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

Xiao-ce Dai

First Hospital of Jiaxing

Xin-xin Yang

Zhejiang Hospital of Traditional Chinese Medicine

Lan Ma

Nantong City No 1 People's Hospital and Second Affiliated Hospital of Nantong University

Guan-min Tang

First Hospital of Jiaxing

Yan-yun Pan

Zhejiang Hospital of Traditional Chinese Medicine

Hui-lin Hu (✉ huhuulin1979@sohu.com)

First Hospital of Jiaxing <https://orcid.org/0000-0003-1619-4682>

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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 (NNT_H) 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 methodical 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 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 combining 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.

7.5 Funding

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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;

References

1. Michalak K, Sobolewska-Wlodarczyk A. Treatment of the Fluoroquinolone-Associated Disability: The Pathobiochemical Implications. 2017: 8023935.
2. Singh S, Nautiyal A. Aortic Dissection and Aortic Aneurysms Associated with Fluoroquinolones: A Systematic Review and Meta-Analysis. *The American journal of medicine* 2017; 130: 1449-57.e9.
3. Sommet A, Benevent J, Rousseau V, et al. What Fluoroquinolones Have the Highest Risk of Aortic Aneurysm? A Case/Non-case Study in VigiBase(R). *J Gen Intern Med* 2019; 34: 502-3.
4. Lee CC, Lee MG, Hsieh R, et al. Oral Fluoroquinolone and the Risk of Aortic Dissection. *Journal of the American College of Cardiology* 2018; 72: 1369-78.
5. Lu N, Hu P, Wang J, et al. Simple Renal Cysts Are Associated With 24-Month Prognosis of Patients With Type B Aortic Dissection and Hypertension. *The Canadian journal of cardiology* 2019.
6. Kochanek KD, Murphy SL, Xu J, Tejada-Vera B. Deaths: Final Data for 2014. *National vital statistics reports : from the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System* 2016; 65: 1-122.
7. Noman AT, Qazi AH, Alqasrawi M, et al. Fluoroquinolones and the risk of aortopathy: A systematic review and meta-analysis. *International journal of cardiology* 2019; 274: 299-302.
8. Bonkat G, Pilatz A, Wagenlehner F. Time to Adapt Our Practice? The European Commission Has Restricted the Use of Fluoroquinolones since March 2019. *Eur Urol* 2019; 76:273-5.
9. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *Jama* 2000; 283: 2008-12.
10. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ (Clinical research ed)* 2009; 339: b2700.
11. GA Wells BS, D O'Connell, J Peterson, V Welch, M Losos, P Tugwell. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2019. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed 05 Jul 2019.
12. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ (Clinical research ed)* 2008; 336: 924-6.
13. Davies HT, Crombie IK, Tavakoli M. When can odds ratios mislead? *BMJ (Clinical research ed)* 1998; 316: 989-91.
14. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ (Clinical research ed)* 2003; 327: 557-60.
15. Laupacis A, Sackett DL, Roberts RS. An assessment of clinically useful measures of the consequences of treatment. *The New England journal of medicine* 1988; 318: 1728-33.
16. C. C. Dr Chris Cates' EBM Website Visual Rx 2019. <http://www.nntonline.net/visualrx>. Accessed 05 Jul 2019.
17. Lee CC, Lee MT, Chen YS, et al. Risk of Aortic Dissection and Aortic Aneurysm in Patients Taking Oral Fluoroquinolone. *JAMA Intern Med* 2015; 175: 1839-47.
18. Daneman N, Lu H, Redelmeier DA. Fluoroquinolones and collagen associated severe adverse events: a longitudinal cohort study. *BMJ Open* 2015; 5: e010077.
19. Pasternak B, Inghammar M, Svanstrom H. Fluoroquinolone use and risk of aortic aneurysm and dissection: nationwide cohort study. *BMJ (Clinical research ed)* 2018; 360: k678.
20. Clouse WD, Hallett JW, Jr., Schaff HV, et al. Acute aortic dissection: population-based incidence compared with degenerative aortic aneurysm rupture. *Mayo Clin Proc* 2004; 79: 176-80.
21. Olsson C, Thelin S, Stahle E, Ekblom A, Granath F. Thoracic aortic aneurysm and dissection: increasing prevalence and improved outcomes reported in a nationwide population-based study of more than 14,000 cases from 1987 to 2002. *Circulation* 2006; 114: 2611-8.

