Relationship between fluoroquinolones and the risk of aortic diseases: a meta-analysis of observational studies

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KEYWORDS
Fluoroquinolones; aortic aneurysm; aortic dissection; meta-analysis
Abstract

Background Our aim was to find possible risk associated between fluoroquinolones and aortic diseases. Methods PubMed, Embase and the Web of Science were searched from inception to July 6, 2019 to identify observational studies that evaluated the risk for aortic diseases associated with users of fluoroquinolones compared with non-users or users of other antibiotics. Primary outcome was the first occurrence of aortic diseases. We used Newcastle Ottawa Scale to assess quality among cohort and case-control studies and the GRADE approach was used for rating strength of evidence and used inverse variance method random-effect model to estimate odds risks (ORs) with 95% CIs and statistical heterogeneity were assessed by the I² statistic. Results Five observational studies that enrolled 2,829,385 patients were reported the relationship between fluoroquinolones and the risk for aortic diseases. Compared with non-users or users of other antibiotics, current fluoroquinolone use had association with a significantly increased risk of occurrence of aortic diseases (adjusted OR, 2.15; 95% CI, 1.66-2.64; P=.000). The risk of past fluoroquinolone use remained high in aortic dissection (adjusted OR, 1.98; 95% CI, 0.97-2.99; P=.000) and aortic aneurysm (adjusted OR, 1.77; 95% CI, 0.98-2.57; P=.000). The quality of evidence was moderate and the Number Need to Treat to Harm (NNTH) for aortic diseases among elderly patients above the age of 50 were current users of fluoroquinolones was estimated to be 1245. Conclusions The current fluoroquinolones use within elderly patients significantly increased the risk for the first occurrence of aortic diseases. Clinicians need to pay attention to these severe adverse events when considering fluoroquinolone use.

Background

Fluoroquinolones are the group of broad-spectrum antibiotics, which can effectively kill or
stop the growth of gram-negative and gram-positive bacteria.[1] Based on this reason, they are routinely prescribed by internists, family practitioners, specialists, subspecialists and surgeons.[2] One coin has two sides; however, several studies reported their serious adverse events such as aortic aneurysm and aortic dissection,[3, 4] when patients used fluoroquinolones. Aortic aneurysm and aortic dissection had high complication rates and risk of mortality,[5, 6] so the FDA announcement added these severe side effects warning on December 20, 2018. Because of these rare but serious events, two meta-analyses evaluated relationships between fluoroquinolones and risk of aortopathy,[2, 7] but these two articles had some limitations such as the quantity of studies. Recently, the European Commission has restricted the use of fluoroquinolones due to its possibility of permanent adverse effects.[8] An informed decision about fluoroquinolones use is needed for individuals whether it is worth to take risk. Hence, it is important for both health care providers and patients to be aware of the risks and benefits of fluoroquinolones using. Then, to expand the research population is necessary and it can make the meta-analysis conclusion more objective.

Based on the previous meta-analyses, our aim was to reevaluate the effect of fluoroquinolones use on the risk of aortic diseases (aortic aneurysm and aortic dissection) compared to controls.

Methods

This meta-analysis adhered to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) [9] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [10] guidelines. The protocol was registered at PROSPERO and its number was CRD42019129056.

2.1 Literature Search

A systematic electronic in PubMed, Embase and Web of Science were performed from
inception to March 2019. Electronic searches were used by exploded Medical Subject Headings (MeSH) terms and related key words. The search terms used were (MeSH exp “aorta” and key words “aorta”) and (MeSH exp “dissection” and key words “dissection”) and (MeSH exp “aortic aneurysm” and key words “aortic aneurysm” and “aneurysm”) and (key word ti “fluoroquinolone*”). The detailed search strategy for each of the database was provided in PROSPERO protocol. We did not make language restriction. Because of ensuring literature saturation, we reran the search on July 6, 2019.

