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Oral Fluoroquinolone and the Risk of Aortic Dissection

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ABSTRACT

BACKGROUND Previous studies raised safety concerns on the association between fluoroquinolone treatment and serious collagen disorders, aortic aneurysm and dissection (AA/AD).

OBJECTIVES This study sought to evaluate this association via a case-crossover analysis in a large national administrative database.

METHODS A case-crossover design was used to compare the distributions of fluoroquinolone exposure for the same patient across a 60-day period before the AA/AD event (hazard period) and 1 randomly selected 60-day period (referent period) between 60 to 180 days before the AA/AD events. In the sensitivity analysis, the authors repeated the main analysis using a 1:5 ratio of hazard period to referent period, to adjust for the effect of time-variant confounders. A disease-risk score–matched time control analysis was performed to investigate the potential time-trend bias. The risks were calculated by a conditional logistic regression model.

RESULTS A total of 1,213 hospitalized AA/AD patients were identified between 2001 and 2011. In the main case-crossover analysis, exposure to fluoroquinolone was more frequent during the hazard periods than during the referent periods (1.6% vs. 0.6%; odds ratio [OR]: 2.71; 95% confidence interval [CI]: 1.14 to 6.46). In the sensitivity analysis, after adjustment for infections and co-medications, the risk remains significant (OR: 2.05; 95% CI: 1.13 to 3.71). An increased risk of AA/AD was observed for prolonged exposure to fluoroquinolones (OR: 2.41 for 3- to 14-day exposure; OR: 2.83 for >14-day exposure). Susceptible period analysis revealed that the use of fluoroquinolone within 60 days was associated with the highest risk of AA/AD. In the case-time-control analysis, there was no evidence that the observed association is due to temporal changes in fluoroquinolone exposure.

CONCLUSIONS Exposure to fluoroquinolone was substantially associated with AA/AD. This risk was modified by the duration of fluoroquinolone use and the length of the hazard period. (J Am Coll Cardiol 2018;72:1369–78)
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Aortic aneurysm (AA), and aortic dissection (AD) are among the deadliest cardiovascular diseases; in fact, without any prompt treatment for AD; the mortality rate is around 100%. Population-based studies reported an annual incidence of AA of 3 to 13.7 per 100,000 population, and AD of 3 to 20 per 100,000 population (1–5). The annual incidence of AA for the elderly population is reported to be much higher at 130 per 100,000 population (6). In addition, the incidence of AA could have likely been underestimated due to the difficulties in diagnosis. Unlike AD, which usually presents with acute

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ABBREVIATIONS AND ACRONYMS

AA = aortic aneurysm

AD = aortic dissection

CI = confidence interval

DRS = disease risk score

LHID = Longitudinal Health Insurance Database

MMP = matrix metalloproteinase

NNH = number needed to harm

OR = odds ratio

chest pain associated to hypertensive crisis, AA is often asymptomatic until either the dissection or the rupture occurs. Extensive efforts to identify the risk factors for AA/AD and to enable early detection, monitoring, and intervention have been made. Aortic wall defects and prolonged hypertension are believed to be the 2 major causes for AA/AD (1,4). Other established risk factors include old age, male sex, atherosclerotic disease and congenital disorders with collagen defects such as Marfan or vascular Ehlers-Danlos syndromes. Recently, 3 independent research groups have reported an association between fluoroquinolones, a commonly prescribed class of antibiotics, and an increase in the risk of AA or AD (7–9). By comparing fluoroquinolone treatment with nontreatment, our group described a 2- to 3-fold increased risk of AA or AD in 1 million general population in Taiwan (7), whereas in a larger cohort consisting of more than 1.7 million elderly patients in Ontario, Daneman et al. (8) demonstrated a 2- to 3-fold increase in AA or AD. By comparing fluoroquinolone treatment with amoxicillin treatment, Pasternak et al. (9) also demonstrated an approximately 2 fold increase in AA or AD in 2.3 million elderly users of fluoroquinolone or amoxicillin.

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Although the exact biological mechanism remains unknown, several plausible mechanisms have been proposed to explain how fluoroquinolones might affect the synthesis or structural integrity of collagen in the aortic wall. First, fluoroquinolones have chelating properties against several metal ions (e.g., calcium, magnesium, aluminum), which are essential for type 1 collagen synthesis (10–12). Second, fluoroquinolones can decrease collagen synthesis by increasing the expression of matrix metalloproteinases, which lead to extracellular matrix degradation and medial layer degeneration (13–19). These aforementioned mechanisms have been corroborated by the findings of a recent in vitro experiment in which human aortic fibroblasts exposed to fluoroquinolone showed an increased capacity for extracellular matrix dysregulation by reducing the collagen and endogenous protease inhibitors expression (20). Lastly, results of experimental studies agreed with the phenotypes observed in congenital disorder with collagen defects, such as vascular Ehlers-Danlos syndrome, whose patients are associated with cystic medial degeneration of the aortic wall, leading to an increased risk of both aortic aneurysmal dilation and dissection (21,22). Despite the biological plausibility and initial epidemiological findings, more studies are needed to confirm the association between the use of fluoroquinolones and AA/AD. Limited by the study design, previous researches could not totally obviate the possibility of residual confounding, because certain potential confounders, such as lifestyle factors, are not registered in administrative databases. Therefore, we sought to address this unresolved issue by conducting a case-crossover and case-time-control study, using a nationwide population-based database. A case-crossover study takes into account the paired nature of the observations (within-subjects comparisons of exposure) so as to match out all intraindividual time-invariant covariates, minimizing the risk of bias due to unmeasured confounding. The disease risk score (DRS)-matched case-time-control study is an analysis of pairwise observations (case-crossover and case-time-control). Therefore, this study not only counters the time-varying factors, but also provides a robust control to minimize the risk of time-trend bias, associated with the case-only design (23).

