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Oral Fluoroquinolones and Risk of Aortic Aneurysm or Dissection: A Nationwide Population-Based Propensity Score Matched Cohort Study

Running Head: Fluoroquinolone Aortic Aneurysm/Dissection Risks

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Abstract

Introduction: The association between oral fluoroquinolones and aortic aneurysm or dissection among the United States population remains unclear and requires investigation.

Objectives: To investigate risk of aortic aneurysm or dissection in patients using oral fluoroquinolones compared to those using macrolides in real-world clinical practice among a large US general population.

Methods: We conducted a retrospective cohort study using MarketScan commercial and Medicare supplemental databases from January 01, 2013 to December 31, 2018. Adult patients with at least one prescription fill for fluoroquinolone or macrolide (control) antibiotics were included. The primary outcome was estimated incidence of aortic aneurysm or dissection associated with use of fluoroquinolones compared to macrolides during a 60-day follow-up period in a 1:1 propensity-score matched cohort. Crude incidence of aortic aneurysm or dissection was estimated as number of cases per 1000 person-years follow-up and adjusted hazard ratios (aHR) with 95% confidence intervals (CI) were estimated using multivariable Cox-proportional hazard regression models.

Results: We identified 3,174,620 patients (1,587,310 in each group) after 1:1 propensity score matching. Crude incidence of aortic aneurysm or dissection was 1.9 cases per 1000 person-years among fluoroquinolone users and 1.2 cases per 1000 person-years among macrolide users. In multivariable Cox regression, compared with macrolides, use of fluoroquinolones was associated with an increased risk of aortic aneurysm or dissection (aHR:1.34; 95% CI:1.17–1.54). The association was primarily driven by a high incidence of aortic aneurysm cases (95.8%). Results of sensitivity (e.g., fluoroquinolone exposure ranging from 7 to 14 days (aHR: 1.47; 95% CI:

1.26–1.71)) and subgroup analyses (e.g., ciprofloxacin (aHR: 1.26; 95% CI: 1.07–1.49), levofloxacin (aHR: 1.44; 95% CI: 1.19–1.52)) remained consistent with main findings.

Conclusion: Fluoroquinolone use was associated with a 34% increased risk of aortic aneurysm or dissection compared to macrolide use among a general US population.

Key Words: Fluoroquinolones, Aortic Aneurysm, Aortic Dissection, Macrolides, Risk Factors

Fluoroquinolones, a class of commonly prescribed antibiotics, are used to treat bacterial infections including pneumonia, acute sinusitis, chronic bronchitis, septicemia, skin infections, bone and joint infections, respiratory, urinary tract, and intra-abdominal infections.[1] Among antibiotics classes, fluoroquinolones are highly utilized.[2-4] Although generally well-tolerated, these drugs have been associated with a wide array of adverse events and safety warnings in the past years. In 2008, the United States Food and Drug Administration (FDA) added a Boxed Warning to their label for an increased risk of tendinitis and tendon rupture.[5] The association between fluoroquinolones and collagen-related disorders such as tendonitis, Achilles tendon rupture, and retinal detachment is well documented in the literature.[6-8] Symptoms associated with myasthenia gravis and risk of peripheral neuropathy were added to the Boxed Warning in 2011 and 2013, respectively.[9] Thereafter, in 2016, the FDA issued another warning to restrict the use of fluoroquinolones for certain uncomplicated infections and warned about the disabling, permanent adverse events involving tendons, muscles, joints, nerves, and central nervous system.[10]

In December 2018, the FDA issued a new drug safety warning that fluoroquinolones might be associated with an increased risk of ruptures (aneurysm) and tears (dissection) in the aorta.[11] Aortic aneurysm is a balloon-like bulge that can occur anywhere in the wall of the aorta and can either rupture (aneurysm) or develop tears (dissection).[12] Although recent studies conducted in Taiwan and Sweden have raised concern about an increased risk of aortic aneurysm associated with the use of fluoroquinolones, these studies had limitations in study design (e.g. lack of active control group, confounding by indication).[13-16] Furthermore, higher prevalence of comorbid conditions including heart disease, hypertension, obesity, and a comparatively worse health status of US adults make generalizability of existing study results limited.[17-19] Despite all recent

warnings and evidence, fluoroquinolones still remain one of the most commonly prescribed antibiotics in the United States with approximately 25 million prescriptions dispensed in 2017.[20] Thus, we aimed to investigate the risk of aortic aneurysm or dissection in patients using oral fluoroquinolones compared to those using macrolides in real-world clinical practice among a large US general population.

Methods

Study Design and Data Source

We conducted a cohort study using the IBM Truven Health Analytics MarketScan Commercial and Medicare Supplemental databases from January 01, 2012 to December 31, 2018. This nationwide administrative claims data captures patient-level medical encounter information across all health care settings (inpatient, outpatient, and pharmacy). The population of commercial data consists of employees and their dependents up to the age of 65 years who are covered by an employer-sponsored insurance. The Medicare supplemental data consists of retirees above the age of 65 years who are covered by Medicare Supplement Insurance. The study was approved by the Institutional Review Board at the University of Florida.

Study Cohort

The study cohort included adult patients aged 18 years or older with at least one prescription fill for oral fluoroquinolone or macrolide antibiotics with ≥3 days' supply from January 01, 2013 to December 31, 2018. The date of first prescription for study antibiotics was defined as the index date. For patients with multiple prescriptions of study antibiotics during the study period, only the first prescription was included in the analysis. To be included, patients were required to be

continuously enrolled in the health plan with both medical and pharmacy benefit coverage for at least 12-months before the index date. Patients were excluded if they had i) any evidence of aortic aneurysm or dissection as identified by inpatient or outpatient diagnostic codes for aortic aneurysm or aortic dissection during the baseline period, ii) a record of any hospitalization or use of study antibiotics during the 6-month period preceding the index date, or iii) filled prescriptions for both study antibiotics on the index date.