2.2 Selection Criteria

Two authors (X.-C. D. and X.-X. Y.) independently conducted the original search, struck out duplicate articles, read the relevant titles and abstracts and classified records as included, excluded or uncertain. Due to ambiguity, the full-text article was acquired to identify eligibility. Discussion and consensus were used to resolve discrepancy.

Published cohort or case-control studies that met the following criteria were included:

Participants: Adults no younger than 18 years treated for any condition with any fluoroquinolone.
Exposures: patients received any of fluoroquinolones: ciprofloxacin, levofloxacin, enoxacin, sparfloxacin, norfloxacin, lomefloxacin, moxifloxacin, pefloxacin, ofloxacin, besifloxacin, gatifloxacin and gemifloxacin.
Control: The placebos included either patients with none antibiotic or exposed to other antibiotics.
Outcomes: the major outcome of interest was the first occurrence of aortic diseases.
Data: studies reported on the unadjusted or the adjusted Relative Risk (RR) or Hazard Ratio (HR) or Odds Ratio (OR) or Risk Difference (RD) and their confidence intervals (CIs) or provided sufficient data to estimate these data.

2.3 Data extraction

Data extraction was performed by X.-C. D. and checked separately by other authors (X.-X. Y. and L. M.). Gathered data including the following: first author, year of publication, participants, interventions, primary outcomes, study design, controls, covariates adjustment, exposure category, crude and adjusted relative risk (RR), hazard ratio (HR) or odds ratio (OR) and 95% confidence intervals. Extracted data were collected into a Word
(Microsoft Corporation) file. coauthors resolved discrepancies by discussion. Different follow-up and durations of fluoroquinolone use were provided in these studies; Although recording all follow-up data, we chose 60-day period from treatment start or follow-up end point because 60-day duration after current fluoroquinolone use had a higher RR, HR or OR.

2.4 Risk of Bias Assessment

Two author (X.-C. D. and G.-M. T.) independently assessed risk of bias using the Newcastle Ottawa Scale (NOS) for Quality Assessment for cohort and case-control studies.[11] NOS rates case-control studies on case definition, representativeness of cases, selection and definition of controls, comparability of controls, Ascertainment of exposure, same method for ascertainment of cases and controls and non-response rate. NOS rates cohort studies on representativeness of the exposed cohort, representativeness of the non-exposed cohort, ascertainment of exposure, outcome of interest was not present at the beginning of study, comparability of cohorts because of the design or analysis, assessment of outcome, follow-up long enough for outcomes to occur and adequacy of follow up of cohorts. Studies were considered as low quality (below 5 stars), moderate quality (5-7 stars’) and high quality (above 7 stars’).

2.5 Accessing Quality of Evidence

The quality of evidence classified as very low, low, moderate, or high for primary outcome according to Grading of Recommendations Assessment, Development, and Evaluation (GRADE) [12] methodology for risk of bias, inconsistency, indirectness, imprecision, and publication bias was independently evaluated by two authors (X.-C. D. and Y.-Y. P.). The GRADE Profiler (Windows-only tool GRADEpro) was used to construct summary tables.
2.6 Statistical Analysis

Random effects model with inverse variance method was used to pool studies’ adjusted RR, HR and OR and we supposed resemblance between OR and other relative measures such as RR or HR because aortic diseases were rare events.[13] So, using OR, RR or HR based on propensity score matching or adjusting whenever available or from adjusted multivariate analysis when propensity score matching was not obtainable. We calculated ORs with 95% confidence intervals (CIs) for overall effect estimate. Heterogeneity across studies was quantified using the $I^2$ statistic; $I^2 > 50\%$ was considered as considerable heterogeneity.[14] $P < .05$ was considered statistically meaning for total included analyses, except where otherwise specified. All statistical analyses were conduct in STATA (Stata Version 14.0; Stata Corporation, College Station, TX, USA).