METHODS

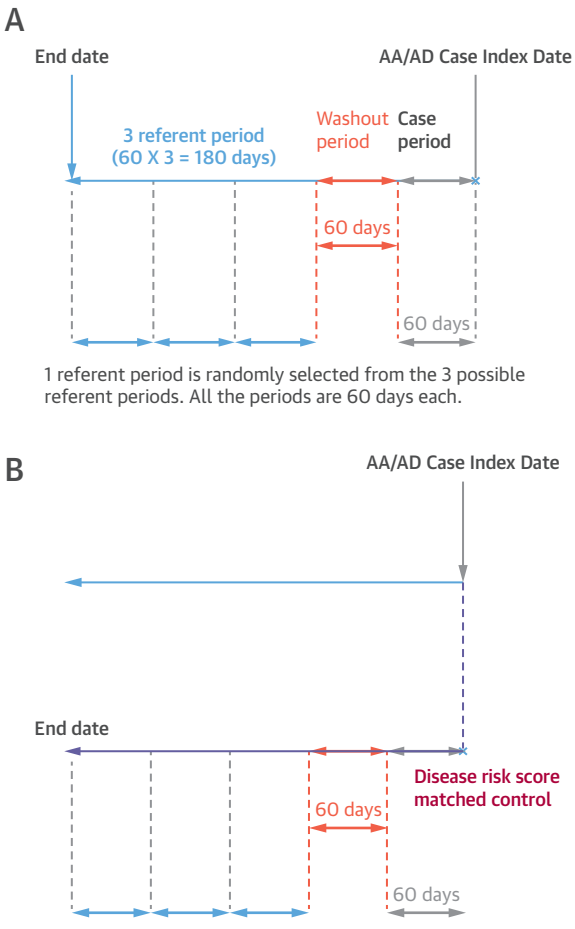
DATA SOURCE. Taiwan has approximately 24 million residents, and 99.5% of them are enrolled in the government-mandated national health insurance program. The national health insurance program has been established since 1995 (24). Specific health insurance data subsets were constructed for research purposes. This study was based on the year 2000 version of the Longitudinal Health Insurance Database (LHID), which randomly sampled 1 million national representative beneficiaries for longitudinal follow-up. A systematic approach was used to ensure that the selected sample could represent the demographic and geographic regional distribution of the entire Taiwanese population. The longitudinal nature of LHID permits researchers to identify a cohort based on diagnoses, health services, and drugs utilization, to track medical history, to establish a prescription drug profile, and to determine the endpoint of drug treatments. The claims history includes patient demographics, inpatient and outpatient electronic claims records, individual diagnoses, operations, and detailed information on prescribed medications. Information on the brand/generic name of the prescribed drugs, route of administration, quantity, and number of days of supply are also available in the LHID database. Patient consent was not required as this is an anonymized electronic database.

STUDY POPULATION. Using the LHID data, we identified all inpatients diagnosed with AA or AD from 2000 to 2011. Cases were required to have International Classification of Diseases (ICD-9-CM) codes for AA (441.1, 441.2, 441.3, 441.4, 441.5, 441.6, 441.7, and 441.9) or AD (441.0, 441.00, 441.01, 441.02, and 441.03), plus diagnostic evidence obtained by advanced imaging studies such as angiography, transesophageal or transthoracic echocardiography, thoracic or abdominal computed tomography, or magnetic resonance imaging. A previous validation study suggested that the combined diagnostic and procedure code definitions for AA or AD has a positive predictive rate of 92% (7).

CASE-CROSSOVER STUDY DESIGN. Our unidirectional case-crossover design was based on the research method initially proposed by Maclure (25). In a case-crossover design, instead of selecting controls from an external population, the participants act as their own controls, providing information on the outcome risk under both exposed and unexposed states. This self-controlled method reduces the possibility of within-person time-invariant confounding, and avoids control selection biases. In the primary analysis, each case contributed 1 hazard period, 1 washout period, and 3 referent periods as depicted in **Figure 1A**. In the sensitivity analysis, each case contributed 1 hazard period, 1 washout period, and 10 referent periods as depicted in Online Figure 1A. The length of each period is 60 days, except for the susceptible period analysis.

DRS-MATCHED CASE-TIME-CONTROL DESIGN. Although case-crossover estimates are not affected by confounding factors that do not change over time, they may still be subjected to bias from exposure trend bias. Exposure trend bias refers to the spurious association between the exposure and the outcome induced by the systematic trends in exposure over calendar time that could not be eliminated using a self-controlled design. For example, a spurious association between fluoroquinolone use and AA/AD may be observed in a case-crossover analysis if the use of fluoroquinolones increases over time in the cases or in the general population. In this setting, Suissa (26) has proposed the "case-time-control" design to control bias from temporal trends in exposure. The case-time-control design performs crossover analyses among the cases as well as in a sample of appropriate controls. The exposure trend measured in the controls is used to adjust for the exposure-outcome association derived from case-crossover analyses. However, a case-time-control design may reintroduce bias if the control group is not selected appropriately to provide good estimates of the expected exposure prevalence in the cases (27). To ensure the selection of a group of appropriate controls, we extended Suisse's case-time-control design by selecting controls using a DRS matching process (**Figure 1B**). Each case in the case-crossover analysis was matched 1:1 to the controls selected by DRS. The DRS is defined as the predicted probability of developing AA/AD among participants not exposed to fluoroquinolones, conditional on a set of measured baseline covariates (Online Table 1). We derived the DRS by a logistic regression model wherein AA/AD was used as the dependent variable and all empirical clinical predictors were treated as independent variables. By

FIGURE 1 Study Design in the Main Analysis



(A) Case-crossover design. **(B)** DRS-matched study design. AA = aortic aneurysm; AD = aortic dissection.