Antibiotic Exposure

FDA-approved oral fluoroquinolones available in the United States including ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin, gemifloxacin, and delafloxacin comprised the exposure group. Oral macrolides including erythromycin, azithromycin, and clarithromycin constituted the active comparison group to address the inherent limitations of confounding by indication in pharmacoepidemiologic studies. We chose macrolides as a comparison group because there is no known association between macrolides and aortic aneurysm or dissection, and their approved indications are similar to those of fluoroquinolones.[21-25]

In a sensitivity analysis, we assessed the association between aortic aneurysm or dissection for each fluroquinolone agent individually compared to macrolides (e.g. ciprofloxacin prescriptions compared to macrolide prescriptions).

Study Outcomes

The primary outcome of our study was the incidence of aortic aneurysm or dissection requiring hospitalization or emergency department visit associated with use of fluoroquinolones compared to macrolides. The outcome was measured using the International Classification of Diseases, 9th

and 10th Edition, Clinical Modification (ICD-9-CM and ICD-10-CM) diagnostic codes for aortic aneurysm or aortic dissection, including with or without rupture, thoracic, abdominal or thoracoabdominal aneurysm or dissection as the primary diagnosis (Supplementary Table 1). This algorithm has been validated previously with a positive predictive value (PPV) of 92% for aortic aneurysm and 100% for dissection cases.[16] In a secondary analysis, outcomes of aortic aneurysm and aortic dissection were analyzed separately. In a sensitivity analysis, we used a less restrictive outcome definition by including cases with aortic aneurysm or dissection diagnosis in any position of the diagnostic codes recorded during inpatient or emergency department encounters.

Consistent with existing literature, patients were considered to be at-risk of the study outcome for a maximum of 60 days following the course of antibiotic therapy (i.e., days of supply + 60 days) after the index date.[16, 26, 27] In a sensitivity analysis, we varied the length of follow-up to up to 90 days and duration of antibiotic exposure (<7 days and 7-14 days)

Patients were followed up from the index date until the occurrence of a study outcome, end of enrollment, end of the study period (December 31, 2018), subsequent antibiotic prescription >7 days gap between prescription fills (gaps of ≤7 days between the end of first prescription and fill date of the subsequent prescription were allowed), switching to another study antibiotic, end of follow-up, or hospital admission unrelated to aortic aneurysm or dissection, whichever occurred first.

Covariates

To balance differences in baseline demographic and clinical characteristics of fluoroquinolone and macrolide users in our analysis, 1:1 propensity score matching was used. Using logistic

regression-based modeling, propensity scores for fluoroquinolone and macrolide users were estimated by regressing the treatment assignment on various baseline covariates of patients including demographics (age, gender), medical conditions reported to be associated with aortic aneurysm or dissection including cardiovascular risk factors and congenital disorders, infectious conditions considered to be potential indications for antibiotics, prescription medication use, and health care resource utilization, as identified from an extensive literature search (Supplementary Table 2).[12-16, 28-41] All medical conditions including comorbidities, cardiovascular, congenital risk factors, and prescription medication use were captured during the 12-month baseline period preceding the index date. The presence of infectious conditions was captured in the 2-week period before index date.

Statistical Analysis

Baseline demographic and clinical characteristics of fluoroquinolone and macrolide users were reported as proportions for categorial variables and means with standard deviations for continuous variables. Differences in the baseline characteristics of the two groups were determined using standardized differences for both before- and after-matching cohorts. A threshold of 10% was used to determine statistically significant differences, with values less than 10% implying well-balanced covariates between the two comparison groups.

After propensity score matching, incidence rates of aortic aneurysm or dissection were reported as the number of aortic aneurysm or dissection cases per 1000 person-years. A Cox proportional hazards regression model was used to estimate the adjusted hazard ratio (aHR) for aortic aneurysm or dissection cases between fluoroquinolone and macrolide users, controlling for age, gender, hypertension, diabetes, cardiovascular conditions including congestive heart failure,

myocardial infarction, peripheral vascular disorders, acute coronary syndrome, and cardiac arrhythmia in addition to propensity score matching.

To assess heterogeneity in measures of association, the following sub-group analyses were performed, i) patients aged ≤50 years compared to those aged >50 years, ii) males compared to females, iii) patients with hypertension versus those without, d) patients with diabetes versus those without, and iv) patients with pre-existing cardiovascular risk factors including congestive heart failure, myocardial infarction, peripheral vascular disorders, acute coronary syndrome, and cardiac arrhythmia versus those without. Additional sensitivity analyses by type of fluoroquinolone agent and duration of antibiotic exposure (<7 days and 7-14 days) were also conducted to assess to robustness of association. Propensity score matching was repeated for each subgroup and sensitivity analysis. Wherever applicable, p-value equal to or less than 0.05 denoted statistically significant differences between comparison groups. For subgroup analysis, a p-value for interaction less than 0.05 was used to denote a significant difference among groups. All statistical analyses were performed using SAS version 9.4., SAS institute, Cary, North Carolina.

Results

Baseline Characteristics

We identified 2,162,433 fluoroquinolone users and 3,715,640 macrolide users between January 2013 and December 2018 (Supplementary Figure 1). After 1:1 propensity score matching, the study cohort included 3,174,620 patients with 1,587,310 in each group. In the propensity score matched cohort, patient demographic characteristics, clinical comorbidities, presence of infectious conditions, medication use, and health care resource utilization were well-balanced

between the two groups as indicated by standardized differences of <0.10 (Table 1). The median (range) duration of drug exposure was 10 (3-35) days for fluoroquinolone users and 5 (3-21) days for macrolide users.