We conducted the number needed to treat to harm (NNTH) [15] and its 95% CI to estimate an absolute measure of effect because the OR represented a relative measure of effect. The NNTH means the number of patients needed to be treated with fluoroquinolones for one additional patient to have an adverse event. We used the pooled ORs to calculate the NNTH using the Rx software to convert the ORs to the NNTH.[16] The baseline risk was acquired from the no antibiotic group or exposure to other antibiotics in the population-based studies.

Results

3.1 Trial selection

Studies flowchart followed the PRISMA is shown in Figure 1. Our initial search yielded 101 articles. A total of 16 records were thought to be preliminarily eligible for inclusion after screening the titles and abstracts and cutting off duplicates. After reviewing the full-text articles, our meta-analysis finally included 5 observational studies.[3, 4, 17-19] This
article was no randomized controlled trials included because the incidence of aortic diseases is low and cannot to be fully captured in randomized controlled trials with insufficient power.[20, 21]

3.2 Trials Characteristics

The study design and main characteristic of the included studies are recapitulated in Table 1. The publishing year of these studies were published between 2015 and 2019. Group sizes ranged from 2,426 to 1,744,360, with 2,829,385 patients in total. All included studies were observational in nature, including two cohort studies,[18, 19] one nested case-control study,[17] one case-crossover design study [4] and one case/no case study [3]. The follow-up was from 60 days to 17 years, except one article [3] did not report follow-up time. All studies took adjustment to report the RR, HR or OR including 3 trials using propensity scores,[17-19] 1 trial using conditional logistic regression model [4] and 1 trial using multivariable logistic regression [3]. All studies evaluated different fluoroquinolones and these trials used a combination of administrative diagnostic codes to identify aortic diseases which was first occurrence for treatment.

3.3 Risk of Bias Assessment

We summarized detailed information about five trials’ selection, comparability and exposure and the risk for bias using NOS is shown in Table 2. Overall, five studies were considered as being at low risk for bias which meant high quality (8 stars for every study).

3.4 Users of Fluoroquinolones vs. Non-users or Users of Other Antibiotics

3.4.1 Primary outcome: the first occurrence of aortic dissection or aortic aneurysm: four trials provided data on the first occurrence of aortic diseases.[3, 4, 17, 19] Compared with non-users or users of other antibiotics, users of fluoroquinolones majorly increased risk of
aortic diseases (adjusted OR, 2.15; 95% CI, 1.66-2.64; \(P=.000\)) (Fig. 2), with low heterogeneity (\(I^2=19.9\%\)).

3.4.2 The first occurrence of aortic dissection and aortic aneurysm respectively: Compared with non-users or users of other antibiotics, users of fluoroquinolones also had an increased risk for aortic dissection (adjusted OR, 1.98; 95% CI, 0.97-2.99; \(P=.000\)), with severe statistical heterogeneity (\(I^2=82.8\%\)) and aortic aneurysm (adjusted OR, 1.77; 95% CI, 0.98-2.57; \(P=.000\)) (Fig.2), with severe statistical heterogeneity (\(I^2=90.8\%\)).

3.4.3 The NNTH for Aortic Aneurysm or Dissection
The NNTH for aortic aneurysm or dissection with current fluoroquinolone use was 1245 (95% CI 873-2168) treatment courses of fluoroquinolones. The effect estimate from our meta-analysis (adjusted OR=2.15) was used and a baseline risk (0.7/1,000 person-years) was provided from a Sweden nationwide cohort [19].

3.4.5 GRADE Evidence and Publication Bias
GRADE level of evidence is moderate for the first occurrence of aortic diseases (Fluoroquinolones’ users vs. non-users or users of other antibiotics) because of study design (observational study) and other considerations (large weight of effect, no dose response gradient and no plausible confounding).

For this meta-analysis of the first occurrence of aortic dissection or aneurysm, we did not report publication bias by statistical tests, such as Egger or Begg test because the number of trials is low.
Discussion

4.1 Main Findings

Our meta-analysis methodically reviewed the presently accessible literature and found that (1) users of fluoroquinolones in contrast to non-users or users of other antibiotics significantly increased risk of aortic diseases for current use; (2) past use of fluoroquinolones (more than 60 days) increased aortic dissection or aneurysm respectively; (3) despite current fluoroquinolones using doubling the risk of the occurrence of aortic dissection or aneurysm, the NNTH was at 1245 based on a moderate level of evidence.

