Original Investigation

Risk of Aortic Dissection and Aortic Aneurysm in Patients Taking Oral Fluoroquinolone

Chien-Chang Lee, MD, ScD; Meng-tse Gabriel Lee, PhD; Yueh-Sheng Chen, MD; Shih-Hao Lee, MA; Yih-Sharng Chen, MD, PhD; Shyr-Chyr Chen, MD, MBA; Shan-Chwen Chang, MD, PhD

IMPORTANCE Fluoroquinolones have been associated with collagen degradation, raising safety concerns related to more serious collagen disorders with use of these antibiotics, including aortic aneurysm and dissection.

OBJECTIVE To examine the relationship between fluoroquinolone therapy and the risk of developing aortic aneurysm and dissection.

DESIGN, SETTING, AND PARTICIPANTS We conducted a nested case-control analysis of 1477 case patients and 147 700 matched control cases from Taiwan's National Health Insurance Research Database (NHIRD) from among 1 million individuals longitudinally observed from January 2000 through December 2011. Cases patients were defined as those hospitalized for aortic aneurysm or dissection. One hundred control patients were matched for each case based on age and sex.

EXPOSURES Current, past, or any prior-year use of fluoroquinolone. Current use was defined as a filled fluoroquinolone prescription within 60 days of the aortic aneurysm or dissection; past use refers to a filled fluoroquinolone prescription between 61 and 365 days prior to the aortic aneurysm; and any prior-year use refers to having a fluoroquinolone prescription filled for 3 or more days any time during the 1-year period before the aortic aneurysm or dissection.

MAIN OUTCOMES AND MEASURES Risk of developing aortic aneurysm or dissection.

RESULTS A total of 1477 individuals who experienced aortic aneurysm or dissection were matched to 147 700 controls. After propensity score adjustment, current use of fluoroquinolones was found to be associated with increased risk for aortic aneurysm or dissection (rate ratio [RR], 2.43; 95% CI, 1.83-3.22), as was past use, although this risk was attenuated (RR, 1.48; 95% CI, 1.18-1.86). Sensitivity analysis focusing on aortic aneurysm and dissection requiring surgery also demonstrated an increased risk associated with current fluoroquinolone use, but the increase was not statistically significant (propensity score–adjusted RR, 2.15; 95% CI, 0.97-4.60).

CONCLUSIONS AND RELEVANCE Use of fluoroquinolones was associated with an increased risk of aortic aneurysm and dissection. While these were rare events, physicians should be aware of this possible drug safety risk associated with fluoroquinolone therapy.

Editor's Note

Supplemental content at jamainternalmedicine.com

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Chien-Chang Lee, MD, ScD, Department of Emergency Medicine, National Taiwan University Hospital, Yunlin Branch, No. 579, Yunlin Road, Douliou 640, Taiwan (cclee100@gmail.com).

JAMA Intern Med. doi:10.1001/jamainternmed.2015.5389
Published online October 5, 2015.

Aortic dissection and aortic aneurysm are major life-threatening diseases worldwide.[1,2] Epidemiology studies show that mortality from aortic aneurysm and dissection has risen over the past decades in many developed countries including the United States, Britain, and Japan, with the rate of increase ranging from 1.2 to 24.8 fold.[3-6] In fact, aortic aneurysm has become the 13th leading cause of death, claiming an estimated 15 000 deaths annually in the United States.[7] Aortic dissection is defined as separation of the layers within the aortic wall, while aortic aneurysm is defined as a localized or diffuse dilation of the aorta.[8,9] Both aortic aneurysm and dissection are caused by weakness of the aortic wall due to congenital defect, hypertension, or chronic inflammation.[8-11] Ruptured aortic aneurysm and dissection are associated with high morbidity and mortality rates.[10,12,13] Many patients even experience out-of-hospital cardiac arrest before the diagnosis of aortic aneurysm or dissection is made.

Congenital disorders with collagen defects such as Marfan syndrome or vascular Ehlers-Danlos syndrome are associated with the pathological change of cystic medial degeneration, predisposing patients to a risk of both aneurysmal dilation and dissection.[13-15] Recently, fluoroquinolones have been associated with a series of collagen-related disorders such as Achilles tendon rupture, tendinopathy at multiple muscle groups, and retinal detachment.[16-23] A recent database study of 6.4 million patients found that use of fluoroquinolones was associated with a 4-fold increased risk of Achilles tendinopathy, and a 2-fold increased risk of tendon rupture.[19]

Not only is tendon composed of collagen, collagen is also a major extracellular matrix component of the aortic wall. As fluoroquinolones may induce degradation of collagen causing tendinopathy, this raises the concern that fluoroquinolones may cause or aggravate aortic aneurysm and dissection by a similar mechanism. To our knowledge, this hypothesis has not been examined in any human studies. The purpose of the present study was to investigate the association between oral fluoroquinolone therapy and the development of aortic aneurysm or dissection in a large, nationwide, longitudinally observed population.

Methods

Population

We performed a nested case-control study using the National Health Insurance Research Database (NHIRD) of Taiwan. The NHIRD contains records of approximately 1 million persons randomly selected from the 24 million beneficiaries of the National Health Insurance of Taiwan. The NHIRD contains complete outpatient and inpatient electronic claim records, individual diagnoses, procedures, and medications prescribed. Several studies have shown that this database is appropriate for use in pharmacoepidemiologic research.[24,25] This study was approved by the institutional review board of the National Taiwan University Hospital, waiving patient written informed consent.

