidelines [9].

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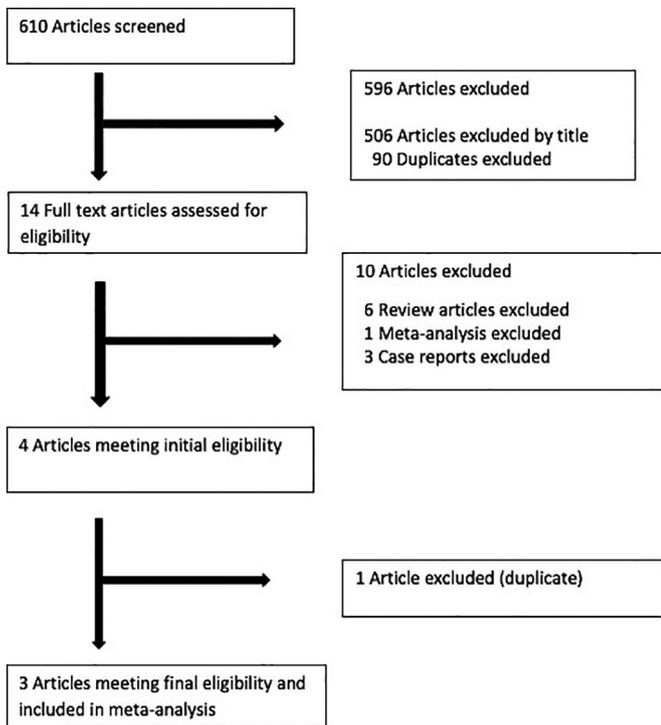


Fig. 1. Flow diagram of the included studies.

2.1. Study selection

Studies that reported on the association between fluoroquinolone use in humans and risk of aortic aneurysm and/or dissection were eligible for inclusion. Included studies provided odds ratio and confidence intervals, or the odds ratio could be calculated from the data provided. Two authors (HA and AB) independently screened the identified studies.

Our initial search retrieved 610 articles. See Fig. 1 for PRISMA flow diagram. After exclusion by title and exclusion of duplicates, 14 articles were selected for detailed review. Of these, 6 were review articles, 3 were case reports, 1 was a meta-analysis, and 1 was a duplicate. Three (3) studies met inclusion criteria and were included in the meta-analysis.

2.2. Search strategy

We searched PubMed, Embase and Scopus for all relevant full text articles published before March 20, 2018, without language restriction. The search keywords used in PubMed were (“aortic aneurysm” OR “aortic dissection”) AND (“fluoroquinolones” OR “ciprofloxacin” OR “Fleroxacin” OR “Enoxacin” OR “Norfloxacin” OR “Ofloxacin” OR “Levofloxacin” OR “Perfloxacin” OR “Moxifloxacin” OR “Gatifloxacin”). The same search was adapted for Embase and Scopus. References of retrieved articles were also reviewed for relevant articles.

2.3. Data collection and quality assessment

A pre specified data collection form was designed to collect relevant study information including characteristics of the included study (design, sample size, setting, year of

publication), study population (age, gender), and primary outcome (aortic aneurysm, aortic dissection or both). Two authors independently extracted required data (AN and AB).

The Newcastle–Ottawa quality assessment scale (NOS) [10] was used to evaluate the quality of observational studies. NOS scale rates observational studies based on 3 parameters: selection, comparability between the exposed and unexposed groups, and exposure/outcome assessment. It assigns a maximum of 4 stars for selection, 2 stars for comparability, and 3 stars for exposure/outcome assessment.

Studies with <5 stars were considered low quality, 5–7 stars moderate quality, and >7 stars high quality. Two reviewers (AQ and MA) assessed the quality of the included studies. Disagreement was resolved by consensus.