4.2 Comparison with Other Meta-analyses

Four meta-analyses on this issue have been published, we summarized the details on Table 3.\[2, 7, 22, 23\] Though the major result of our meta-analysis was consistent with these former meta-analyses, differences or new findings between ours and the former ones were be noted. At first, these meta-analyses included no more than five studies. By contrast, our meta-analysis included 5 observational studies with 2,829,385 patients in total. So our meta-analysis was the up-to-date and the broadest one and can consolidate the results of former meta-analyses. Secondly, we found that three of these meta-analyses used the HR of aortic aneurysm replaced the HR of aortic diseases;\[7, 22, 23\] it may reduce the risk of occurrence of aortic diseases. We excluded this study,\[18\] when combing with the OR together. Thirdly, we reevaluated the NNTH for aortic aneurysm or dissection because we also found Lee et al.\[17\] had a more statistically significant RR than two meta-analyses \[7, 23\] pooled. Finally, after adjusting the data, we reevaluated the evidence quality of primary outcome to help medical care providers make clinical decisions.
4.3 Implications for Clinical Practice

This meta-analysis demonstrated the underlying risk of first occurrence of aortic diseases among elderly population above the age of 50 when these patients were currently exposed to fluoroquinolones. The interesting thing was the risk of past use of fluoroquinolones (longer than 60 days prior to the index date) lower than the risk of current use (within 60 days). What’s more, when doctors weigh these severe effects and beneficial outcomes, the NNTH of aortic diseases should be taken into consideration. So, for the health care providers, if old patients have to use fluoroquinolones even on the basis of the antimicrobial stewardship program, the regular follow-up on the former 60-day will be important.

There are multiple risks of fluoroquinolones use. Regarding of ciprofloxacin, several studies showed that could inhibit collagen production in tenocytes.[24, 25] Another study suggested patients with aortic aneurysm, aortic dissection or Marfan syndrome had a higher risk for aortic rupture when being exposed to fluoroquinolones.[26] Moreover, compared with intravenous fluoroquinolones, oral ones had a higher risk and levofloxacin was not only associated with aortic aneurysm but also associated with aortic dissection.[27] Based on these findings, future studies should focus on age stratification, evaluation for every fluoroquinolone’s risk of aortic aneurysm or dissection and different exposure time which may provide additional information because the aortic diseases were rarely adverse events which cannot be able to do randomized controlled trials.

Strengths And Limitations

An important strength of our meta-analysis was conformity with the PRISMA and MOOSE guidelines and the GRADE by the recommendations of the Cochrane Collaboration; we also
registered the protocol at PROSPERO. To reevaluate the NNTH for current fluoroquinolones use, we pooled the statistically significant OR among study and exclude one study which reported aortic aneurysm and aortic dissection separately.

Our meta-analysis had some limitations as well. At first, the involved studies were all observational designs and conducted in various patient groups, clinical settings and statistical methods. Secondly, the year of age in included studies was above 50, lack of the year of age from 18 to 49. Thirdly, one study of the past use of fluoroquinolones had a negative risk for aortic dissection. Last, some of these studies did not report each fluoroquinolone made comparison with all other fluoroquinolones and the follow-up of each study was not parallel. Thus, the risk for aortic aneurysm and aortic dissection respectively had a significant heterogeneity. We also do not make the meta-regression and publication bias because the absence of individual data and the number of studies was limited.

Conclusions

Our meta-analysis suggested that current fluoroquinolone use had a majorly increase of first occurrence for aortic diseases, although the evidence quality was moderate and the absolute risk was fairly modest. Hence, physicians and surgeons should pay attention to the risk of aortic diseases associated with fluoroquinolone use.