Risk of Aortic Aneurysm or Dissection

We identified 548 cases of aortic aneurysm or dissection among fluoroquinolone users and 328 cases among macrolide users (Table 2). The crude incidence of aortic aneurysm or dissection was 1.93 cases per 1000 person-years among fluoroquinolone users and 1.20 cases per 1000 person-years among macrolide users. In the multivariable Cox proportional hazards regression model, use of fluoroquinolone antibiotics was associated with a higher risk of aortic aneurysm or dissection compared to the use of macrolide antibiotics (aHR: 1.34; 95% Confidence Intervals (CI): 1.17-1.54).

In secondary analyses, 525 cases of aortic aneurysm with crude incidence of 1.85 cases per 1000 person-years were identified among fluoroquinolone users and 304 cases with crude incidence of 1.11 cases per 1000 person-years among macrolide users. In Cox regression, the association was consistent with an increased risk of aortic aneurysm among fluoroquinolone users compared to macrolide users (aHR: 1.38; 95% CI: 1.20-1.59). The association was non-significant for aortic dissection among fluoroquinolone users versus macrolide users (aHR: 0.92; 95% CI: 0.55-1.55). After dividing the follow-up period into 10-day intervals, about 52% (n=286) and 54% (n=177) of cases of aortic aneurysm or dissection occurred within the first 30-days of fluoroquinolone and macrolide treatment initiation, respectively (Supplementary Table 4).

Sensitivity and subgroup Analyses

In the sensitivity analysis by type of fluoroquinolone agent, the association of an aortic aneurysm or dissection outcome was significant among ciprofloxacin (aHR: 1.26; 95% CI: 1.07-1.49) and levofloxacin (aHR: 1.44; 95% CI: 1.19–1.52) users compared to macrolide users, but was not significant in moxifloxacin users (aHR: 0.94; 95% CI: 0.64–1.38) (Table 3). In the analysis by duration of exposure, fluoroquinolone users with 7 to 14 days of supply were associated with a significantly higher risk of an outcome (aHR: 1.47; 95% CI: 1.26–1.71), whereas the association in fluoroquinolone users with a supply of <7 days (aHR: 1.02; 95% CI: 0.72–1.32) was insignificant. When cases with relevant diagnostic codes in any position of inpatient or emergency encounters during a 60–day follow up period were included in the analysis the association of fluoroquinolone use and an outcome was significant (aHR: 1.45; 95% CI: 1.30–1.60) and remained consistent when follow-up duration was extended up to 90 days (aHR: 1.26; 95% CI: 1.13–1.43). The association was significant for aortic aneurysm and insignificant for aortic dissection when aortic aneurysm and dissection were analyzed separately.

In the subgroup analysis stratified by various demographic and clinical conditions, findings remained consistent indicating robust findings. The association appeared to be stronger among patients >50 years versus patients ≤ 50 years (aHR:1.31 vs 1.14, respectively). (Table 4).

Discussion

In this propensity score-matched cohort analysis of US adults, the use of fluoroquinolones was associated with a significantly higher risk of aortic aneurysm or dissection compared to an active comparator group using macrolides during a 60-day follow-up period. The association was primarily driven by aortic aneurysm and was significant in levofloxacin and ciprofloxacin users but not in moxifloxacin users compared to macrolide users. In addition, the association was

significant in fluoroquinolone users with 7 to 14 days of medication supply compared to macrolides. Results remained consistent among various subgroups stratified by demographic (age, gender) and clinical characteristics (diabetes, hypertension, cardiovascular conditions).

A cohort study conducted in Sweden reported that fluoroquinolone use was associated with a 66% increased rate of aortic aneurysm or dissection (HR: 1.66; 95% CI: 1.12–2.46) compared to amoxicillin use among adults aged 50 years or older.[16] The much larger magnitude of association observed in that study could be explained by differences in the selection of control group, antibiotic prescribing patterns, and population evaluated. Amoxicillin being a narrow-spectrum antibiotic with limited gram-negative coverage is less preferred than fluoroquinolones for patients with severe infections or comorbid conditions.[42, 43] In addition, in that study the risk of aortic aneurysm or dissection was examined only among adults older than 50 years of age, who in our study had an almost 5 times higher incidence rate than those younger than 50 years. A cohort study among adults 65 years or older in Canada reported a hazard ratio of 2.24 (95% CI: 2.02–2.49) for the association between oral fluroquinolones and aortic aneurysm.[15] The study lacked a comparison group as fluoroquinolone use was compared with no antibiotic use and adjusted for only a limited number of covariates indicating residual and unmeasured confounding issues. In a nested case-control study conducted in Taiwan,[13] current use of fluoroquinolones was associated with an increased risk of aortic aneurysm or dissection cases in an elderly Taiwanese population (Relative Risk (RR): 1.75; 95% CI: 1.11–2.74). Another recently published nested case-control study in the Korean population over 40 years of age found that fluoroquinolone use within 60 days was associated with a 53% increased risk of aortic aneurysm and dissections (OR: 1.53; 95% CI: 1.46–1.62).[27] These last two studies, however, lacked an active comparator group and underlying confounding factors resulting in a possible overestimation of the effect size. A

self-controlled case-crossover study conducted in Taiwan found increased odds of fluoroquinolone exposure (OR: 2.71; 95% CI: 1.13–3.71) in an elderly population with aortic aneurysm or dissection events.[14] A cohort study conducted in the commercially insured population aged 18 to 64 years in the United States found that fluoroquinolone use was associated with increased incidence of aortic aneurysm (HR: 1.20; 95% CI: 1.17–1.24) when compared to other antibiotics including amoxicillin-clavulanate, azithromycin, cephalexin, clindamycin, and sulfamethoxazole-trimethoprim.[44]The slightly lower risk observed in that study compared to what our study found can be explained by that study's exclusion of older individuals (≥65 years).