Study Cohort

Using the NHIRD, we assembled a study cohort that was longitudinally observed from January 1998 through December 2011. Since the NHIRD is a closed cohort, there is mortality during the follow-up period. We used the years 1998 and 1999 as the preenrollment period in which 18 074 prevalent users of fluoroquinolone and 236 prevalent cases of aortic aneurysm or dissection were removed from our cohort. A total of 238 982 patients younger than 18 years as of January 1, 2000, were also identified and not allowed to enter the cohort. Finally, 741 652 patients remained in our cohort. Patients were observed from January 1, 2000, until the diagnosis of aortic aneurysm or dissection, termination of health insurance coverage, death, or end of the study period, whichever came first. The mean duration of follow-up was 3613.3 days. The timeline of the study cohort is shown in the eFigure in the Supplement.

Identification of Outcomes

Primary outcome measures were the first occurrence of aortic aneurysm or dissection requiring hospitalization during the follow-up period. The following criteria were used to identify aortic aneurysm or dissection cases in inpatients: *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes of aortic aneurysm (441.1, 441.2, 441.3, 441.4, 441.5, 441.6, 441.7, and 441.9) and aortic dissection (441.0, 441.00, 441.01, 441.02, and 441.03) plus the use of advanced imaging studies such as thoracic or abdominal computed tomography, transesophageal or transthoracic echocardiography, magnetic resonance imaging, or angiography.

Current regulation in Taiwan does not allow the linkage between the NHIRD database and medical records, so we tested the accuracy of our outcome definition by performing an independent validation in a tertiary medical center. During the study period, we identified 218 hospitalized patients with a primary or secondary diagnosis of aortic aneurysm or aortic dissection, of which 182 patients underwent advanced imaging studies. After review of medical records, we verified that 167 of 182 patients had symptoms compatible with aggravation of aortic aneurysm or acute onset of aortic dissection. Thus, the combined diagnostic and procedure code definitions for aortic aneurysm or aortic dissection has a positive predictive rate of 92% (167/182).

In sensitivity analysis, we used a more specific outcome definition by combining these criteria with surgical procedures for aortic aneurysm or dissection, which include the Bentall procedure, aortic resection, and graft replacement involving thoracic or abdominal aorta.

The hospital admission date or the event date for patients with aortic aneurysm and dissection was assigned to be the index date.

Medication Exposure

Medication exposure was assessed as of the index date for aortic aneurysm and dissection cases. Use of fluoroquinolone was assumed whenever there was any order for a reimbursement code of oral fluoroquinolone with a prescription length of 3 days or longer. Fluoroquinolones are drugs that contain any of the following active compounds: ciprofloxacin, levofloxacin, ofloxacin, sparfloxacin, norfloxacin, lomefloxacin, moxifloxacin, gemifloxacin, enoxacin, or pefloxacin. *Current use* refers

to patients having a fluoroquinolone prescription filled within 60 days of the index date, and *past use* refers to patients having a prescription filled between 61 and 365 days prior to the index date. *Any prior-year use* refers to having a fluoroquinolone prescription that was filled for 3 or more days in the 1-year period before the index date.

Population Controls

We selected controls by using a risk set sampling scheme. One hundred controls were selected for each case, matched on 5-year age class, sex, and the index date of case diagnosis.

Covariates

Based on literature reports,[2,13,17,21,22] we identified 96 covariates (**Table 1**) in the following categories: demographics, cardiovascular comorbidities, risk factors for aortic aneurysm and dissection, intensity of health care facility utilization, and use of specific medications. The graphic timeline of our covariate collection can be found in the eFigure in the Supplement. Covariates for chronic comorbidities and risk factors were collected from the year 1998 to the year before the start of the fluoroquinolone exposure period (eFigure [aqua arrow line] in the Supplement). Utilization of health care facilities and the use of specific medications were assessed in the 1-year period before fluoroquinolone exposure (eFigure [red arrow line] in the Supplement). To capture the indication for fluoroquinolone prescription, we included a set of infectious diseases as covariates (eTable 1 in the Supplement) and collected this information along with the 1-year fluoroquinolone exposure period (eFigure [black arrow line] in the Supplement). We used a combined weighted comorbidity index to quantify each individual's burden of comorbidity. This score combines the Charlson index with the Elixhauser system to offer improvements in comorbidity summarization over the Charlson index alone.[26]

Statistical Analysis

Under a time-matched case-control sampling scheme, the odds ratios estimate the rate ratios (RRs). Incidence RRs of aortic aneurysm or dissection (plus 95% CIs) were estimated by using conditional logistic regression analysis adjusted for all covariates. In addition to conventional multivariate analysis, we constructed a propensity score for adjustment and matching. Using the entire cohort, we derived the propensity score using a logistic regression model that included all potential predictors for fluoroquinolone therapy. Propensity score matching was conducted using a greedy matching algorithm without any trimming. To avoid unrealistic linear assumption of continuous variables in the regression model, such as age, comorbidity score, and propensity score, we entered these variables into the model with a main term plus a quadratic term to allow a nonlinear association between these variables and the outcome. To further assess the robustness of our results, we performed duration response analyses by testing the linear association between the ordinal categories of drug use duration and the risk of incident aortic aneurysm and dissection. We also performed subgroup analyses in high-risk patients. Predefined subgroups included male vs female sex and age 70 years or younger vs greater than 70 years. Statistical analysis was carried out using SAS software, version 9.3 (SAS Institute Inc).

Results

A total of 1477 cases of aortic aneurysm or dissection were identified, and 147 700 controls were selected. Characteristics of case patients and controls are listed in Table 1. Slightly more case patients were diagnosed with aortic aneurysm than aortic dissection (850 vs 662), and 35 patients were diagnosed with both aortic aneurysm and dissection. In most instances, patients with aortic aneurysm or dissection were found to have a higher burden of cardiovascular diseases, higher Charlson index, and greater use of cardiovascular medication than controls.