Abbreviations

1. ORs; odds risks
2. NNTH; the Number Need to Treat to Harm
3. MOOSE; Meta-analysis of Observational Studies in Epidemiology
4. PRISMA; Preferred Reporting Items for Systematic Reviews and Meta-Analyses
5. MeSH; Medical Subject Headings
6. RR; Relative Risk  
7. HR; Hazard Ratio  
8. RD; Risk Difference  
9. CIs; confidence intervals  
10. NOS; Newcastle Ottawa Scale  
11. GRADE; Grading of Recommendations Assessment, Development, and Evaluation  

Declarations  

7.1 Ethics approval and consent to participate  
Not applicable;  

7.2 Consent for publication  
Not applicable;  

7.3 Availability of data and materials  
Because this is a meta-analysis, all of data included in this study could be found in the included references.  

7.4 Competing interests  
The authors declare that they have no competing interests.  

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7.6 Authors' contributions  
X.-C. D. contributed to the conception and design of this study, acquisition of data, analysis and interpretation of data, drafting and revising of the article, and final approval of the version to be published; X.-X. Y., L. M. and Y.-Y. P. contributed to acquisition of data, analysis and interpretation of data, drafting the article, and final approval of the version to be published; G.-M. T. contributed to check the acquired data and final approval.
of the version to be published; H.-L. H. contributed to the conception and design of the study, analysis and interpretation of data, revising the article, and final approval of the version to be published. All authors have read and approved the manuscript.

7.7 Acknowledgements

Not applicable;

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Tables

**Table 1A** Characteristics of Included Observational Studies Comparing Fluoroquinolone Use With non-use or exposure to other for the risk for aortic diseases
| Study Authors Year | Participants | Interventions | Primary Outcomes | Study design | Control | Follow up | Covariates Adjustment |
|--------------------|--------------|---------------|-----------------|--------------|---------|-----------|-----------------------|
| Lee et al. 2015    | Adults in the National Health Insurance Research Database (NHIRD) of Taiwan from 1998 to Dec 2011. | Use any of fluoroquinolones: ciprofloxacin, levofloxacin, ofloxacin, sparfloxacin, norfloxacin, lomefloxacin, moxifloxacin, gemifloxacin, enoxacin, pefloxacin | 1477 individuals of first occurrence of aortic Aneurysm(AA) or dissection(AD) requiring hospitalization | A nested case-control analysis | 147,700 controls using a risk set sampling scheme at the same database | 3613.3 days | Demographic cardiovascular comorbidities factors for aortic aneurysm and dissection, intensity of health care utilization, and use of specific medications. |

**Table 1B** Characteristics of Included Observational Studies Comparing Fluoroquinolone Use With non-use or exposure to other for the risk for aortic diseases

Use With non-use or exposure to other for the risk for aortic diseases
| Study Authors Year | Participants | Interventions | Primary Outcomes | Study design | Control | Follow-up |
|--------------------|--------------|---------------|------------------|--------------|---------|-----------|
| Daneman et al. 2015 | an inception cohort with uniform accrual of all Ontario adults turning age 65, during a 15-year period between April 1997 and March 2012 | ciprofloxacin, norfloxacin, levofloxacin, moxifloxacin, and ofloxacin (n=657 950) | aortic aneurysm and aortic rupture or dissection in hospital and emergency departments | population-based longitudinal cohort study of elderly patients in Ontario, Canada | Adults with no prescriptions of fluoroquinolones (n=1 086 410) | 2 to 17 years |

**Table 1C** Characteristics of Included Observational Studies Comparing Fluoroquinolone Use With non-use or exposure to other for the risk for aortic diseases

| Authors Year | Participants | Interventions | Controls | Primary outcomes | Study design | Follow-up | Adjustments |
|--------------|--------------|---------------|----------|------------------|--------------|-----------|-------------|
| Lee et al. 2018 | all inpatients diagnosed with AA or AD from 2000 to 2011 in Longitudinal Health Insurance Database | ciprofloxacin, levofloxacin, ofloxacin, sparfloxacin, norfloxacin, lomefloxacin, moxifloxacin, gemifloxacin, enoxacin, pefloxacin (N=12 13) | DRS matching process among participants not exposed to fluoroquinolones (N=12 13) | aortic aneurysm or aortic dissection | unidirectional case-crossover design | 60-180 days | A disease-risk score–matched time control analysis was performed to investigate the potential time-trend bias. Risks were calculated by a conditional logistic regression model |