In the context of FDA warnings and existing studies, our findings provide evidence that fluoroquinolones are associated with an increased risk of aortic aneurysm in a general US population, although the magnitude of association was not as pronounced as in previous studies reported in populations from other countries. In addition, our study demonstrates that the association was consistent in ciprofloxacin and levofloxacin users, and in users with 7 to 14 days of fluoroquinolone exposure. Our findings are inconclusive regarding the associations in moxifloxacin users and in those with 3 to 7 days of fluoroquinolone exposure which could be attributed to the small sample size. Future research with adequately powered studies is required to confirm or deny these findings. Our study highlights that the risk of aortic aneurysm was consistent across subgroups of patients stratified by baseline demographic and clinical comorbidities (age, gender, diabetes, hypertension, cardiovascular risk-factors). Hence, fluoroquinolones should be used with caution in all adults, and could be avoided in patients with

pre-existing cardiovascular risk factors and/or collagen-related disorders, unless absolutely necessary or when benefits outweigh the risks.

Several pharmacological mechanisms in the literature offer potential explanations behind fluoroquinolones leading to aortic aneurysm or dissection. It is demonstrated that fluoroquinolone agents upregulate the production of proteolytic enzymes such as multiple matrix metalloproteinase (MMP) including MMP-1, MMP-2, MMP-13.[45, 46] This leads to degradation of extracellular matrix which is primarily composed of collagen and elastin fibrils. As the strength of the aortic wall depends on the composition of extracellular matrix, the increased production of MMP enzymes in the presence of fluoroquinolones negatively impacts the aortic wall in a dose-dependent mechanism.[13, 15, 47-52] In addition, both in vitro and in vivo studies have demonstrated that aortic aneurysm/dissection develops gradually over the years, and fluoroquinolones can potentially increase the risk or worsen already existing aortic aneurysm/dissection in a time-and dose-dependent mechanism by stimulating the production of MMPs. However, further research establishing the causal association between fluoroquinolones and aortic aneurysm/dissection is warranted.

Our study has several strengths. To address the inherent limitation of confounding in observational studies, we used an active comparator group comprised of macrolides users. Macrolides are a class of antibiotic with no known association with aortic aneurysm or dissection and are prescribed for similar infections as fluoroquinolones.[53, 54] Our methodological approach to use propensity score matching followed by multivariable Cox proportional hazards regression allowed for adjustment of differences in baseline demographic and clinical conditions of the two groups, while accounting for any residual confounding in the regression model. In addition, we

used a nationwide, large administrative claims dataset representative of population covered by an employer-sponsored insurance and Medicare supplemental health insurance allowing for drug exposure and outcome assessment in real-world settings. Lastly, large sample size of our study allowed us to assess the heterogeneity of treatment effects in various subgroups of patients, stratified by demographic (e.g. age, gender) and clinical conditions (e.g. hypertension, diabetes, cardiovascular comorbidities).

Our study has several limitations. First, as we relied on filled prescriptions to capture drug exposure, it is not possible to determine if patients actually used the medications as prescribed. However, we do not expect this issue to be differential between fluoroquinolone and macrolide users. Second, our study replied on ICD codes reported in claims data to measure outcome events. Although the PPVs of our algorithm were 92% for aortic aneurysm and 100% for dissection cases in validation studies, outcome misclassification cannot be ruled out. However, coding errors are likely to be distributed evenly among groups. Third, although we used propensity score matching and adjusted for many potential confounders known to be associated with aortic aneurysm or dissection, there may be some unmeasured confounders (e.g., smoking, illicit drug use) that might affect our findings. Fourth, our analysis was restricted to oral antibiotics dispensed in outpatient settings, and it is difficult to establish a correlation between dose/concentration of fluoroquinolone agents and aortic aneurysm or dissection in our claims-based dataset. In addition, our findings are not applicable to inpatient use of fluoroquinolones. Fifth, our study examined this association in patients with either an employer-sponsored or Medicare supplemental insurance, and may not be generalizable to the entire US population.

In conclusion, in this propensity-score matched cohort analysis of a US population, we observed a 34% increased risk of aortic aneurysm or dissection associated with the use of fluoroquinolones, compared with macrolides. The association remained consistent in subgroup and sensitivity analyses, especially for ciprofloxacin, levofloxacin, and durations of fluoroquinolone exposure ranging from 7 to 14 days. These findings highlight that fluroquinolones should be used with caution for populations of all ages.

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Author Contributions: Dr. Park had full access to all of the study data and assumes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: All authors

Acquisition, analysis, or interpretation of data: All authors

Drafting of the manuscript: Garg

Critical revision of the manuscript for important intellectual content: All authors

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References:

1. Hooper DC, Wolfson JS. Fluoroquinolone antimicrobial agents. N Engl J Med 1991;6:384-94. doi: 10.1056/NEJM199102073240606.
2. St-Jean A, Chateau D, Dahl M, et al. Regional variation in the potentially inappropriate first-line use of fluoroquinolones in Canada as a key to antibiotic stewardship? A drug utilization review study. BMC Infect Dis 2021;1:733.
3. Bratsman A, Mathias K, Laubscher R, Grigoryan L, Rose S. Outpatient fluoroquinolone prescribing patterns before and after US FDA boxed warning. Pharmacoepidemiol Drug Saf 2020;6:701-07.
4. Baggs J, Fridkin SK, Pollack LA, Srinivasan A, Jernigan JA. Estimating National Trends in Inpatient Antibiotic Use Among US Hospitals From 2006 to 2012. JAMA Intern Med 2016;11:1639-48.
5. Information for Healthcare Professionals:
Fluoroquinolone Antimicrobial Drugs [ciprofloxacin (marketed as Cipro and generic ciprofloxacin), ciprofloxacin extended-release (marketed as Cipro XR and Proquin XR), gemifloxacin (marketed as Factive), levofloxacin (marketed as Levaquin), moxifloxacin (marketed as Avelox), norfloxacin (marketed as Noroxin), and ofloxacin (marketed as Floxin)], Available from http://wayback.archive-it.org/7993/20170112032310/http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm126085.htm. Accessed December 04, 2020.
6. Sode J, Obel N, Hallas J, Lassen A. Use of fluroquinolone and risk of Achilles tendon rupture: a population-based cohort study. Eur J Clin Pharmacol 2007;5:499-503. doi: 10.1007/s00228-007-0265-9. Epub 2007 Mar 3.
7. Etminan M, Forooghian F, Brophy JM, Bird ST, Maberley D. Oral fluoroquinolones and the risk of retinal detachment. JAMA 2012;13:1414-9. doi: 10.001/jama.2012.383.
8. Stephenson AL, Wu W, Cortes D, Rochon PA. Tendon Injury and Fluoroquinolone Use: A Systematic Review. Drug Saf 2013;9:709-21. doi: 10.1007/s40264-013-0089-8.
9. FDA Drug Safety Communication: FDA requires label changes to warn of risk for possibly permanent nerve damage from antibacterial fluoroquinolone drugs taken by mouth or by injection, Available from http://wayback.archive-it.org/7993/20170112031629/http://www.fda.gov/Drugs/DrugSafety/ucm365050.htm. Accessed December 04, 2020.
10. FDA Drug Safety Communication: FDA updates warnings for oral and injectables fluoroquinolone antibiotics due to disabling side effects., Available from https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-updates-warnings-oral-and-injectable-fluoroquinolone-antibiotics. Accessed November 20, 2020.
11. FDA Drug Safety Communication: FDA warns about increased risk of ruptures or tears in the aorta blood vessel with fluoroquinolone antibiotics in certain patients., Available from https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-increased-risk-ruptures-or-tears-aorta-blood-vessel-fluoroquinolone-antibiotics. Accessed November 20, 2020.

12. Kent KC. Clinical practice. Abdominal aortic aneurysms. N Engl J Med 2014;22:2101-8. doi: 10.1056/NEJMcp1401430.
13. Lee CC, Lee MT, Chen YS, Lee SH, Chen SC, Chang SC. Risk of Aortic Dissection and Aortic Aneurysm in Patients Taking Oral Fluoroquinolone. JAMA Intern Med 2015;11:1839-47. doi: 10.001/jamainternmed.2015.5389.
14. Lee CC, Lee MG, Hsieh R, et al. Oral Fluoroquinolone and the Risk of Aortic Dissection. J Am Coll Cardiol 2018;12:1369-78. doi: 10.016/j.jacc.2018.06.067.
15. Daneman N, Lu H, Redelmeier DA. Fluoroquinolones and collagen associated severe adverse events: a longitudinal cohort study. BMJ Open 2015;11:e010077. doi: 10.1136/bmjopen-2015-77.
16. Pasternak B, Inghammar M, Svanstrom H. Fluoroquinolone use and risk of aortic aneurysm and dissection: nationwide cohort study. BMJ 2018;doi:10.1136/bmj.k678.
17. Michaud PC, Goldman D, Lakdawalla D, Gailey A, Zheng Y. Differences in health between Americans and Western Europeans: Effects on longevity and public finance. Soc Sci Med 2011;2:254-63. doi: 10.1016/j.socscimed.2011.05.027. Epub 11 Jun 2.
18. Thorpe KE, Howard DH, Galactionova K. Differences in disease prevalence as a source of the U.S.-European health care spending gap. Health Aff (Millwood) 2007;6:w678-86. doi: 10.1377/hlthaff.26.6.w678. Epub 2007 Oct 2.
19. Banks J, Marmot M, Oldfield Z, Smith JP. Disease and disadvantage in the United States and in England. JAMA 2006;17:2037-45. doi: 10.1001/jama.295.17.2037.
20. Centers for Disease Control and Prevention: Outpatient Antibiotic Prescriptions — United States, Available from https://www.cdc.gov/antibiotic-use/community/programs-measurement/state-local-activities/outpatient-antibiotic-prescriptions-US-2017.html. Accessed December 04, 2020.
21. FDA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021721s020_020635s57_020634s52_lbl.pdf. "Generic"
22. FDA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/019537s086lbl.pdf. "Generic"
23. FDA. ZDL. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/050710s039,050711s036,050784s023lbl.pdf,
24. Patel PH HM. Macrolides. In: StatPearls. Treasure Island, FL: StatPearls Publishing, 2023.
25. Rodvold KA, Piscitelli SC. New oral macrolide and fluoroquinolone antibiotics: an overview of pharmacokinetics, interactions, and safety. Clin Infect Dis 1993;S192-9.
26. Khaliq Y, Zhanel GG. Fluoroquinolone-associated tendinopathy: a critical review of the literature. Clin Infect Dis 2003;11:1404-10. doi: 10.086/375078. Epub 2003 May 20.
27. Son N, Choi E, Chung SY, Han SY, Kim B. Risk of aortic aneurysm and aortic dissection with the use of fluoroquinolones in Korea: a nested case-control study. BMC Cardiovasc Disord 2022;1:44.
28. Goldfinger JZ, Halperin JL, Marin ML, Stewart AS, Eagle KA, Fuster V. Thoracic aortic aneurysm and dissection. J Am Coll Cardiol 2014;16:1725-39.
29. Blanchard JF, Armenian HK, Friesen PP. Risk factors for abdominal aortic aneurysm: results of a case-control study. Am J Epidemiol 2000;6:575-83.