Main Analyses

As summarized in **Table 2**, all 3 types of fluoroquinolone users (current, past, or any prior-year use) had increased risk of aortic aneurysm or dissection. Current use of fluoroquinolone was associated with the highest risk of aortic aneurysm or dissection (RR, 2.93; 95% CI, 2.17-3.97) in our crude analysis. The increase in risk of aortic aneurysm or dissection remained after adjusting for individual confounders (RR, 2.28; 95% CI, 1.67-3.13), adjustment by propensity score (RR, 2.43; 95% CI, 1.83-3.22), and propensity score matching (RR, 1.75; 95% CI, 1.11-2.74). The crude (RR, 1.82; 95% CI, 1.44-2.29) and propensity score–matched effect estimates (RR, 1.19; 95% CI, 0.85-1.66) for past use of fluoroquinolone were all attenuated compared with current use. The crude (RR, 2.11; 95% CI, 1.75-2.55) and propensity score–matched effect estimates (RR, 1.37; 95% CI, 1.04-1.79) for any prior-year use of fluoroquinolone fell between those of current and past use.

Sensitivity Analyses

To verify the robustness of the primary results and examine the various effects of outcome definitions, we repeated the primary analyses on different outcome definitions: aortic aneurysms only, aortic dissection only, aortic aneurysms undergoing surgery only, aortic dissection undergoing surgery only, and aortic aneurysm or dissection undergoing surgery (**Table 3**). In all the outcome definitions, a higher risk of aortic aneurysm or dissection was associated with use of fluoroquinolone. This was also true in the strictest definition for aortic aneurysm and dissection, where only those who had undergone aortic aneurysm- or dissection-related surgical procedures were included.

Subgroup Analysis and Duration-Response Analysis

To further assess the robustness of our results, we stratified the study population based on age and sex. We found that the risk increase of aortic aneurysm or dissection in any prior-year use of fluoroquinolone was more substantial in patients older than 70 years (RR, 1.72; 95% CI, 1.37-2.16) than in patients 70 years or younger (RR, 1.46; 95% CI, 0.98-2.18). The risk increase for aortic aneurysm or dissection was also more

Table 1. Descriptive Characteristics of Patients With Aortic Aneurysm and/or Aortic Dissection and Controls

Characteristic[a]	Study Participants, No. (%) (n = 147 177)[b]			*P* Value	
	Aortic Aneurysm (n = 850)	Aortic Dissection (n = 662)	Controls (n = 147 700)	Aortic Aneurysm vs Control	Aortic Dissection vs Control
Demographics					
Male sex	630 (74.1)	473 (71.5)	107 600 (72.9)	.40	.41
Age, mean (SD), y	74.7 (11.7)	66.2 (14.5)	71.0 (13.7)	<.001	<.001
Index year					
2000	59 (6.9)	44 (6.7)	10 000 (6.8)	.96	.99
2001	60 (7.1)	46 (7.0)	10 500 (7.1)		
2002	56 (6.6)	48 (7.3)	10 400 (7.0)		
2003	76 (8.9)	53 (8.0)	12 300 (8.3)		
2004	54 (6.4)	52 (7.9)	10 400 (7.0)		
2005	62 (7.3)	63 (9.5)	12 500 (8.5)		
2006	67 (7.9)	56 (8.5)	12 000 (8.1)		
2007	78 (9.2)	60 (9.1)	13 200 (8.9)		
2008	61 (7.2)	49 (7.4)	11 000 (7.5)		
2009	76 (8.9)	58 (8.8)	12 900 (8.7)		
2010	113 (13.3)	71 (10.7)	17 800 (12.1)		
2011	88 (10.4)	62 (9.4)	14 700 (10.0)		
Geographic Area					
Large central city	356 (41.9)	281 (42.4)	61 939 (42.2)	.54	.28
Mid-sized central city	226 (26.6)	185 (28.0)	36 941 (25.2)		
Suburban	189 (22.2)	130 (19.6)	32 208 (21.9)		
Countryside	79 (9.3)	66 (10.0)	15 581 (10.6)		
Annual Insurance Premiums (New Taiwan Dollars)					
0 (Dependent)	102 (12.0)	78 (11.8)	17 971 (12.3)	<.001	.09
1-19 999	416 (48.9)	256 (38.7)	50 095 (34.2)		
20 000-39 999	244 (28.7)	231 (34.9)	57 030 (38.9)		
≥40 000	88 (10.4)	97 (14.7)	21 573 (14.7)		
Related Cardiovascular Diseases					
Congestive heart failure	228 (26.8)	118 (17.8)	18 844 (12.8)	<.001	<.001
Cerebrovascular disease	331 (38.9)	178 (26.9)	33 843 (22.9)	<.001	.02
Myocardial infarction/acute coronary syndromes	71 (8.4)	33 (5.0)	4901 (3.3)	<.001	.02
Stroke or transient ischemic attack	149 (17.5)	81 (12.2)	14 553 (9.9)	<.001	.04
Peripheral arterial disease	45 (5.3)	27 (4.1)	5490 (3.7)	.02	.63
Angina	188 (22.1)	102 (15.4)	17 377 (11.8)	<.001	.01
Other ischemic heart disease	411 (48.4)	234 (35.4)	42 176 (28.6)	<.001	<.001
Cerebral atherosclerosis	48 (5.7)	16 (2.4)	4830 (3.3)	<.001	.21
Percutaneous coronary/coronary artery bypass graft intervention	27 (3.2)	13 (1.9)	1429 (0.9)	<.001	.01
Bedridden status	62 (7.3)	38 (5.7)	6800 (4.6)	<.001	.17
Risk Factors					
Diabetes	226 (26.6)	123 (18.6)	38 315 (25.9)	.65	<.001
Tobacco use	17 (2.0)	12 (1.8)	991 (0.7)	<.001	<.001
Hypertension	662 (77.9)	481 (72.7)	78 406 (53.1)	<.001	<.001
Lipid disorder	300 (35.3)	214 (32.3)	41 570 (28.1)	<.001	.02
Marfan syndrome	1 (0.1)	2 (0.3)	0	NA	NA
Cardiovascular syphilis	5 (0.6)	2 (0.3)	14 (0.01)	<.001	<.001
Trauma (motor vehicle traffic accident)	2 (0.2)	3 (0.4)	883 (0.6)	.17	.63
Aortic valve disorders	118 (13.9)	66 (10.0)	5654 (3.8)	<.001	<.001
Obstructive sleep apnea	201 (23.7)	132 (19.9)	26 051 (17.6)	<.001	.13
Chronic obstructive pulmonary disease	372 (43.8)	208 (31.4)	44 181 (29.9)	<.001	.42
Ischemic heart disease	311 (36.6)	184 (27.8)	32 204 (21.8)	<.001	<.001
Chronic kidney disease	95 (11.2)	51 (7.7)	7578 (5.1)	<.001	.01