TABLE 1 Baseline Characteristics of Cases (N = 1,213)

Demographics	
Male	879 (72.46)
Age, yrs	70.58 ± 13.77
Insurance premiums	
Dependent	137 (11.29)
$1-$19,999	529 (43.61)
$20,000-$39,999	394 (32.48)
≥$40,000	153 (12.61)
Comorbidity	
Hypertension	745 (61.42)
Ischemic heart disease	241 (19.87)
Chronic obstructive pulmonary disease	220 (18.14)
Lipid disorder	185 (15.25)
Diabetes mellitus	160 (13.19)
Asthma	105 (8.99)
Obstructive sleep apnea	106 (8.74)
Cardiac valve disease	86 (7.09)
Chronic kidney disease	44 (3.63)
Atrial fibrillation	37 (3.05)
Seizure disorder	14 (1.15)
Decubitus ulcer	8 (0.66)
Conduction disorder	6 (0.49)
Smoking related disease	5 (0.41)
Amputation	3 (0.25)
Trauma (motor vehicle traffic accident)	1 (0.08)
Psychotropic poisoning	1 (0.08)
Marfan syndrome	0 (0.00)
Ehlers-Danlos syndrome	0 (0.00)
Cardiovascular syphilis	0 (0.00)
Charlson index	1.39 ± 1.75
Health care utilization	
Number of OPD visit	30.28 ± 27.34
Number of ED visit	0.35 ± 1.06
Number of hospitalizations	0.47 ± 1.35
Use of medications	
NSAIDs	385 (31.74)
Aspirin	358 (29.51)
Statins	103 (8.49)
ACE inhibitors	189 (15.58)
Anticoagulant agents	138 (11.38)
Antiarrhythmic agents	40 (3.30)
Beta-blockers	214 (17.64)
Calcium-channel blockers	470 (38.75)

Values are n (%) or mean ± SD.
ACE = angiotensin-converting enzyme; ED = emergency department; NSAID = nonsteroidal anti-inflammatory drug; OPD = outpatient department.

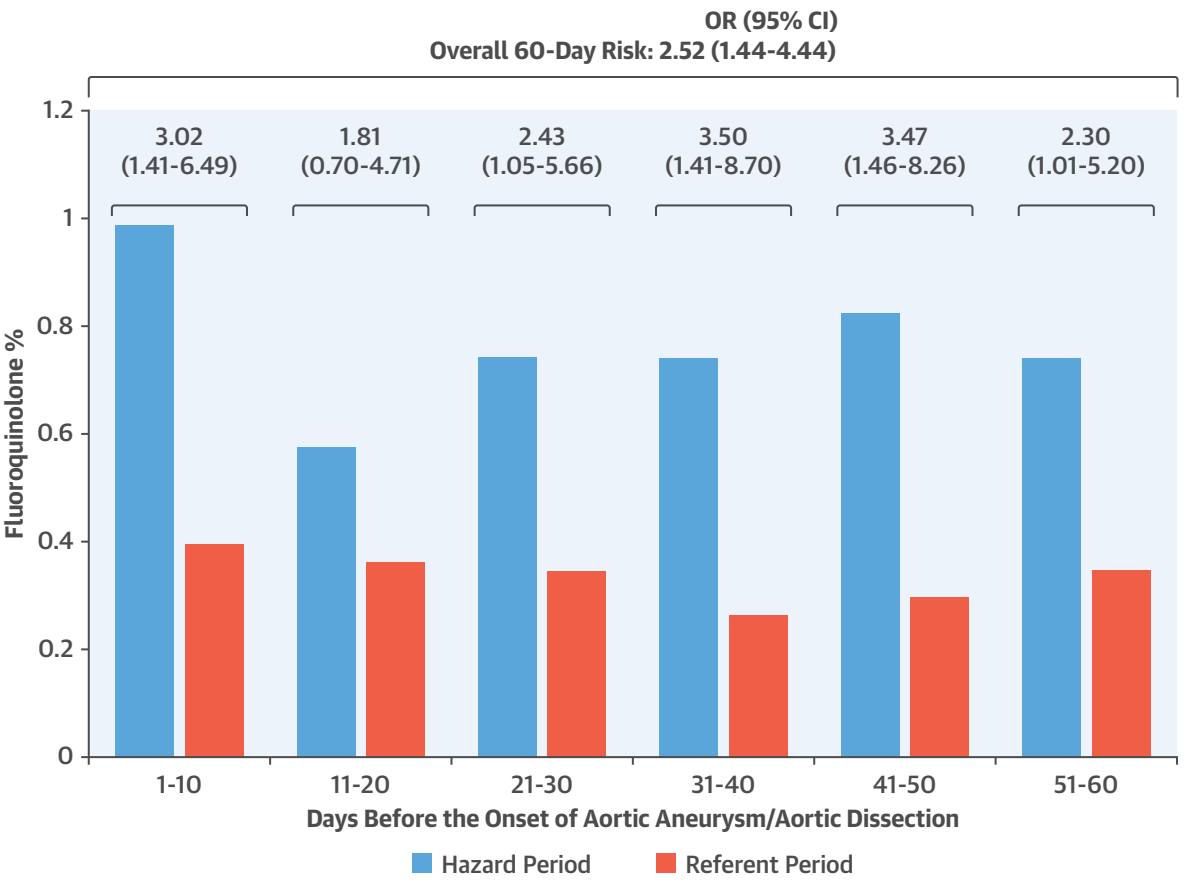
using the DRS matching rather than random selection, we selected a group of controls with similar characteristics to the cases. In Online Table 1, we report the C-statistics of the DRS model, component variables, and the respective weights of the component variables. In Online Table 2, we show that the standardized differences of all baseline covariates between case patients and control patients were <10% after DRS matching.