22. Yu X, Jiang DS, Wang J, et al. Fluoroquinolone Use and the Risk of Collagen-Associated Adverse Events: A Systematic Review and Meta-Analysis. *Drug Safety* 2019; 42:1025-33.
23. Rawla P, El Helou ML, Vellipuram AR. Fluoroquinolones and the risk of aortic aneurysm or aortic dissection: A systematic review and meta-analysis. *Cardiovasc Hematol Agents Med Chem* 2019;17:3-10.
24. Menon A, Pettinari L, Martinelli C, et al. New insights in extracellular matrix remodeling and collagen turnover related pathways in cultured human tenocytes after ciprofloxacin administration. *Muscles, ligaments and tendons journal* 2013; 3: 122-31.
25. LeMaire SA, Zhang L, Luo W, et al. Effect of Ciprofloxacin on Susceptibility to Aortic Dissection and Rupture in Mice. *JAMA Surg* 2018; 153: e181804.
26. Frankel WC, Trautner BW, Spiegelman A, Grigoryan L, LeMaire SA. Patients at Risk for Aortic Rupture Often Exposed to Fluoroquinolones during Hospitalization. *Antimicrob Agents Chemother* 2019; 63: e01712-18.
27. Meng L, Huang J, Jia Y, Huang H, Qiu F. Assessing fluoroquinolone-associated aortic aneurysm and dissection: Data mining of the public version of the FDA adverse event reporting system. *International journal of clinical practice* 2019; 73: e13331.

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	Exposure category	Outcomes	Propensity score adjusted RR (95%CI)
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	Demographics, cardiovascular comorbidities, risk factors for aortic aneurysm and dissection, intensity of health care facility utilization, and use of specific medications. Using indication for fluoroquinolone and a combined weighted comorbidity index.	Current use;	AA or AD	2.43 (1.83-3.22)
								Within 60 days of the index date	AA	2.36 (1.66-3.36)
									AD	2.55 (1.58-4.11)
								past use; 61 and 365 days prior to the index date	AA or AD	1.48 (1.18-1.86)
									AA	1.19 (0.87-1.62)
									AD	2.00 (1.44-2.79)
								Any prior-year use; in the 1-year period before the index date	AA or AD	1.74 (1.44-2.09)
									AA	1.52 (1.19-1.94)
									AD	2.15 (1.61-2.85)

Table 1B 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	Exposure category	Outcomes	adjusted HR (95%CI)
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	demographic, healthcare utilisation and comorbidity variables	using any fluoroquinolone to 30 days following treatment	AA	2.24, (2.02-2.49)
									AD	2.84, (2.32-3.50)

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	Exposure category
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=1213)	DRS matching process among participants not exposed to fluoroquinolones (N=1213)	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	Using the predefined 6 day window during the case or reference period a reimbursement code of oral fluoroquinolone with a prescription length of 3 or more.

Table 1D 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	Exposure category	Outcomes	adjusted ROR
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	NR	age, sex, year of report, continent of report, notifier type, and number of drugs prescribed were analyzed by multivariable logistic regression	Exposure to fluoroquinolones vs. amoxicillin exposure	AA or AD	2.78, 95% CI 1.83-4.23

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

Authers Year	Participants	Interventions	Controls	Primary outcomes	Study design	Follow- up	Adjustments	Exposure category	Outcomes	Propensity scores 60-day risk period HR (95%CI)	Proper scores 61 to 120 days fr risk period HR (95%C
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	a 60-day period from start of treatment (days 1 to 60, starting from the date when the prescription was filled. a secondary analysis investigating the subsequent 60 days (days 61 to 120)	aortic aneurysm or dissection	1.66; (1.12- 2.46)	aortic aneury 1.90 (1 to 2.96 aortic dissec 0.93 (C -2.29)

Table 2 Risk of bias of observational studies reporting on aortic diseases using New Castle Ottawa Scale