(continued)

Table 1. Descriptive Characteristics of Patients With Aortic Aneurysm and/or Aortic Dissection and Controls (continued)

Characteristic[a]	Study Participants, No. (%) (n = 147 177)[b]			*P* Value	
	Aortic Aneurysm (n = 850)	Aortic Dissection (n = 662)	Controls (n = 147 700)	Aortic Aneurysm vs Control	Aortic Dissection vs Control
Asthma	197 (23.2)	122 (18.4)	24 769 (16.8)	<.001	.26
Cardiac valve disease	170 (20.0)	88 (13.3)	11 232 (7.6)	<.001	<.001
Conduction disorder	26 (3.1)	9 (1.4)	1906 (1.3)	<.001	.89
Atrial fibrillation	70 (8.2)	23 (3.5)	4926 (3.3)	<.001	.87
Obesity	7 (0.8)	10 (1.5)	850 (0.6)	.35	.01
Malignant hypertension	45 (5.3)	24 (3.6)	3716 (2.5)	<.001	.07
Schizophrenia	1 (0.1)	3 (0.5)	918 (0.6)	.06	.59
Psychotropic poisoning	1 (0.1)	1 (0.1)	118 (0.08)	.70	.52
Seizure disorder	28 (3.3)	12 (1.8)	2442 (1.6)	<.001	.76
Decubitus ulcer	17 (2.0)	6 (0.9)	1268 (0.9)	<.001	.90
Any infectious disease past 365 days	211 (24.8)	113 (17.1)	19 074 (12.9)	<.001	<.001
Charlson index	5.3 (2.5)	4.5 (2.3)	4.2 (2.3)	<.001	.01
OPD and Hospitalization Within 1 Year Before Index Date					
OPD visits, No.	28.6 (23.8)	22.4 (21.6)	21.1 (19.4)	<.001	.07
Emergency department visits, No.	0.34 (1.0)	0.24 (0.7)	0.18 (0.7)	<.001	.03
Hospitalizations, No.	0.44 (0.9)	0.36 (2.3)	0.25 (0.7)	<.001	<.001
Medication Use					
NSAIDs	353 (41.5)	272 (41.1)	51 514 (34.9)	<.001	<.001
Aspirin	311 (36.6)	158 (23.9)	28 693 (19.4)	<.001	.01
Systemic immunosuppressive agents and biologics	3 (0.4)	1 (0.2)	298 (0.2)	.32	.76
Systemic corticosteroids	148 (17.4)	109 (16.5)	19 722 (13.4)	<.001	.02
DMARDs	10 (1.2)	7 (1.1)	1292 (0.9)	.34	.62
Statin	114 (13.4)	70 (10.6)	11 713 (7.9)	<.001	.01
ACE inhibitors	190 (22.4)	122 (18.4)	19 148 (12.9)	<.001	<.001
β-Agonist	128 (15.1)	75 (11.3)	15 713 (10.6)	<.001	.58
Angiotensin receptor blocker	196 (23.1)	116 (17.5)	17 363 (11.8)	<.001	<.001
Anticoagulant (antithrombotic agents)	109 (12.8)	61 (9.2)	9464 (6.4)	<.001	.01
Antiarrhythmic	36 (4.2)	21 (3.2)	2798 (1.9)	<.001	.02
β-Blocker (selective + nonselective)	186 (21.9)	152 (22.9)	21 861 (14.8)	<.001	<.001
Calcium channel blockers	412 (48.5)	302 (45.6)	41 069 (27.8)	<.001	<.001
Digoxin	54 (6.4)	23 (3.5)	3684 (2.5)	<.001	.12
Loop diuretics	125 (14.7)	57 (8.6)	9340 (6.3)	<.001	.01
Insulin	5 (0.6)	2 (0.3)	929 (0.6)	.88	.29
Oral hypoglycemic	77 (9.1)	44 (6.7)	17 654 (11.9)	.01	<.001
Fibrate lipid-lowering agent	34 (4.0)	22 (3.3)	4352 (2.9)	.07	.57
Nitrate antianginal	154 (18.1)	68 (10.3)	10 674 (7.2)	<.001	.01
Peripheral vasodilators	81 (9.5)	43 (6.5)	8573 (5.8)	<.001	.46
Antidepressants	104 (12.2)	59 (8.9)	11 362 (7.7)	<.001	.25
Benzodiazepine	313 (36.8)	191 (28.9)	38 057 (25.8)	<.001	.08
Parkinson medication	68 (8.0)	31 (4.7)	7273 (4.9)	<.001	.76
Antipsychotics	6 (0.7)	2 (0.3)	772 (0.5)	.46	.43
Hydroxyzine	12 (1.4)	7 (1.1)	1441 (0.9)	.19	.84
Anticonvulsants	19 (2.2)	9 (1.4)	2476 (1.7)	.20	.52

Abbreviations: ACE, angiotensin-converting enzyme; DMARD, disease-modifying antirheumatic drug; NSAIDs, nonsteroidal anti-inflammatory drugs; NA, not applicable; OPD, outpatient department.