EXPOSURE ASSESSMENT AND DEFINITION. We assessed medications and other potential time-variant confounding exposures (such as infectious complications) using the predefined 60-day window during the case or reference period. A detailed list of the potential time-variant confounders is presented in Online Table 3. Exposure to fluoroquinolone was identified by a reimbursement code of oral fluoroquinolones with a prescription length of 3 days or more. Fluoroquinolones are drugs that contain any of the following active compounds: ciprofloxacin, levofloxacin, ofloxacin, sparfloxacin, norfloxacin, lomefloxacin, moxifloxacin, gemifloxacin, enoxacin, or pefloxacin. Users with exposure to other cardiovascular-related medications (nonsteroidal anti-inflammatory drugs, aspirin, statins, angiotensin-converting enzyme inhibitors, anticoagulant agents, antiarrhythmic agents, beta-blockers, and calcium channel blockers) were defined as having a drug prescription record ≧3 days in the predefined period.

STATISTICAL ANALYSIS. Descriptive results were expressed as mean ± SD for continuous variables and as frequencies and percentages (%) for categorical variables (**Table 1**). Normally distributed variables were compared with Student's *t*-test, and non-normally distributed variables were compared with Mann-Whitney *U* test. In the main analysis, we compared exposure to fluoroquinolone between the hazard period and 1 randomly selected referent period (**Figure 1**), using either the case-crossover or control-crossover analysis. Statistical significance was examined using McNemar's test. Odds ratios (ORs) for AA/AD associated with the use of fluoroquinolone and 95% confidence intervals (CIs) were calculated by conditional logistic regression. The case-time-control ORs were determined by dividing the case-crossover OR by the control-crossover OR.

In the sensitivity analyses, we repeated the main analysis using a 1:5 ratio of hazard period to referent period to adjust for the effect of time-variant confounders (Online Figure 1). In addition, we varied the length of hazard periods and corresponding washout and referent periods. We shortened (**Central Illustration**) or extended the length of hazard periods from 60 days to either 120 or 180 days (Online Figure 2). To further explore the strength of causal relationship, we performed a duration-response analysis. Users of fluoroquinolones were classified into 3 duration categories (<3 days, 3 to 14 days, and >14 days) dependent on the cumulative prescription lengths of fluoroquinolones in the hazard period. The association between the use of fluoroquinolones with different treatment durations and the risk of AA/AD

CENTRAL ILLUSTRATION **Fluoroquinolones and the Risk of Aortic Aneurysm/Aortic Dissection Within 60 Days**



Lee, C.-C. et al. J Am Coll Cardiol. 2018;72(12):1369–78.

CI = confidence interval; OR = odds ratio.

was then analyzed with conditional logistic regression. Finally, we estimated the number needed to harm (NNH) for AA/AD assuming the population incidence of AA/AD to be 6 to 130/100,000 patient-years (3,6). This calculation was derived from the calculation of risk difference based on the relative risk approximated by the OR derived from the case-time-control study. All analyses were conducted using SAS Statistical software V.9.4 (SAS Institute, Cary, North Carolina).