**Table 1D** Characteristics of Included Observational Studies Comparing Fluoroquinolone
| Authors Year | Participants | Interventions | Controls | Primary outcomes | Study design |
|-------------|--------------|---------------|----------|----------------|-------------|
| Sommet et al. 2019 | patients ≥ 50 years diagnosed with AA or AD from 1972 to 2017 in the World Health Organization Global Individual Case Safety Reports (ICSRs) Database (N=172588) | Levofloxacin, Ciprofloxacin, Moxifloxacin, Ofloxacin, Gatifloxacin, Tosufloxacin | same included patients with amoxicillin (N=40658) | aortic aneurysm or aortic dissection | The case/non-case study method |

**Table 1E** Characteristics of Included Observational Studies Comparing Fluoroquinolone Use With non-use or exposure to other for the risk for aortic diseases

| Authors Year | Participants | Interventions | Controls | Primary outcomes | Study design | Follow-up | Adjustment |
|-------------|--------------|---------------|----------|----------------|-------------|-----------|------------|
| Pasternak et al. 2018 | population included all adults in Sweden who received a prescription for fluoroquinolones or amoxicillin during the study and who were aged 50 years or older from July 2006 to December 2013 | Fluoroquinolones exposure (360088) | amoxicillin use (n=360088) | the first clinical encounter of aortic aneurysms or dissections | a cohort study based on linked nationwide data from Swedish registers | 120 days | propensity scores |
**Table 2** Risk of bias of observational studies reporting on aortic diseases using New Castle Ottawa Scale