[a] The following characteristics were not reported because no cases with aortic aneurysm or aortic dissection were found: amphetamine abuse, Ehlers-Danlos syndrome, bicuspid aortic value, coarctation of the aortic, giant-cell arteritis, Takayasu disease, Turner syndrome, opioid poisoning, and use of lithium.

[b] Numbers of patients in the 3 categories total 35 more than 147 177 because 35 patients had both aortic aneurysm and aortic dissection.

substantial in female patients (RR, 1.83; 95% CI, 1.27-2.64) than in male patients (RR, 1.61; 95% CI, 1.28-2.03).

We also investigated the duration-response relationship between duration of fluoroquinolone therapy and risk of aor-

Table 2. Rate Ratios Associated With Aortic Aneurysm or Dissection, and Different Types of Fluoroquinolone Use

Fluoroquinolone Use[a]	Effect Estimate, Rate Ratio (95% CI)			
	Matched on Age Group, Sex, and Year	Adjusted by Individual Confounders	Propensity Score Adjusted	Propensity Score Matched
Current	2.93 (2.17-3.97)[b]	2.28 (1.67-3.13)[b]	2.43 (1.83-3.22)[b]	1.75 (1.11-2.74)[d]
Past	1.82 (1.44-2.29)[b]	1.49 (1.18-1.90)[c]	1.48 (1.18-1.86)[b]	1.19 (0.85-1.66)
Any use in prior year	2.11 (1.75-2.55)[b]	1.69 (1.39-2.06)[b]	1.74 (1.44-2.09)[b]	1.37 (1.04-1.79)[d]

[a] Current use refers to patients having a fluoroquinolone prescription filled within 60 days of the index date; past use refers to patients having a prescription filled between 61 and 365 days prior to the index date; any use in prior year refers to having a fluoroquinolone prescription that was filled for 3 or more days in the 1-year period before the index date.

[b] $P < .001$.

[c] $P < .01$.

[d] $P < .05$.

Table 3. Rate Ratios Associated With Different Aortic Aneurysm and Aortic Dissection Definitions and Different Types of Fluoroquinolone Use

Type of Fluoroquinolone Use[a]	Effect Estimate, Rate Ratios (95% CI)	
	Matched on Age Group, Sex, and Year	Propensity Score Adjusted
Aortic aneurysm only		
Current	2.98 (2.05-4.32)[b]	2.36 (1.66-3.36)[b]
Past	1.45 (1.05-2.00)[c]	1.19 (0.87-1.62)
Any in prior year	1.88 (1.46-2.41)[b]	1.52 (1.19-1.94)[b]
Aortic dissection only		
Current	2.93 (1.79-4.80)[b]	2.55 (1.58-4.11)[b]
Past	2.27 (1.53-3.17)[b]	2.00 (1.44-2.79)[b]
Any in prior year	2.45 (1.85-3.25)[b]	2.15 (1.61-2.85)[b]
Aortic aneurysm undergoing surgery only		
Current	2.27 (0.92-5.58)	1.99 (0.79-4.98)
Past	1.11 (0.52-2.37)	1.02 (0.47-2.21)
Any in prior year	1.41 (0.78-2.54)	1.28 (0.69-2.35)
Aortic dissection undergoing surgery only		
Current	4.14 (1.25-13.67)[c]	3.50 (1.04-11.84)[c]
Past	0.48 (0.07-3.44)	0.42 (0.06-3.07)
Any in prior year	1.40 (0.51-3.89)	1.22 (0.43-3.46)
Aortic aneurysm or aortic dissection undergoing surgery		
Current	2.45 (1.15-5.27)[c]	2.15 (0.97-4.60)
Past	0.97 (0.49-1.99)	0.88 (0.43-1.82)
Any in prior year	1.35 (0.80-2.30)	1.21 (0.70-2.08)

[a] Current use refers to patients having a fluoroquinolone prescription filled within 60 days of the index date; past use refers to patients having a prescription filled between 61 and 365 days prior to the index date; any use in prior year refers to having a fluoroquinolone prescription that was filled for 3 or more days in the 1-year period before the index date.

[b] $P < .001$.

[c] $P < .05$.

tic aneurysm and dissection (**Table 4**). It was found that as the duration of fluoroquinolone therapy increased from 3 to 14 days to greater than 14 days, there was an increasing risk of aortic aneurysm and dissection in both the crude incidence (2.60% vs 2.92%) and the propensity score–adjusted effect estimate (RR, 1.60; 95% CI, 1.10-2.52 vs RR, 1.81; 95% CI, 0.91-3.17).

Discussion

In this population-based study of Taiwanese adults, current use of fluoroquinolone was associated with more than a 2-fold increased risk of aortic aneurysm or dissection. Past use and any prior-year use were similarly associated with an increased, although attenuated, risk for these severe adverse events. Longer duration of fluoroquinolone therapy was also associated with higher incidence of aortic aneurysm or dissection. The risk increase of aortic aneurysm or dissection was more substantial in patients older than 70 years and in female patients.