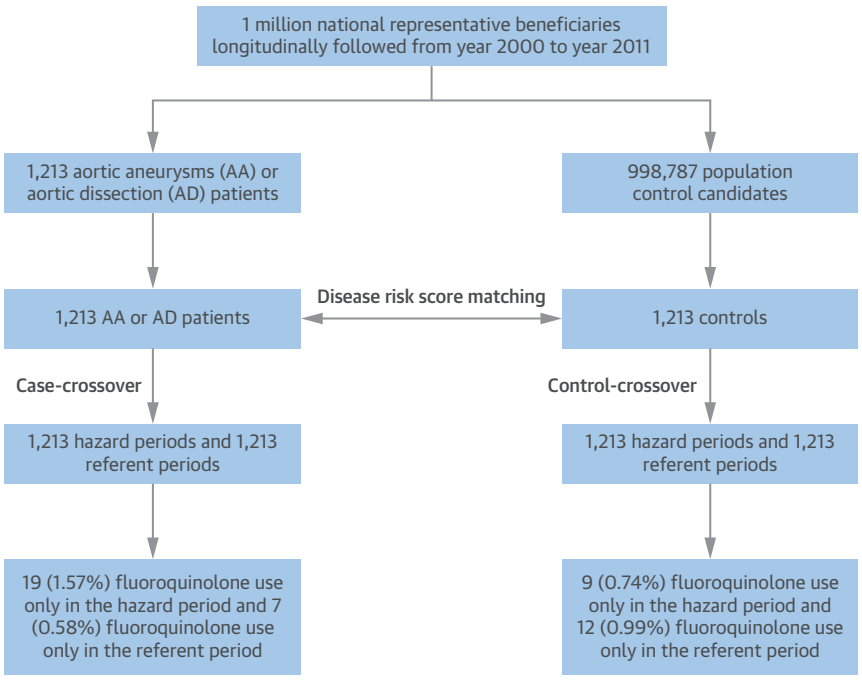
RESULTS

CHARACTERISTICS OF CASE PATIENTS. From 2002 to 2011, a total of 1,213 patients with AA/AD fulfilled the eligibility criteria (Figure 2). The general characteristics of the patients are shown in Table 1. We found that the majority of the AA/AD patients were male, elderly, and had a high prevalence of cardiovascular diseases related to AA/AD. The 5 most common comorbidity conditions were hypertension (61.2%), ischemic heart disease (19.9%), chronic obstructive pulmonary disease (18.1%), lipid disorder (15.3%), and diabetes mellitus (13.2%).

CHARACTERISTICS OF DRS-MATCHED CONTROL PATIENTS. To study the background temporal trend of fluoroquinolone use, we performed DRS matching to select a group of controls with similar characteristics to the cases. The similarities between case and control patients were evidenced by the small standardized differences of the baseline covariates between the 2 groups (Online Table 2).

MAIN ANALYSES. In Table 2, we present the within-subjects occurrence of exposed and unexposed periods (case-crossover, control-crossover) and an

FIGURE 2 Flow Chart of Cohort Selection in the Main Analysis



Abbreviations as in Figure 1.

analysis of pair-wise observation (case-time-control) by using a 1:1 ratio of hazard period to referent period. In the case-crossover analysis, the risk of AA/AD was significantly increased with exposure to fluoroquinolone (OR: 2.71; 95% CI: 1.14 to 6.46). In the control-crossover analysis, which represents the spurious association that may have been introduced by the background increase or decrease of fluoroquinolone use, we did not observe an increased risk of AA/AD (OR: 0.75; 95% CI: 0.32 to 1.78). In the case-time-control analysis, which is determined by the ratio between the case-crossover OR and the control-crossover OR, exposure to fluoroquinolone was still associated with substantially increased risk of AA/AD.

SENSITIVITY ANALYSES. In the sensitivity analysis (Table 3), we investigated whether time-variant confounders might affect the risk of AA/AD by using a 1:5 ratio of hazard period to referent period. In the case-crossover analysis, exposure to fluoroquinolones was associated with a substantially increased risk of AA/AD before (OR: 2.52; 95% CI: 1.44 to 4.44) and after adjustment of potential time-varying confounders (OR: 2.05; 95% CI: 1.13 to 3.71). Results of control-crossover and case-time-control studies are similar to the main analysis.

DURATION RESPONSE ANALYSIS. To gain insight into whether increasing the length of fluoroquinolone therapy might affect the risk of AA/AD, we carried out a duration response analysis (Table 4). Using patients exposed to fluoroquinolones for <3 days as a reference group, we found that longer exposure to fluoroquinolones was associated with a higher risk of AA/AD. Compared with patients exposed to fluoroquinolones for a period shorter than 3 days, patients exposed for 3 to 14 days were associated with a 2.4-fold increased risk of AA/AD (OR: 2.41; 95% CI: 1.25 to 4.65) and patients with more than 14 days of fluoroquinolone exposure were associated with a 2.8-fold increase risk of AA/AD (OR: 2.83; 95% CI: 1.06 to 7.57). The trend p value was significantly <0.01.

SUSCEPTIBLE PERIOD ANALYSIS. In Table 5, we show the analysis of the relationship between the temporal proximity of fluoroquinolone prescriptions and odds of AA/AD by varying the hazard period length. We used a 1:1 ratio of hazard period to referent period design for this analysis. Exposure to fluoroquinolone within 60 days of AA/AD diagnosis was associated with the highest risk (OR: 2.70; 95% CI: 1.87 to 21.40). When the hazard period extends to

TABLE 2 Main Analysis on the Estimates of the Relationship Between Exposure of Fluoroquinolone and AD or AAs

	Exposed Only in Hazard Period	Exposed Only in Referent Period	Exposed in Both Periods	Nonexposed in Both Periods	Odds Ratio (95% CI)*
Case-crossover	19	7	2	1,185	2.71 (1.14–6.46)
Control-crossover	9	12	2	1,190	0.75 (0.32–1.78)
Case-time-control	NA	NA	NA	NA	3.61 (3.56–3.63)

Values are n, unless otherwise indicated. *Calculated by McNemar's test: the ratio of subjects exposed only in the hazard period to subjects exposed in referent period.
AA = aortic dissection; AD = aortic aneurysm; CI = confidence interval; NA = not applicable.

120 days and 180 days, we did not find a significant association between the exposure to fluoroquinolone and the risk of AA/AD.

Therefore, we divided the 60-day risk period divided into 10-day intervals, and used a 1:5 ratio of hazard period to referent period design for this analysis. Throughout all the 6 intervals, the hazard period has a higher exposure to fluoroquinolone than the corresponding referent period (**Central Illustration**).