2.4. Analytical method

A meta-analytical approach using inverse variance method was used to pool studies' adjusted odds ratio or hazards ratio into a random effects model. We used odds or hazards ratios from propensity score matching whenever available or from adjusted multivariate analysis when propensity score matching was not available. The primary outcome of interest was occurrence of aortic aneurysm or dissection with current fluoroquinolone use (defined as within 60 days from occurrence of the outcome) in comparison to control. Odds ratio, with its 95% confidence interval (CI), was used to calculate the overall effect estimate.

A sensitivity analysis was carried out to test the association between fluoroquinolone use and incidence of aortic aneurysm alone and aortic dissection alone in comparison to control group. Further, we conducted a pre-specified subgroup analysis using data from propensity score matched analyses only.

Heterogeneity among included studies was assessed using χ^2 and I^2 tests. The I^2 statistic describes the proportion of variation in treatment estimate that is not related to sampling error [11]. A value of zero indicates no heterogeneity, 25%–49% low, 50%–74% moderate, and 75% a high degree of heterogeneity.

Two sided P value of <0.05 was considered statistically significant for all included analyses. The statistical software Review Manager, version 5.3.5 (The Nordic Cochrane Center, The Cochrane Collaboration, 2018, Copenhagen, Denmark) was used for all analyses.

3. Results

3.1. Search result and characteristics of the included studies

Three articles met the inclusion criteria and were included in the final analysis (Fig. 1).

All included studies were observational in nature, one nested case control [6] and 2 cohort studies [5,7]. A total of 941,639 subjects were included in the primary outcome assessment of the meta-analysis.

Lee et al. [6] have conducted a nested case-control study using the National Health Insurance Database of Taiwan. Daneman et al. [5] conducted a population-based longitudinal cohort study of subjects ≥ 65 years old in Ontario, Canada. Pasternak et al. [7] studied all adults >50 years old who received a fluoroquinolone prescription during the study period. Included studies scored high on the NOS. Table 1 illustrates the general characteristics of included studies.

3.2. Meta-analysis

Current use of fluoroquinolones, defined as within 60 days, was associated with significantly elevated risk of developing aortic aneurysm

Table 1
General characteristics of the included studies.

Study ID	Study design	Country of the study	Primary outcome	Analytic methods	Age	Female proportion	Study participants (N)	Control group (N)	Quality assessment ^{††}
Lee et al. [6]	Nested case control	Taiwan	Aortic aneurysm or dissection	I. Multivariate adjustment II. Propensity adjusted analysis III. Propensity matched analysis	74.7 years (mean)	25.9%	1477 cases	147,700 control	Moderate quality
Daneman et al. [5]	Longitudinal cohort study	Canada	Severe collagen associated adverse events defined as tendon ruptures, retinal detachments and aortic aneurysms	Multivariate adjustment	≥ 65 years at time of accrual	51.2%	657,950 fluoroquinolones users	1,086,410 fluoroquinolones non users	High quality
Pasternak et al. [7]	Nationwide cohort study	Sweden	Aortic aneurysm or dissection	Propensity score matched analysis	67.9 years (mean)	55%	560,768 episodes of fluoroquinolone use	440,504 episodes of amoxicillin use	High quality

N: Number, π : Based on Newcastle Ottawa Scale [10].

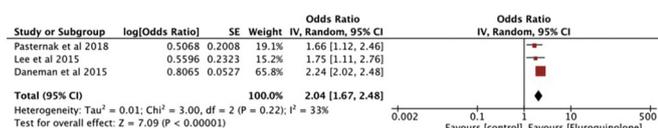


Fig. 2. Random effect model meta-analysis of the risk of aortic aneurysm or dissection among fluoroquinolone users in comparison to nonuser.

and/or dissection in comparison to controls, (OR = 2.04; 95% CI [1.67, 2.48]). There was only a mild degree of between study heterogeneity, $I^2 = 33\%$, Fig. 2.