Lee et al. 2015		NOS SCORES:00000000
Selection		
	Adequate case definition	An independent validation had a positive predictive rate of 92%; A more specific outcome definition by combining with surgical procedures;
	Representativeness of cases	Representative cases
	Selection of controls	Population based
	Definition of controls	One hundred controls were selected for each case, matched on 5-year age class, sex, and the index date of case diagnosis.
Comparability		
	Comparability of controls	Study control for all 96 covariates by using conditional logistic regression analysis. A propensity score for adjustment and matching due to conventional multivariate analysis. Cases have a higher burden of cardiovascular diseases, higher Charlson index, and greater use of cardiovascular medication than controls
Exposure		
	Ascertainment of exposure	Records of patients having a fluoroquinolone prescription
	Same method for ascertainment of cases and controls	YES
	Non-response rate	Non respondents described
Daneman et al.2015		NOS SCORES:00000000
Selection		
	Representativeness of the exposed cohort	Truly representative of the average age above or equal to 65 adults in population-based Ontario Registered Persons Database.
	Representativeness of the non-exposed cohort	Drawn from the same database
	Ascertainment of exposure	Records of fluoroquinolone prescriptions for individuals in database.
	Outcome of interest was not present at the beginning of study	No, interest outcomes were identified at inception of this study
Comparability		
	Comparability of cohorts because of the design or analysis	Study controls for negative tracer and positive tracer
Outcome		
	Assessment of outcome	by International Classification of Diseases 9th and 10th diagnoses
	Follow-up long enough for outcomes to occur	A minimum of 2 years and a maximum of 17 years follow-up
	Adequacy of follow up of cohorts	complete
Pasternak et al.2018		NOS SCORES:00000000
Selection		
	Representativeness of the exposed cohort	True representativeness; All adults in Sweden who use fluoroquinolones or amoxicillin during the study and who were aged 50 years or older in database (nationwide data from Swedish registers).
	Representativeness of the non-exposed cohort	Drawn from the same database.
	Ascertainment of exposure	A first diagnosis of aortic aneurysm or dissection (admission to hospital or emergency department for aortic aneurysm or dissection, or death due to aortic aneurysm or dissection) associated with oral fluoroquinolone use.
	Outcome of interest was not present at the beginning of study	No, interest outcomes were identified at inception of this study
Comparability		
	Comparability of cohorts because of the design or analysis	Study controls for potential confounding from differences in baseline health status use propensity score matched design. propensity scores using to control for potential confounders, treatment episodes of fluoroquinolone and amoxicillin use
Outcome		
	Assessment of outcome	diagnoses according to ICD-10 (international classification of diseases, 10th revision) and data for surgical procedures.
	Follow-up long enough for outcomes to occur	120-day follow up
	Adequacy of follow up of cohorts	complete
Sommet et al.2018		NOS SCORES:00000000
Selection		
	Adequate case definition	Cases were ICSRs (the World Health Organization Global Individual Case Safety Reports) containing the term "aortic aneurysms and dissections" according to the MedDRA dictionary.
	Representativeness of cases	obviously representative series of cases
	Selection of controls	Population based
	Definition of controls	all other reports except aortic aneurysms and dissections at the same database
Comparability		
	Comparability of controls	Adjusted for age, sex, year of report, continent of report, notifier type, and number of drugs prescribed were analyzed by multivariable logistic regression.
Exposure		
	Ascertainment of exposure	Fluoroquinolones and amoxicillin use was found by National pharmacovigilance systems
	Same method for ascertainment	YES

	of cases and controls	
	Non-response rate	Non respondents described
Lee et al.2018		NOS SCORES:00000000
Selection		
	Adequate case definition	Cases were required to have International Classification of Diseases (ICD-9-CM) codes for AA or AD, plus diagnostic evidence obtained by advanced imaging studies such as angiography, transesophageal or 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-crossover design instead of selecting controls from an external population
Comparability		
	Comparability of controls	self-controlled method reduces the possibility of within-person time-invariant confounding, and avoids control selection biases. case-time-control design to adjust for the exposure-outcome association derived from case-crossover analyses.
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	YES
	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, 1.98; 95% CI, 0.97-2.99)
					AA (OR, 1.77; 95% CI, 0.98-2.57)
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.

Figures

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

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