As the use of fluoroquinolones increases, the occurrence of uncommon fluoroquinolone-associated complications, including seizure, tendon rupture, torsades de pointes, hepatotoxic effects, and dysglycemia, is gradually increasing.[27,28] Recently, a population-based study enrolling 989 591 patients in Canada suggested that treatment with oral fluoroquinolones was associated with increased risk of retinal detachment.[29] This significant association between fluoroquinolones and retinal detachment was also demonstrated in a study conducted in Taiwan.[21] Another connective-tissue disease—tendinopathy—was found to be associated with the use of fluoroquinolones in 2 studies conducted in the United Kingdom: a population-based case-control study using the General Practice Research Database[30] and a case-crossover study using the Health Improvement Network database.[19] We note that aortic aneurysm and dissection share pathophysiologic characteristics with retinal detachment and tendinopathy.[19,21,23,29-31]

As for the risk period, a recent review reported fluoroquinolone-associated tendon rupture occurring after fluoroquinolone use of between 2 and 31 days (median, 7 days).[32] Etminan et al[29] showed that current users experience the highest risk of a retinal detachment within 5 days of beginning fluoroquinolone use. In the study by van der Linden et al,[31] current use of fluoroquinolone was associated with a 7.1-fold increased risk of developing Achilles tendon rupture compared with nonuse. Our results demonstrating a higher risk of aortic aneurysm and dissection within 60 days of fluoroquinolone therapy are in concordance with these findings.

While the exact mechanism of how use of fluoroquinolone can cause aortic aneurysm and dissection is unknown, there are several possibilities. The strength of the aortic wall

Table 4. Risk of Aortic Aneurysm or Aortic Dissection Associated With Increasing Duration of Fluoroquinolone Use

Duration of Fluoroquinolone Use, d	Case/Person-years, No. (Incidence Rate, %)	Propensity Score–Adjusted Rate Ratio (95% CI)
<3 [Reference]	1432/147 495 (0.97)	1 [Reference]
3-14	33/1271 (2.60)	1.60 (1.10-2.52)[a]
>14	12/411 (2.92)	1.81 (0.91-3.17)

[a] $P < .05$.

relies on the structural integrity of the extracellular matrix proteins, which are regulated by proteolytic enzymes such as matrix metalloproteinases (MMPs).[33-35] It has been demonstrated that MMPs play an important role in the pathogenesis of aortic aneurysm and dissection. Dysregulation of MMP production and activity leads to extracellular matrix degradation and medial layer degeneration.[33,36-38] Examination of smooth muscle cells from abdominal aortic aneurysm shows an upregulated expression of MMP-9 and MMP-2.[39] Fluoroquinolone has been shown to affect the synthesis of collagen in the tendon cell[40] and disorganization of the extracellular matrix in the cornea.[41] Animal studies have shown that ciprofloxacin may induce the expression of MMP-9 and MMP-2 in cornea tissue[42] and MMP-2 in tendon tissue.[40] Both MMP-2 and MMP-9 are gelatinases that have collagenolytic activity.[43,44] Collagen and elastin are the primary extracellular matrix components of the aortic wall, and these elements make up approximately 50% of the dry weight of normal arteries.[45] Therefore, it is possible that fluoroquinolones destroy the collagen and connective tissue along the aortic wall causing aortic aneurysm and dissection as they do on tendon and cornea.

In Taiwan, fluoroquinolone prescriptions for adults almost doubled between 2000 and 2011, from 2.1% to 3.8% (eTable 3 in the Supplement). With the rapid increase in the fluoroquinolone use, it is likely that fluoroquinolone therapy may constitute a substantial contributor to the burden of aortic aneurysm or dissection. If we assume that the adverse effects observed in the present study were caused by fluoroquinolone use, approximately 2.8% to 5.2% of incident aortic aneurysm or dissection cases may be attributable to this risk factor (eEquations in the Supplement). Given the global burden of aortic aneurysm and dissection and the growing use of fluoroquinolones worldwide, well-designed studies in other populations, especially high-risk populations, should be conducted to validate our findings. Animal studies aimed to clarify the pathophysiological mechanism of this association would also be valuable.

Results of our study should be interpreted in light of both its strengths and limitations. To overcome the confounding bias, we constructed a propensity score from the source population to balance the difference in baseline characteristics between users and nonusers of fluoroquinolone. Despite the efforts, residual confounding from poorly measured or unmeasured covariates cannot be totally excluded. We lacked data on lifestyle factors, including smoking, alcohol drinking, and body mass index. We adjusted these factors by including related diseases such as chronic obstructive pulmonary disease, peptic ulcer disease, coronary artery disease, malnutrition, alcohol-related disorders, and diabetes mellitus.

Another limitation is the small number of aortic aneurysm and dissection events associated with the use of fluoroquinolone. The small number of events prevents us from carrying out propensity-score matching in subgroup analyses. A propensity score–matched model looks at a subpopulation with the closest attributes, while the propensity score–adjusted model looks at the entire study population. Thus, this might cause appreciable difference in the propensity score–adjusted and propensity score–matched result. We decided to focus our discussion on the propensity score–adjusted result because the result is based on a population effect.

The possibility of protopathic bias, interpreted as symptoms preceding the diagnosis of aortic aneurysm and dissection leading to prescription of fluoroquinolones, cannot be totally ruled out. Some cases of aortic dissection can be presented initially as pericarditis, and certain fluoroquinolones may be used to treat pericarditis if it is believed to be of bacterial origin. Another scenario is that infective aneurysm may be an indication for fluoroquinolone prescription preceding the hospitalization for aortic aneurysm or dissection. However, we found that both infective aneurysm and pericarditis were rare in our sample, accounting for only 2.6% and 0.4% of cases, respectively. In addition, fever is a rare manifestation of aortic aneurysm and dissection, and it would be hard to explain why the association takes more than 60 days to manifest. On further analysis, we found that the main indications for fluoroquinolone prescription in our case patients were lower respiratory tract infections, urinary tract infections, and soft-tissue infections instead.