30. Yuan H, Han X, Jiao D, Zhou P. A Case-Control Study of Risk Factors of Abdominal Aortic Aneurysm. Heart Surg Forum 2016;5:E224-e28.
31. Ando K, Kaneko N, Doi T, Aoshima M, Takahashi K. Prevalence and risk factors of aortic aneurysm in patients with chronic obstructive pulmonary disease. J Thorac Dis 2014;10:1388-95.
32. Dransfield MT, Huang F, Nath H, Singh SP, Bailey WC, Washko GR. CT emphysema predicts thoracic aortic calcification in smokers with and without COPD. Copd 2010;6:404-10.
33. Chun KC, Teng KY, Chavez LA, et al. Risk factors associated with the diagnosis of abdominal aortic aneurysm in patients screened at a regional Veterans Affairs health care system. Ann Vasc Surg 2014;1:87-92.
34. Takagi H, Umemoto T. Association of chronic obstructive pulmonary, coronary artery, or peripheral artery disease with abdominal aortic aneurysm rupture. Int Angiol 2017;4:322-31.
35. Matsushita K, Kwak L, Ballew SH, et al. Chronic kidney disease measures and the risk of abdominal aortic aneurysm. Atherosclerosis 2018;107-13.
36. Sung PH, Yang YH, Chiang HJ, et al. Risk of aortic aneurysm and dissection in patients with autosomal-dominant polycystic kidney disease: a nationwide population-based cohort study. Oncotarget 2017;34:57594-604.
37. Shovman O, Tiosano S, Comaneshter D, Cohen AD, Amital H, Sherf M. Aortic aneurysm associated with rheumatoid arthritis: a population-based cross-sectional study. Clin Rheumatol 2016;11:2657-61.
38. Caglayan AO, Dundar M. Inherited diseases and syndromes leading to aortic aneurysms and dissections. Eur J Cardiothorac Surg 2009;6:931-40.
39. Gawinecka J, Schönrath F, von Eckardstein A. Acute aortic dissection: pathogenesis, risk factors and diagnosis. Swiss Med Wkly 2017;w14489.
40. Lavall D, Schäfers HJ, Böhm M, Laufs U. Aneurysms of the ascending aorta. Dtsch Arztebl Int 2012;13:227-33.
41. Hernesniemi JA, Vänni V, Hakala T. The prevalence of abdominal aortic aneurysm is consistently high among patients with coronary artery disease. J Vasc Surg 2015;1:232-40.e3.
42. Chow AW, Benninger MS, Brook I, et al. Executive Summary: IDSA Clinical Practice Guideline for Acute Bacterial Rhinosinusitis in Children and Adults. Clinical Infectious Diseases 2012;8:1041-45.
43. Harris AM, Hicks LA, Qaseem A. Appropriate Antibiotic Use for Acute Respiratory Tract Infection in Adults: Advice for High-Value Care From the American College of Physicians and the Centers for Disease Control and Prevention. Ann Intern Med 2016;6:425-34. doi: 10.7326/M15-1840. Epub 2016 Jan 19.
44. Newton ER, Akerman AW, Strassle PD, Kibbe MR. Association of Fluoroquinolone Use With Short-term Risk of Development of Aortic Aneurysm. JAMA Surg 2021;3:264-72.
45. Tsai WC, Hsu CC, Tang FT, Wong AM, Chen YC, Pang JH. Ciprofloxacin-mediated cell proliferation inhibition and G2/M cell cycle arrest in rat tendon cells. Arthritis Rheum 2008;6:1657-63. doi: 10.002/art.23518.
46. Tsai WC, Hsu CC, Chen CP, et al. Ciprofloxacin up-regulates tendon cells to express matrix metalloproteinase-2 with degradation of type I collagen. J Orthop Res 2011;1:67-73. doi: 10.1002/jor.21196.

47. Sendzik J, Shakibaei M, Schafer-Korting M, Lode H, Stahlmann R. Synergistic effects of dexamethasone and quinolones on human-derived tendon cells. Int J Antimicrob Agents 2010;4:366-74. doi: 10.1016/j.ijantimicag.2009.10.009. Epub 10 Jan 19.
48. Akiyama M, Ohtani H, Sato E, Nagura H, Tabayashi K. Up-regulation of matrix metalloproteinase-2 and membrane-type 1-matrix metalloproteinase were coupled with that of type I procollagen in granulation tissue response after the onset of aortic dissection. Virchows Arch 2006;6:811-21. doi: 10.1007/s00428-006-0194-5. Epub 2006 Apr 12.
49. Wen D, Zhou XL, Li JJ, et al. Plasma concentrations of interleukin-6, C-reactive protein, tumor necrosis factor-alpha and matrix metalloproteinase-9 in aortic dissection. Clin Chim Acta 2012;1-2:198-202. doi: 10.1016/j.cca.2011.09.029. Epub 11 Oct 6.
50. Reviglio VE, Hakim MA, Song JK, O'Brien TP. Effect of topical fluoroquinolones on the expression of matrix metalloproteinases in the cornea. BMC Ophthalmol 2003;doi:10.1186/471-2415-3-10.
51. Sharma C, Velpandian T, Baskar Singh S, Ranjan Biswas N, Bihari Vajpayee R, Ghose S. Effect of fluoroquinolones on the expression of matrix metalloproteinase in debrided cornea of rats. Toxicol Mech Methods 2011;1:6-12. doi: 10.3109/15376516.2010.529183. Epub 2010 Nov 9.
52. LeMaire SA, Zhang L, Zhang NS, et al. Ciprofloxacin accelerates aortic enlargement and promotes dissection and rupture in Marfan mice. J Thorac Cardiovasc Surg 2022;3:e215-e26.
53. Highlights of Prescribing Information, Available from https://www.accessdata. fda .gov/drugsatfda_docs/label/2008/021721s020_020635s57_020634s52_lbl.pdf. Accessed December 04, 2020.
54. Highlights of Prescribing Information, Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/050733s043lbl.pdf. Accessed December 04, 2020.
55. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care. 2005;43(11):1130-1139. doi:10.1097/01.mlr.0000182534.19832.83