| Selection | Lee et al. 2015 | Daneman et al.2015 | Pasternak et al.2018 | Sommet et al.2018 |
|-----------|-----------------|---------------------|----------------------|---------------------|
| Adequate case definition | Adequate case definition | Adequate case definition | Adequate case definition | Adequate case definition |
| An independent validation had a positive to positive outcome definition by | An independent validation had a positive to positive outcome definition by | An independent validation had a positive to positive outcome definition by | An independent validation had a positive to positive outcome definition by |
| A more specific outcome definition by | A more specific outcome definition by | A more specific outcome definition by | A more specific outcome definition by |
| NOS SCORES:★★★★★★★★ | NOS SCORES:★★★★★★★★ | NOS SCORES:★★★★★★★★ | NOS SCORES:★★★★★★★★ |
| Representativeness of cases | Representativeness of cases | Representativeness of cases | Representativeness of cases |
| Population based | Population based | Population based | Population based |
| Definition of controls | One hundred controls were selected for diagnosis. | One hundred controls were selected for diagnosis. | One hundred controls were selected for diagnosis. |
| NOS SCORES:★★★★★★★★ | NOS SCORES:★★★★★★★★ | NOS SCORES:★★★★★★★★ | NOS SCORES:★★★★★★★★ |
| Selection of controls | Selection of controls | Selection of controls | Selection of controls |
| Population based | Population based | Population based | Population based |
| Definition of controls | One hundred controls were selected for diagnosis. | One hundred controls were selected for diagnosis. | One hundred controls were selected for diagnosis. |
| NOS SCORES:★★★★★★★★ | NOS SCORES:★★★★★★★★ | NOS SCORES:★★★★★★★★ | NOS SCORES:★★★★★★★★ |
| Representativeness of cases | Representativeness of cases | Representativeness of cases | Representativeness of cases |
| Representative cases | Representative cases | Representative cases | Representative cases |
| NOS SCORES:★★★★★★★★ | NOS SCORES:★★★★★★★★ | NOS SCORES:★★★★★★★★ | NOS SCORES:★★★★★★★★ |
| Selection of controls | Selection of controls | Selection of controls | Selection of controls |
| Population based | Population based | Population based | Population based |
| Definition of controls | One hundred controls were selected for diagnosis. | One hundred controls were selected for diagnosis. | One hundred controls were selected for diagnosis. |
| NOS SCORES:★★★★★★★★ | NOS SCORES:★★★★★★★★ | NOS SCORES:★★★★★★★★ | NOS SCORES:★★★★★★★★ |
| Representativeness of controls | Representativeness of controls | Representativeness of controls | Representativeness of controls |
| Study control for all 96 covariates by | Study control for all 96 covariates by | Study control for all 96 covariates by | Study control for all 96 covariates by |
| A propensity score for adjustment and | A propensity score for adjustment and | A propensity score for adjustment and | A propensity score for adjustment and |
| Cases have a higher burden of cardiovascular medication than controls | Cases have a higher burden of cardiovascular medication than controls | Cases have a higher burden of cardiovascular medication than controls | Cases have a higher burden of cardiovascular medication than controls |
| NOS SCORES:★★★★★★★★ | NOS SCORES:★★★★★★★★ | NOS SCORES:★★★★★★★★ | NOS SCORES:★★★★★★★★ |
| Comparability of controls | Comparability of controls | Comparability of controls | Comparability of controls |
| Study control for all 96 covariates by | Study control for all 96 covariates by | Study control for all 96 covariates by | Study control for all 96 covariates by |
| A propensity score for adjustment and | A propensity score for adjustment and | A propensity score for adjustment and | A propensity score for adjustment and |
| Cases have a higher burden of cardiovascular medication than controls | Cases have a higher burden of cardiovascular medication than controls | Cases have a higher burden of cardiovascular medication than controls | Cases have a higher burden of cardiovascular medication than controls |
| NOS SCORES:★★★★★★★★ | NOS SCORES:★★★★★★★★ | NOS SCORES:★★★★★★★★ | NOS SCORES:★★★★★★★★ |
| Exposure | Exposure | Exposure | Exposure |
| Ascertainment of exposure | Ascertainment of exposure | Ascertainment of exposure | Ascertainment of exposure |
| Records of patients having a fluoroquinolone prescription. | Records of patients having a fluoroquinolone prescription. | Records of patients having a fluoroquinolone prescription. | Records of patients having a fluoroquinolone prescription. |
| Same method for ascertainment of cases and controls | Same method for ascertainment of cases and controls | Same method for ascertainment of cases and controls | Same method for ascertainment of cases and controls |
| Non-response rate | Non-response rate | Non-response rate | Non-response rate |
| Non respondents described | Non respondents described | Non respondents described | Non respondents described |
| Outcome | Outcome | Outcome | Outcome |
| Assessment of outcome | Assessment of outcome | Assessment of outcome | Assessment of outcome |
| by International Classification of Diseases. | by International Classification of Diseases. | by International Classification of Diseases. | by International Classification of Diseases. |
| Follow-up long enough for outcomes to occur | Follow-up long enough for outcomes to occur | Follow-up long enough for outcomes to occur | Follow-up long enough for outcomes to occur |
| A minimum of 2 years and a maximum of 10 years. | A minimum of 2 years and a maximum of 10 years. | A minimum of 2 years and a maximum of 10 years. | A minimum of 2 years and a maximum of 10 years. |
| Adequacy of follow up of cohorts | Adequacy of follow up of cohorts | Adequacy of follow up of cohorts | Adequacy of follow up of cohorts |
| complete | complete | complete | complete |
| Outcome | Outcome | Outcome | Outcome |
| Assessment of outcome | Assessment of outcome | Assessment of outcome | Assessment of outcome |
| by International Classification of Diseases. | by International Classification of Diseases. | by International Classification of Diseases. | by International Classification of Diseases. |
| Follow-up long enough for outcomes to occur | Follow-up long enough for outcomes to occur | Follow-up long enough for outcomes to occur | Follow-up long enough for outcomes to occur |
| 120-day follow up | 120-day follow up | 120-day follow up | 120-day follow up |
| Adequacy of follow up of cohorts | Adequacy of follow up of cohorts | Adequacy of follow up of cohorts | Adequacy of follow up of cohorts |
| complete | complete | complete | complete |
| Outcome | Outcome | Outcome | Outcome |
| Assessment of outcome | Assessment of outcome | Assessment of outcome | Assessment of outcome |
| by International Classification of Diseases. | by International Classification of Diseases. | by International Classification of Diseases. | by International Classification of Diseases. |
| Follow-up long enough for outcomes to occur | Follow-up long enough for outcomes to occur | Follow-up long enough for outcomes to occur | Follow-up long enough for outcomes to occur |
| 120-day follow up | 120-day follow up | 120-day follow up | 120-day follow up |
| Adequacy of follow up of cohorts | Adequacy of follow up of cohorts | Adequacy of follow up of cohorts | Adequacy of follow up of cohorts |
| complete | complete | complete | complete |
of cases and controls
Non-response rate
Non respondents described