Another limitation of our study was that we defined aortic aneurysm and dissection disease on the basis of *ICD-9-CM* codes with compatible orders of imaging examinations. We cannot rule out the possibility that aortic aneurysms may be newly diagnosed on imaging tests such as computed tomographic scans, which are sometimes ordered during acute infections requiring antibiotic use. Thus, there might be detection bias in certain patients with aortic aneurysm. By using a more rigorously defined outcome, aortic aneurysm or dissection requiring operation, we found results similar to those of the main analyses. Therefore, we believe that detection bias, if any, cannot fully explain the association we observed in this study.

Conclusions

We found that use of fluoroquinolones was associated with an approximately 2-fold increase in risk of aortic aneurysm and dissection within 60 days of exposure. Although our results cannot establish cause and effect, it is not likely that more detailed information on a larger population at relatively high risk of aortic aneurysm or dissection will become available in the immediate future. The ambiguity of the present data and the lack of direct supporting literature mean that clinicians should continue to be vigilant for the appearance of aortic aneurysm and dissection in high-risk patients treated with fluoroquinolones.

ARTICLE INFORMATION

Accepted for Publication: August 18, 2015.

Published Online: October 5, 2015. doi:10.1001/jamainternmed.2015.5389.

Author Affiliations: Department of Emergency Medicine, National Taiwan University Hospital, Taipei, Taiwan (C.-C. Lee, M.-t. G. Lee, S.-H. Lee, S.-C. Chen); Department of Emergency Medicine, National Taiwan University Hospital, Yunlin Branch, Douliou, Taiwan (C.-C. Lee); Department of General Medicine, National Taiwan University Hospital, Yunlin Branch, Douliou, Taiwan (C.-C. Lee); Department of Diagnostic Radiology, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan (Yueh-Sheng Chen); Department of Cardiovascular Surgery, National Taiwan University Hospital, Taipei, Taiwan. (Yih-Sharng Chen); Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan (Chang).

Author Contributions: Dr C.-C. Lee had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: C.-C. Lee, Yueh-Sheng Chen, Yih-Sharng Chen, S.-C. Chen.
Acquisition, analysis, or interpretation of data: C.-C. Lee, M.-t.G. Lee, S.-H. Lee, Chang.
Drafting of the manuscript: C.-C. Lee, S.-C. Chen.
Critical revision of the manuscript for important intellectual content: C.-C. Lee, M.-t.G. Lee, Yueh-Sheng Chen, S.-H. Lee, Yih-Sharng Chen, Chang.
Statistical analysis: C.-C. Lee, M.-t.G. Lee, S.-H. Lee.
Obtained funding: C.-C. Lee.
Administrative, technical, or material support: C.-C. Lee.
Study supervision: C.-C. Lee, Yueh-Sheng Chen, Yih-Sharng Chen, S.-C. Chen, Chang.

Conflict of Interest Disclosures: None reported.

Funding/Support: This work was supported by Taiwan National Science Foundation grants NSC101-3114-Y-002-003, NSC 104-2811-B-002-060, and NSC104-2314-B-002-039-MY3 and by National Taiwan University Hospital Yunlin Branch Research Grant NTUHYL101.N014.

Role of the Funder/Sponsor: The funding institutions had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We thank Anna Delprato, PhD, BioScience Project, for proofreading this manuscript. We also thank the staff of the Core Labs, Department of Medical Research, National Taiwan University Hospital for their technical support.

REFERENCES

1. Sampson UK, Norman PE, Fowkes FG, et al. Global and regional burden of aortic dissection and aneurysms: mortality trends in 21 world regions, 1990 to 2010. *Glob Heart*. 2014;9(1):171-180.

2. Sidloff D, Choke E, Stather P, Bown M, Thompson J, Sayers R. Mortality from thoracic aortic diseases and associations with cardiovascular risk factors. *Circulation*. 2014;130(25):2287-2294.

3. Filipovic M, Goldacre MJ, Roberts SE, Yeates D, Duncan ME, Cook-Mozaffari P. Trends in mortality and hospital admission rates for abdominal aortic aneurysm in England and Wales, 1979-1999. *Br J Surg*. 2005;92(8):968-975.

4. Gillum RF. Epidemiology of aortic aneurysm in the United States. *J Clin Epidemiol*. 1995;48(11):1289-1298.

5. Hu YH, Shimizu H, Kawakami N, Takatsuka N, Ido M, Hirose H. Increasing trends in mortality rate of aortic aneurysms in Japan, 1955-90. *Tohoku J Exp Med*. 1993;171(3):221-228.

6. Lilienfeld DE, Gunderson PD, Sprafka JM, Vargas C. Epidemiology of aortic aneurysms: I. Mortality trends in the United States, 1951 to 1981. *Arteriosclerosis*. 1987;7(6):637-643.

7. Kuivaniemi H, Platsoucas CD, Tilson MD III. Aortic aneurysms: an immune disease with a strong genetic component. *Circulation*. 2008;117(2):242-252.

8. Erbel R, Alfonso F, Boileau C, et al; Task Force on Aortic Dissection, European Society of Cardiology. Diagnosis and management of aortic dissection. *Eur Heart J*. 2001;22(18):1642-1681.

9. Kamalakannan D, Rosman HS, Eagle KA. Acute aortic dissection. *Crit Care Clin*. 2007;23(4):779-800.

10. De León Ayala IA, Chen YF. Acute aortic dissection: an update. *Kaohsiung J Med Sci*. 2012;28(6):299-305.

11. Li JZ, Eagle KA, Vaishnava P. Hypertensive and acute aortic syndromes. *Cardiol Clin*. 2013;31(4):493-501.

12. Baumann F, Makaloski V, Diehm N. Aortic aneurysms and aortic dissection: epidemiology, pathophysiology and diagnostics [in German]. *Internist (Berl)*. 2013;54(5):535-542.