NUMBER NEEDED TO HARM. Assuming the population incidence of AA/AD in the fluoroquinolone naive population to be 6/100,000 patient-years, and the risk ratio approximated by the aforementioned risk (OR: 2.71; 95% CI: 1.14 to 6.46), for every 9,747 (95% CI: 3,052 to 119,047) persons receiving fluoroquinolones for more than 3 days, 1 excess case of AA/AD would happen. In 2012 in the United States, an estimated 25,250,000 outpatients were prescribed with fluoroquinolones, which could have led to an excess of 2,591 (95% CI: 212 to 8,172) attributable cases of AA/AD.

Given a higher underlying risk of AA/AD in the elderly population (130/100,000 patient-years for patients >65 years of age), the NNH will be 5-fold higher at 516 (95% CI: 141 to 5,495).

DISCUSSION

In this case-crossover study based on a large population-based database, we confirmed that the use of fluoroquinolones was associated with a 2-fold increase in the risk of AA/AD, not confounded by time-invariant characteristics. Consistently, in the DRS-matched case-time-control study, we found no significant risk of exposure-trend bias. Further duration response analysis showed that an increased length of fluoroquinolone exposure was associated with an increased risk of AA/AD. Susceptible period analysis revealed that the use of fluoroquinolone within 60 days was associated with the highest risk of AA/AD.

Our findings are consistent with previous studies investigating the association between fluoroquinolone use and collagen-associated adverse events. A recently published study in January 2018 (9), and a meta-analysis in December 2017 (28) reported that there were only 3 epidemiological studies addressing the risk of AA/AD associated with fluoroquinolone use, and our findings were consistent with the results. In these 3 parallel-designed studies, the risk of AA/AD associated with the use of fluoroquinolones ranged from 2- to 3-fold (7–9). Pasternak et al. (9) and our previous study (7) also reported that the hazard period was 60 days, and there was no increased risk of AA/AD when the hazard period was extended beyond 60 days. Because the previous study used a parallel design, we also compared our results to other types of fluoroquinolone-associated collagen adverse event in a case-crossover setting. Wise et al. (29) performed a case-crossover study in the U.K. population-based database to study the quinolone-associated tendon disorders. They found that the use of fluoroquinolones within 30 days was

TABLE 3 Sensitivity Analysis Investigating Whether Time-Variant Confounders Might Affect the Risk of AA/AD by Using a 1:5 Ratio of Hazard Period to Referent Period

	Exposed Individuals in Hazard Period (n = 1,213)	Exposed Individuals in Referent Period (n = 6,065)	Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)*
Case-crossover	21 (0.017)	48 (0.008)	2.52 (1.44–4.44)	2.05 (1.13–3.71)
Control-crossover	11 (0.009)	56 (0.0092)	0.98 (0.50–1.92)	0.83 (0.42–1.64)
Case-time-control	NA	NA	2.57 (2.31–2.88)	2.47 (2.26–2.69)

Values are n (%), unless otherwise indicated. *Calculated by multivariate conditional logistic regression with adjustment of time-varying confounders.
Abbreviations as in Table 2.

TABLE 4 Duration-Response Analysis

Cumulative Fluoroquinolone Use	Exposed Individuals in Hazard Period (n = 1,213)	Exposed Individuals in Referent Period (n = 6,065)	Odds Ratio (95% CI)
<3 days	1,192 (98.27)	6,017 (99.21)	Reference group
3–14 days	14 (1.15)	32 (0.53)	2.41 (1.25–4.65)
>14 days	7 (0.58)	16 (0.26)	2.83 (1.06–7.57)

Values are n (%), unless otherwise indicated.
Abbreviations as in Table 2.

associated with a 4.3-fold increased risk of developing tendinitis and a 2.0-fold increased risk of developing tendon rupture (29). Raguideau et al. (30) found that use of fluoroquinolone was associated with a 1.46-fold increased risk of retinal detachment using a hazard period of 10 days, and did not observe any increase in the risk extending the hazard period to either 11 to 30 days or 31 to 60 days. Our case-crossover results demonstrating a 2.7-fold increase in the risk of AA/AD using a hazard period of 60 days are in concordance with these findings.

Typically, AA/AD develop slowly in patients, but our data suggest that use of fluoroquinolone can contribute in the short term to aneurysm progression or rupture that may require emergency department visits and hospitalization. Because an epidemiological study does not permit direct mechanistic insights into the short time frame on how fluoroquinolone initiates or aggravates AA/AD, we summarized existing experimental studies for computability. Experimental studies have demonstrated several molecular mechanisms responsible for the short time frame on fluoroquinolone-associated collagen toxicity. Collagen degradation is regulated by the balance between the lytic activity of the matrix metalloproteinases (MMPs) and the tissue inhibitors of the MMPs (TIMPs). In an experiment that cultured human tendon with fluoroquinolones for 4 days, increasing the fluoroquinolone concentration resulted in increased MMP activity and collagen degradation (31). Furthermore, Guzzardi et al. (20) also demonstrated collagen degradation and decreased TIMPs activity in human aortic fibroblasts cultured with 2 days fluoroquinolones. Unlike the previous studies using tendon cells from healthy objects, the aortic fibroblasts were obtained from surgical specimen of patients with aortopathy, further strengthening its clinical correlation. The use of 3 cumulative days of fluoroquinolone prescription as a cutoff value to distinguish use from nonuse was supported by the findings in the in vitro studies. In fact, in human tenocytes, after 4 cumulative days of fluoroquinolone treatment, an 8-fold increase in the apoptosis marker, caspase-3, could be observed (32).