Lee et al.2018
NOS SCORES:★★★★★★★★

Selection
Adequate case definition
Cases were required to have International Classification of Diseases (ICD-9-CM) codes for AA or AD, plus diagnostic evidence ob transthoracic echocardiography, thoracic or abdominal computed tomography, or magnetic resonance imaging.

Representativeness of cases
Representative cases

Selection of controls
Population based

Definition of controls
self-controlled method based on case-time-control design to adjust for the exposure-outcome association derived from case-crossover analyses.

Comparability
Comparability of controls
self-controlled method reduces the possibility of within-person time-invariant confounding, and avoids control selection biases.

Exposure
Ascertainment of exposure
Exposure to fluoroquinolone was identified by a reimbursement code of oral fluoroquinolones with a prescription length of 3 days or more.

Same method for ascertainment of cases and controls

Non-response rate
Non respondents described

Table 3 Comparison With Other Previous Meta-analyses

| Author/Year | Singh S et al. 2017 | Noman AT et al. 2019 | Yu X et al. 2019 | Rawla P et al. 2019 | Current Meta-analysis |
|-------------|---------------------|----------------------|------------------|---------------------|----------------------|
| Number of observational studies | 2 | 3 | 3 | 4 | 5 |
| Number of participants | 1,893,537 | 2,613,713 | 2,613,713 | 2,616,139 | 2,829,385 |
| Year of search strategy | 2017 | 2018 | 2019 | 2018 | 2019 |
| OR/RR of AA or AD | AA (OR, 2.25; 95% CI, 2.03-2.49) | AA or AD (OR, 2.04; 95% CI, 1.67-2.48) | AA or AD (OR, 2.20; 95% CI, 1.92-2.52) | AA or AD (RR, 2.14; 95% CI, 1.93-2.36) | AA or AD (OR, 2.15; 95% CI, 1.66-2.64) |
| | AD (OR, 2.79; 95% CI, 2.31-3.37) | AD (OR, 2.25; 95% CI, 1.42-3.56) | AD (OR, 2.79; 95% CI, 0.97-2.99) |
| GRADE | moderate | moderate | NR | moderate | moderate |
| NNTH | 618(AA) | 1376 | NR | NR | 1245 |

AD = aortic dissection; AA = aortic aneurysm; GRADE = Grading of Recommendations Assessment, Development, and Evaluation; NNTH = Number Need to Treat to Harm; NR = not report.
Figure 1

Selection of observational studies for the meta-analysis.
Figure 2

The Risk of Aortic Diseases among Fluoroquinolones Users in comparison to Non-users or Users of Other Antibiotics
Supplementary Files

This is a list of supplementary files associated with the primary manuscript. Click to download.

PRISMA-Checklist.doc