Table 1. Baseline demographic and clinical characteristics of fluoroquinolone and macrolide users after propensity score matching

	Fluoroquinolone n= 1,587,310		Macrolide n= 1,587,310		Standardized difference
	N	%	N	%	
Age, Mean (SD), years	49.1 (16.8)		47.8 (15.8)		0.08
Age Groups (years)					0.04
18-34	353,142	22.2	360,254	22.7	
35-44	261,458	16.5	278,278	17.5	
45-54	338,398	21.3	365,191	23.0	
55-64	394,624	24.9	407,056	25.6	
>65	239,688	15.1	176,531	11.1	
Males	723,370	45.6	723,370	45.6	0.00
Region					0.05
Northeast	288,207	18.2	301,618	19.0	
North Central	340,794	21.5	341,564	21.5	
South	671,714	42.3	622,753	39.2	
West	267,993	16.9	303,198	19.1	
Insurance					0.04
Comprehensive	126,147	7.9	96,338	6.1	
HMO	181,283	11.4	193,826	12.2	
POS	99,700	6.3	98,450	6.2	
PPO	874,037	55.1	888,143	56.0	
Clinical Comorbidities					
Congestive heart failure	40,818	2.6	33,245	2.1	0.03
Myocardial infarction	11,573	0.7	9,870	0.6	0.01
Cerebrovascular disease	44,897	2.8	36,669	2.3	0.03
Transient ischemic attack	34,605	2.2	27,822	1.8	0.03
Peripheral vascular disorders	41,184	2.6	28,692	1.8	0.05
Acute coronary syndrome	35,778	2.3	31,809	2.0	0.02
Cardiac arrhythmia	137,169	8.6	121,855	7.7	0.03
Valvular disease	50,366	3.1	40,098	2.5	0.03
Marfan syndrome	129	0.0	107	0.0	0.00
Loeys Dietz Ehlers	244	0.0	225	0.0	0.00
Turner syndrome	132	0.0	108	0.0	0.00
Aortic coarctation	52	0.0	47	0.0	0.00
Diabetes	191,050	12.0	172,676	10.9	0.04
COPD	155,232	9.8	141,210	8.9	0.03

Malignancy	75,748	4.8	62,458	3.9	0.04
Liver disease	42,108	2.6	32,168	2.0	0.04
Renal disease	31,788	2.0	26,164	1.6	0.03
Rheumatic disease	24,820	1.6	22,513	1.4	0.01
Hypertension	487,119	30.7	451,690	28.5	0.05
Hyperlipidemia	305,162	19.2	287,795	18.1	0.03
Drug abuse	13,120	0.8	12,669	0.8	0.00
Obesity	122,896	7.7	118,966	7.5	0.01
Infectious Conditions					
Pneumonia	53,047	3.3	53,932	3.4	0.00
Upper respiratory tract infection	85,703	5.4	87,792	5.5	0.01
Acute respiratory infection	251,647	15.9	265,899	16.8	0.02
Gastrointestinal infection	112,699	7.1	123,810	7.8	0.04
Genitourinary infection	83,376	5.3	94,427	5.9	0.03
Skin infection	58,563	3.7	45,919	2.9	0.04
Medication Use					
NSAIDS	261,413	16.5	261,117	16.5	0.00
Glucocorticoids	418,726	26.4	385,269	24.3	0.05
ACE inhibitors	177,469	11.2	163,858	10.3	0.03
Angiotensin receptor blockers	93,898	5.9	86,118	5.4	0.02
Calcium-channel blockers	158,870	10.0	143,514	9.0	0.03
β blockers	186,574	11.8	164,737	10.4	0.04
Loop diuretics	49,463	3.1	38,730	2.4	0.04
Cardiac glycosides	7,445	0.5	4,924	0.3	0.03
Nitrates	31,010	2.0	26,829	1.7	0.02
Anticoagulants	38,492	2.4	30,558	1.9	0.03
Hypoglycemics	160,765	10.1	145,898	9.2	0.03
Lipid lowering agents	414,375	26.1	385,782	24.3	0.04
β-agonists	14,605	0.9	14,360	0.9	0.00
Number of outpatient visits, Mean (SD)	11.0 (12.8)		10.4 (12.4)		0.05
Number of inpatient visits, Mean (SD)	0.03 (0.2)		0.02 (0.2)		0.03

SD, standard deviation; HMO, health maintenance organization; POS, point of service; PPO, preferred provider organization; COPD, chronic obstructive pulmonary disease; NSAIDS, Non-steroidal anti-inflammatory drugs; ACE, Angiotensin converting enzyme.

Table 2. Risk of aortic aneurysm or dissection, aortic aneurysm, and aortic dissection with fluoroquinolone versus macrolide use in propensity score-matched cohort

	Number of patients	Person-years	Number of events	Incidence (per 1000 person-years)	Adjusted hazard ratio* (95% CI)	p
Aortic aneurysm or dissection						
Fluoroquinolone	1,587,310	284,358	548	1.93	1.34 (1.17-1.54)	<0.01
Macrolide	1,587,310	272,799	328	1.20	Reference	
Aortic aneurysm						
Fluoroquinolone	1,587,310	284,359	525	1.85	1.38 (1.20-1.59)	<0.01
Macrolide	1,587,310	272,800	304	1.11	Reference	
Aortic dissection						
Fluoroquinolone	1,587,310	284,404	31	0.11	0.92 (0.55-1.55)	0.92
Macrolide	1,587,310	272,827	27	0.09	Reference	

CI, confidence interval; *Adjusted hazard ratio was estimated using multivariate Cox-proportional hazards regression adjusting for age, sex, hypertension, diabetes, and cardiovascular conditions including congestive heart failure, myocardial infarction, peripheral vascular disorders, acute coronary syndrome, and cardiac arrhythmia.