TABLE 5 Susceptible Period Analysis Using Different Length of Hazard Period

Length of Hazard Period	Number of Exposed Patients in Hazard Periods	Number of Exposed Patients in Referent Periods	Odds Ratio (95% CI)
60 days	21	5	2.70 (1.87–21.40)
120 days	29	24	1.25 (0.70–2.25)
180 days	32	27	1.28 (0.70–2.11)

Abbreviations as in Table 2.

Fluoroquinolones are one of the most commonly prescribed antimicrobial agents around the world. With a wide spectrum of antimicrobial activity and superior pharmacokinetic and bioavailability profiles, the global prescription of fluoroquinolones has rapidly increased, almost doubling, from 4.75 billion to 7.81 billion doses in the last decade (33). In the United States alone, fluoroquinolone prescriptions have more than tripled, from 7 million in 1995 to 22 million in 2002 (34). With an estimated 25 million people prescribed with fluoroquinolones in the United States annually, which is expected to increase even more, it is clear that fluoroquinolones may contribute substantially to the current and future burdens of AA/AD. Based on our calculations, even though the NNH is as large as 11,111, the high prevalence of fluoroquinolone use may still translate to a substantial burden of AA/AD worldwide. In fact, with a population incidence of AA/AD in the unexposed people of 6/100,000 patient-years, 2,272 cases of AA/AD could be solely attributed to the prescription of fluoroquinolones.

STUDY STRENGTHS AND LIMITATIONS. Results of our study should be interpreted in light of both strengths and weaknesses. A major strength of this study is the use of 3 levels of defense against confounding: a crossover configuration to control for time-invariant confounders (known and unknown); regression modeling to adjust for measured patient-specific time-variant confounders (e.g., infection and medication profiles over time); and DRS-matched case-time-control analysis to investigate the effect of potential exposure trend bias in a case-only design. Second, we used a large, nationally representative database, which not only maximized the generalizability of our findings, but also provided us with sufficient statistical power for rare events like AA/AD. In addition, we were able to quantify the public health impact by calculating NNH and estimating attributable excess cases of AA/AD.

However, several limitations should be noted. First, as with all administrative databases, there is no information on adherence to prescriptions. We assumed good correspondence between dispensing

record and drug intake, and cannot exclude the possibility of misclassification of exposure. It is likely that such exposure misclassification was random, not biasing our results. Second, given the observational nature of this study, the association between fluoroquinolones and AA/AD can only be confirmed by a randomized controlled study. However, a sufficiently powered clinical trial would be a challenging task given the rare incidence of AA/AD in the general population (6 to 16.3/100,000 person-years). In addition, randomized controlled trials of fluoroquinolones usually exclude patients with a high burden of cardiovascular comorbidities, who are a vulnerable population to fluoroquinolone-associated great vessel injuries. Thus, it unlikely that a large prospective trial will be available in the near future. The biological plausibility of the association, the coherence between experimental and epidemiological finding, and the analogous findings of similar collagen adverse events suggest that clinicians should carefully weigh the benefit against potential harm of fluoroquinolone for treating patients with minor infections.

CONCLUSIONS

Using a case only design to address the residual confounding that may occur in a parallel-designed epidemiological study, we confirmed a 2.5-fold risk of AA/AD during fluoroquinolone treatment. Although the rare incidence of AA/AD attenuates the public health impact, the rapid increase of fluoroquinolone consumption still poses a large burden of AA/AD in the general population. Clinicians are advised to consider alternative antibiotic regimens in patients with pre-existing collagen-related disorder or aortic aneurysm.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Fluoroquinolones, a class of antibiotics commonly prescribed for treatment of lower respiratory tract or urinary infections, are associated with a 2.5-fold increased risk of aortic aneurysm and dissection. Physicians should weigh the anticipated benefits against potential risks when selecting fluoroquinolones for patients with aortic disease when alternative management strategies are available.

TRANSLATIONAL OUTLOOK: Further studies are needed to explore the mechanisms by which fluoroquinolones affect collagen synthesis and the stability of the aortic wall and identify patients most susceptible to fluoroquinolone-associated aortic disruption.

REFERENCES

1. Khan IA, Nair CK. Clinical, diagnostic, and management perspectives of aortic dissection. Chest 2002;122:311–28.

2. Pacini D, Di Marco L, Fortuna D, et al. Acute aortic dissection: epidemiology and outcomes. Int J Cardiol 2013;167:2806–12.

3. Howard DP, Banerjee A, Fairhead JF, et al. Population-based study of incidence and outcome of acute aortic dissection and premorbid risk factor control: 10-year results from the Oxford Vascular Study. Circulation 2013;127:2031–7.

4. Wang SW, Huang YB, Huang JW, Chiu CC, Lai WT, Chen CY. Epidemiology, clinical features, and prescribing patterns of aortic aneurysm in Asian population from 2005 to 2011. Medicine (Baltimore) 2015;94:e1716.

5. Cheng SW, Ting AC, Tsang SH. Epidemiology and outcome of aortic aneurysms in Hong Kong. World J Surg 2003;27:241–5.

6. Howard DP, Banerjee A, Fairhead JF, et al. Population-based study of incidence of acute abdominal aortic aneurysms with projected impact of screening strategy. J Am Heart Assoc 2015;4:e001926.