3.3. Subgroup analyses

Fluoroquinolone use was associated with significantly elevated risk of developing aortic aneurysm in comparison to control group, (OR = 2.23; 95% CI [2.03, 2.46]; $I^2 = 0\%$), Fig. 3. Moreover, when analysis was restricted to the development of aortic dissection, fluoroquinolone use remained positively associated with the risk of aortic dissection, (OR = 2.25; 95% CI [1.42, 3.56]; $I^2 = 65\%$). When we analyzed only data from propensity score matched analyses, fluoroquinolone use was also associated with significantly elevated risk of developing aortic aneurysm or dissection in comparison to control group, (OR = 1.70; 95% CI [1.26, 2.29]; $I^2 = 0\%$).

4. Discussion

Our results showed that current fluoroquinolones use, defined as within 60 days from occurrence of aortic aneurysm or dissection, was significantly associated with development of aortic aneurysm and dissection with none to moderate degree of between studies heterogeneity. The association was robust in the primary outcome (development of aortic aneurysm and/or dissection) with only mild degree of heterogeneity and among all subgroup analyses including zero degree of heterogeneity when analysis was restricted to development of aortic aneurysm only without dissection.

The association is modest to strong given the effect size, consistency in the findings, temporal relationship, and biological plausibility. One explanation for development of aortic aneurysm and use of fluoroquinolones is originated from the observation of increased matrix metalloproteinase enzymes level and degradation of type I collagen in tendon with ciprofloxacin use [12]. Matrix metalloproteinase enzymes 2 and 9 have been shown to induce aortic aneurysm in mice and development of aortic aneurysm in humans [13,14].

Our findings are consistent with a prior meta-analysis on the topic that included only 2 studies, although that meta-analysis might have overestimated the risk given both included studies had no comparable active arm. We have included in our meta-analysis the most recently published paper by Pasternak et al. that studied the entire Sweden population over the age of 50 years and compared fluoroquinolones with an active comparable arm (amoxicillin) in a propensity score matched analysis.

The number needed to harm (cause an episode of aortic aneurysm or dissection) is estimated to be 1376 treatment courses of fluoroquinolones. We have used the overall effect estimate from our meta-analysis (OR = 2.04) and a baseline risk as 0.7 per 1000 person-years, as reported from Sweden nationwide cohort study. The number

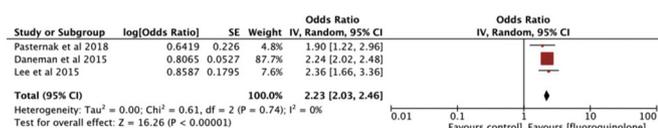


Fig. 3. Random effect model meta-analysis of the risk of aortic aneurysm among fluoroquinolones users in comparison to nonuser.

needed to harm seems negligible, however, fluoroquinolones are one of the most commonly prescribed and misused antibiotics. One study estimated that 1 out of 3 fluoroquinolones prescriptions were unnecessary [15]. Therefore, even at this number needed to harm, the risk of aortopathy is real and alarming given the devastating outcome, including death. Moreover, the incidence of aortic aneurysm and dissection is noted to be on rise in some parts of the world [16] and that may be explained among other reasons by the misuse of fluoroquinolones if a causal pathway is to be believed.

4.1. Limitations

Our study has several limitations related to the observational nature of the included studies with all inherited biases of observational designs. However, current evidence represents the best available and it would be unethical to design an experimental study to verify the current hypothesis of an association between fluoroquinolones use and risk of aortopathy. Moreover, all included studies were of good quality and 2 of them were population based studies.

5. Conclusion

Our findings indicate that current fluoroquinolone use was significantly associated with increased risk of aortic aneurysm and dissection. Health care providers need to be aware of this serious association and use fluoroquinolones judiciously. Adherence to antimicrobial stewardship program wouldn't only decrease the risk of antimicrobial resistance but may also prevent the serious consequence like aortic aneurysm and dissection from improper use of fluoroquinolones.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcard.2018.09.067>.

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