13. Criado FJ. Aortic dissection: a 250-year perspective. *Tex Heart Inst J*. 2011;38(6):694-700.

14. Schoenhoff F, Schmidli J, Czerny M, Carrel TP. Management of aortic aneurysms in patients with connective tissue disease. *J Cardiovasc Surg (Torino)*. 2013;54(1)(suppl 1):125-134.

15. Steindl K. Marfan syndrome and related connective tissue disorders [in German]. *Praxis (Bern 1994)*. 2013;102(24):1483-1488.

16. Kaleagasioglu F, Olcay E. Fluoroquinolone-induced tendinopathy: etiology and preventive measures. *Tohoku J Exp Med*. 2012;226(4):251-258.

17. Lewis T, Cook J. Fluoroquinolones and tendinopathy: a guide for athletes and sports clinicians and a systematic review of the literature. *J Athl Train*. 2014;49(3):422-427.

18. Tsai WC, Yang YM. Fluoroquinolone-associated tendinopathy. *Chang Gung Med J*. 2011;34(5):461-467.

19. 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(12):1228.e23-1228.e28.

20. Kapoor KG, Hodge DO, St Sauver JL, Barkmeier AJ. Oral fluoroquinolones and the incidence of rhegmatogenous retinal detachment and symptomatic retinal breaks: a population-based study. *Ophthalmology*. 2014;121(6):1269-1273.

21. Kuo SC, Chen YT, Lee YT, et al. Association between recent use of fluoroquinolones and rhegmatogenous retinal detachment: a population-based cohort study. *Clin Infect Dis*. 2014;58(2):197-203.

22. Pasternak B, Svanström H, Melbye M, Hviid A. Association between oral fluoroquinolone use and retinal detachment. *JAMA*. 2013;310(20):2184-2190.

23. van der Linden PD, van de Lei J, Nab HW, Knol A, Stricker BH. Achilles tendinitis associated with fluoroquinolones. *Br J Clin Pharmacol*. 1999;48(3):433-437.

24. Chen GL, Hsiao FY, Dong YH, Shen LJ, Wu FL. Statins and the risk of liver injury: a population-based case-control study. *Pharmacoepidemiol Drug Saf*. 2014;23(7):719-725.

25. Lai EC, Yang YH, Lin SJ, Hsieh CY. Use of antiepileptic drugs and risk of hypothyroidism. *Pharmacoepidemiol Drug Saf*. 2013;22(10):1071-1079.

26. Gagne JJ, Glynn RJ, Avorn J, Levin R, Schneeweiss S. A combined comorbidity score predicted mortality in elderly patients better than existing scores. *J Clin Epidemiol*. 2011;64(7):749-759.

27. Owens RC Jr, Ambrose PG. Antimicrobial safety: focus on fluoroquinolones. *Clin Infect Dis*. 2005;41(suppl 2):S144-S157.

28. Lee MT, Lee SH, Chang SS, et al. Comparative effectiveness of different oral antibiotics regimens for treatment of urinary tract infection in outpatients: an analysis of national representative claims database. *Medicine (Baltimore)*. 2014;93(28):e304.

29. Etminan M, Forooghian F, Brophy JM, Bird ST, Maberley D. Oral fluoroquinolones and the risk of retinal detachment. *JAMA*. 2012;307(13):1414-1419.

30. van der Linden PD, Sturkenboom MC, Herings RM, Leufkens HM, Rowlands S, Stricker BH. Increased risk of Achilles tendon rupture with quinolone antibacterial use, especially in elderly patients taking oral corticosteroids. *Arch Intern Med*. 2003;163(15):1801-1807.

31. van der Linden PD, Sturkenboom MC, Herings RM, Leufkens HG, Stricker BH. Fluoroquinolones and risk of Achilles tendon disorders: case-control study. *BMJ*. 2002;324(7349):1306-1307.

32. Khaliq Y, Zhanel GG. Fluoroquinolone-associated tendinopathy: a critical review of the literature. *Clin Infect Dis*. 2003;36(11):1404-1410.

33. 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(6):811-821.

34. Karakaya O, Barutcu I, Esen AM, et al. Relationship between circulating plasma matrix metalloproteinase-9 (gelatinase-B) concentration and aortic root dilatation. *Am J Hypertens*. 2006;19(4):361-365.

35. Wen D, Zhou XL, Li JJ, et al. Plasma concentrations of interleukin-6, C-reactive protein, tumor necrosis factor-α and matrix metalloproteinase-9 in aortic dissection. *Clin Chim Acta*. 2012;413(1-2):198-202.

36. 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(5):1045-1052.

37. Kurihara T, Shimizu-Hirota R, Shimoda M, et al. Neutrophil-derived matrix metalloproteinase 9 triggers acute aortic dissection. *Circulation*. 2012;126(25):3070-3080.

38. 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(3):220-225.

39. Dilmé JF, Bellmunt S, Camacho M, et al. Influence of cardiovascular risk factors on levels of matrix metalloproteinases 2 and 9 in human abdominal aortic aneurysms. *Eur J Vasc Endovasc Surg*. 2014;48(4):374-381.

40. 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;29(1):67-73.

41. 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;3:10.

42. 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;21(1):6-12.

43. Nagase H, Woessner JF Jr. Matrix metalloproteinases. *J Biol Chem*. 1999;274(31):21491-21494.

44. Aimes RT, Quigley JP. Matrix metalloproteinase-2 is an interstitial collagenase. Inhibitor-free enzyme catalyzes the cleavage of collagen fibrils and soluble native type I collagen generating the specific 3/4- and 1/4-length fragments. *J Biol Chem*. 1995;270(11):5872-5876.

45. Vouyouka AG, Pfeiffer BJ, Liem TK, Taylor TA, Mudaliar J, Phillips CL. The role of type I collagen in aortic wall strength with a homotrimeric. *J Vasc Surg*. 2001;33(6):1263-1270.