7. 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.

8. Daneman N, Lu H, Redelmeier DA. Fluoroquinolones and collagen associated severe adverse events: a longitudinal cohort study. BMJ Open 2015;5:e010077.

9. Pasternak B, Inghammar M, Svanström H. Fluoroquinolone use and risk of aortic aneurysm and dissection: nationwide cohort study. BMJ 2018;360:k678.

10. Shakibaei M, Pfister K, Schwabe R, Vormann J, Stahlmann R. Ultrastructure of Achilles tendons of rats treated with ofloxacin and fed a normal or magnesium-deficient diet. Antimicrob Agents Chemother 2000;44:261–6.

11. Khaliq Y, Zhanel GG. Fluoroquinolone-associated tendinopathy: a critical review of the literature. Clin Infect Dis 2003;36:1404–10.

12. Badal S, Her YF, Maher LJ. Nonantibiotic effects of fluoroquinolones in mammalian cells. J Biol Chem 2015;290:22287–97.

13. 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;448:811–21.

14. Chen L, Wang X, Carter SA, et al. A single nucleotide polymorphism in the matrix metalloproteinase 9 gene (-8202A/G) is associated with

thoracic aortic aneurysms and thoracic aortic dissection. J Thorac Cardiovasc Surg 2006;131:1045–52.

15. Kurihara T, Shimizu-Hirota R, Shimoda M, et al. Neutrophil-derived matrix metalloproteinase 9 triggers acute aortic dissection. Circulation 2012;126:3070–80.

16. Manabe T, Imoto K, Uchida K, Doi C, Takanashi Y. Decreased tissue inhibitor of metalloproteinase-2/matrix metalloproteinase ratio in the acute phase of aortic dissection. Surg Today 2004;34:220–5.

17. Ohuchi E, Imai K, Fujii Y, Sato H, Seiki M, Okada Y. Membrane type 1 matrix metalloproteinase digests interstitial collagens and other extracellular matrix macromolecules. J Biol Chem 1997;272:2446–51.

18. Corps AN, Harrall RL, Curry VA, Fenwick SA, Hazleman BL, Riley GP. Ciprofloxacin enhances the stimulation of matrix metalloproteinase 3 expression by interleukin-1β in human tendon-derived cells. Arthritis Rheum 2002;46:3034–40.

19. Pender SL, MacDonald TT. Matrix metalloproteinases and the gut: new roles for old enzymes. Curr Opin Pharmacol 2004;4:546–50.

20. Guzzardi D, Teng G, Svystonyuk D, et al. Fluoroquinolone induces human aortic fibroblast-mediated extracellular matrix dysregulation. Can J Cardiol 2017;33 Suppl:S38–9.

21. Sykes EM. Colon perforation in Ehlers-Danlos syndrome: report of two cases and review of the literature. Am J Surg 1984;147:410–3.

22. Germain DP. Clinical and genetic features of vascular Ehlers-Danlos syndrome. Ann Vasc Surg 2002;16:391–7.

23. Delaney JA, Suissa S. The case-crossover study design in pharmacoepidemiology. Stat Methods Med Res 2009;18:53–65.

24. Hsing AW, Ioannidis JPA. Nationwide population science: lessons from the Taiwan national health insurance research database. JAMA Intern Med 2015;175:1527–9.

25. Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. Am J Epidemiol 1991;133:144–53.

26. Suissa S. The case-time-control design. Epidemiology 1995;6:248–53.

27. Wang S, Linkletter C, Maclure M, et al. Future-cases as present controls to adjust for exposure-trend bias in case-only studies. Epidemiology 2011;22:568–74.

28. Singh S, Nautiyal A. Aortic dissection and aortic aneurysms associated with fluoroquinolones: a systematic review and meta-analysis. Am J Med 2017;130:1449–57.e9.

29. Wise BL, Peloquin C, Choi H, Lane NE, Zhang Y. Impact of age, sex, obesity, and steroid use on quinolone-associated tendon disorders. Am J Med 2012;125:1228.e23–8.

30. Raguideau F, Lemaitre M, Dray-Spira R, et al. Association between oral fluoroquinolone use and retinal detachment. JAMA Ophthalmol 2016;134:415–21.

31. Corps AN, Harrall RL, Curry VA, Fenwick SA, Hazleman BL, Riley GP. Ciprofloxacin enhances the stimulation of matrix metalloproteinase 3 expression by interleukin-1beta in human tendon-derived cells. A potential mechanism of fluoroquinolone-induced tendinopathy. Arthritis Rheum 2002;46:3034–40.

32. Sendzik J, Shakibaei M, Schäfer-Korting M, Stahlmann R. Fluoroquinolones cause changes in extracellular matrix, signalling proteins, metalloproteinases and caspase-3 in cultured human tendon cells. Toxicology 2005;212:24–36.

33. Van Boeckel TP, Gandra S, Ashok A, et al. Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. Lancet Infect Dis 2014;14:742–50.

34. Shapiro DJ, Hicks LA, Pavia AT, Hersh AL. Antibiotic prescribing for adults in ambulatory care in the USA, 2007-09. J Antimicrob Chemother 2014;69:234–40.

KEY WORDS aortic and arterial diseases, aortic aneurysm, aortic dissection, fluoroquinolones

APPENDIX For supplemental figures and tables, please see the online version of this paper.