Table 3. Risk of aortic aneurysm or dissection with fluoroquinolone versus macrolide use in propensity score-matched sensitivity analyses

	Episodes	Person-years	Number of events	Incidence (per 1000 person-years)	Adjusted hazard ratio (95% CI)	p
Type of fluoroquinolone exposure						
Ciprofloxacin	989,156	176,514	330	1.87	1.26 (1.07-1.49)	<0.01

Macrolide	989,156	169,869	219	1.28	Reference	
Moxifloxacin	165,636	31,810	58	1.82	0.94 (0.64-1.38)	0.75
Macrolide	165,636	28,455	52	1.82	Reference	
Levofloxacin	504,635	88,822	260	2.92	1.44 (1.19-1.52)	<0.01
Macrolide	504,635	86,124	187	2.17	Reference	
Duration of fluoroquinolone exposure						
Fluoroquinolone (< 7 days)	370,933	63,582	99	1.61	1.02 (0.72-1.32)	0.98
Macrolide	370,933	61,659	87	1.36	Reference	
Fluroquinolone (7-14 days)	1,129,504	200,971	438	2.27	1.47 (1.26-1.71)	<0.01
Macrolide	1,129,504	193,403	268	1.38	Reference	
Primary diagnosis with 90-days follow-up						
Aortic Aneurysm or dissection						
Fluoroquinolone	1,587,310	397,463	699	1.85	1.26 (1.13-1.43)	<0.01
Macrolide	1,587,310	387,115	455	1.17	Reference	
Aortic Aneurysm						
Fluoroquinolone	1,587,310	397,465	671	1.69	1.29 (1.14-1.45)	<0.01
Macrolide	1,587,310	387,116	428	1.10	Reference	
Aortic Dissection						
Fluoroquinolone	1,587,310	397,548	40	0.10	1.03 (0.65-1.63)	0.90
Macrolide	1,587,310	387,168	34	0.08	Reference	

Table 3. Continued

	Episodes	Person-years	Events	Incidence (per 1000 person-years)	Adjusted hazard ratio (95% CI)	p
Primary or secondary diagnosis with 60-days follow-up						
Aortic Aneurysm or dissection						
Fluoroquinolone	1,587,310	284,330	992	3.49	1.45 (1.30-1.60)	<0.01
Macrolide	1,587,310	272,786	551	2.01	Reference	
Aortic Aneurysm						
Fluoroquinolone	1,587,310	284,322	955	3.36	1.44 (1.30-1.61)	<0.01
Macrolide	1,587,310	272,788	529	1.93	Reference	
Aortic Dissection						
Fluoroquinolone	1,587,310	284,402	56	0.20	1.14 (0.76-1.71)	0.53
Macrolide	1,587,310	272,826	40	0.15	Reference	

CI, confidence interval; Adjusted hazard ratio was estimated using multivariate Cox-proportional hazards regression adjusting for age, sex, hypertension, diabetes, and cardiovascular conditions including congestive heart failure, myocardial infarction, peripheral vascular disorders, acute coronary syndrome, and cardiac arrhythmia.

Ofloxacin, gemifloxacin, and delafloxacin were not analyzed in sensitivity analysis due to their low sample sizes.

Table 4. Risk of aortic aneurysm or dissection with fluoroquinolone versus macrolide in propensity score-matched subgroup analyses

	Episodes	Person-years	Events	Incidence (per 1000 person-years)	Adjusted hazard ratio (95% CI)	$P_{interaction}$
Age						0.04
≤50 years						
Fluoroquinolone	810,341	153,180	103	0.7	1.14 (1.02-1.48)	
Macrolide	810,341	145,959	65	0.4	Reference	
>50 years						
Fluoroquinolone	777,494	139,599	531	3.80	1.31 (1.14-1.51)	
Macrolide	777,494	133,442	391	2.39	Reference	
Sex						0.58
Males						
Fluoroquinolone	719,419	130,116	390	3.00	1.38 (1.18-1.62)	
Macrolide	719,419	123,469	239	1.93	Reference	
Females						
Fluoroquinolone	863,355	153,486	164	1.07	1.20 (0.93-1.54)	
Macrolide	863,355	147,724	104	0.70	Reference	
Hypertension						0.65
Present						
Fluoroquinolone	469,420	83,739	348	4.16	1.30 (1.10-1.53)	
Macrolide	469,420	80,125	234	2.90	Reference	
Absent						
Fluoroquinolone	1,106,420	198,709	180	0.91	1.36 (1.08-1.71)	
Macrolide	1,106,420	188,038	122	0.60	Reference	
Diabetes						0.24
Present						
Fluoroquinolone	179,134	31,195	111	3.48	1.45 (1.08-1.96)	
Macrolide	179,134	30,515	70	2.29	Reference	

Diabetes

Absent						
Fluoroquinolone	1,398,843	250,896	424	1.70	1.24 (1.06-1.44)	
Macrolide	1,398,843	239,829	277	1.15	Reference	
CV Risk Factors						0.09
Present						
Fluoroquinolone	190,345	33,464	226	6.75	1.23 (1.05-1.50)	
Macrolide	190,345	32,349	176	5.44	Reference	
Absent						
Fluoroquinolone	1,388,750	249,566	306	1.23	1.43 (1.18-1.72)	
Macrolide	1,388,750	238,818	173	0.72	Reference	

*CI: Confidence intervals; CV: Cardiovascular