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ORIGINAL RESEARCH

Association Between Aortic Aneurysm and Aortic Dissection With Fluoroquinolones Use in Patients With Urinary Tract Infections: A Population-Based Cohort Study

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BACKGROUND: Fluoroquinolones are first-line antibiotics recommended for the treatment of complicated urinary tract infections (UTIs), with frequent reports of adverse effects of aortic aneurysm (AA) and aortic dissection (AD). We examined whether fluoroquinolones can increase the risk of AA and AD in patients with UTIs in the Taiwanese population.

METHODS AND RESULTS: We used the National Health Insurance Research Database to identify patients diagnosed with UTIs under single antibiotic treatment of fluoroquinolones and first-, second-, or third-generation cephalosporins. An AA and AD diagnosis within a year constituted the study event. Multivariable analysis with a multiple Cox regression model was applied for comparing the hazard risk of AA and AD between fluoroquinolones and first- or second-generation cephalosporins. Propensity score matching was performed to reduce the potential for bias caused by measured confounding variables. Among 1 249 944 selected patients with UTIs, 28 568 patients were assigned to each antibiotic group after propensity score matching. The incidence of AA and AD was not significantly different between the fluoroquinolones and first- or second-generation cephalosporins (adjusted HR [aHR], 0.86 [95% CI, 0.59–1.27]). However, the mortality increased in the fluoroquinolones group (aHR, 1.10 [95% CI, 1.04–1.16]).

CONCLUSIONS: Compared with first- or second-generation cephalosporins, fluoroquinolones were not associated with increased risk of AA and AD in patients with UTI. However, a significant risk of mortality was still found in patients treated with fluoroquinolones. The priority is to control infections with adequate antibiotics rather than exclude fluoroquinolones considering the risk of AA and AD for patients with UTI.

Key Words: aortic aneurysm ■ aortic dissection ■ fluoroquinolones ■ urinary tract infections

Urinary tract infections (UTIs), including cystitis and pyelonephritis, are the most common outpatient infections worldwide. The prevalence of UTIs increases with age, and UTIs are predominant in women.[1] The overall prevalence of UTIs in women was approximately 11%, and it increased to approximately 20% in women aged over age 65 years and 20% to 30% in women with multiple UTI recurrences.[2,3] In addition, UTIs account for a higher number of infections (>560 000) than other hospital-acquired infections, with an estimated mortality rate of 2.3%; this rate can increase to 26% in the presence of bacteremia or septic shock.[4]

According to the European Association of Urology guidelines on urological infections, UTIs can be classified into uncomplicated and complicated types according to sex, anatomical and functional abnormalities, and comorbidities.[5] The antimicrobials cephalosporins

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CLINICAL PERSPECTIVE

What Is New?

- From a Taiwan nationwide cohort, the use of fluoroquinolones was not associated with an increased risk of aortic aneurysm and aortic dissection in patients with urinary tract infections, compared with the use of first- or second-generation cephalosporins.

What Are the Clinical Implications?

- Fluoroquinolones should be used appropriately in indicating infectious diseases with less concern of adverse effects of aortic aneurysm and aortic dissection.

Nonstandard Abbreviations and Acronyms

AA	aortic aneurysm
AD	aortic dissection
NHIRD	National Health Insurance Research Database
PSM	propensity score matching

and fluoroquinolones are recommended for disease management because of their high oral bioavailability and broad spectrum, and because of the susceptibility of causative pathogens to these antibiotics. Fluoroquinolones, including ciprofloxacin, levofloxacin, and moxifloxacin, have been widely used to treat various infections ranging from respiratory infections to UTIs. The European Association of Urology guidelines recommend the use of first- or second-generation cephalosporins for uncomplicated cystitis and recurrent UTIs. For uncomplicated pyelonephritis, fluoroquinolones and third-generation cephalosporins are recommended, with both antibiotics administered through oral and intravenous routes. For complicated UTIs, fluoroquinolones can be prescribed to patients with less-severe symptoms, and third-generation cephalosporins can be prescribed to patients with systemic symptoms.

Studies have reported the adverse effects of fluoroquinolones,[6] including photosensitivity,[7] a prolonged QT interval,[8] tendinitis and tendon rupture,[9] hepatic toxicity, and central nervous system–related events (eg, seizures).[10] Moreover, several observational studies have suggested a positive association of fluoroquinolones with aortic aneurysm (AA) and aortic dissection (AD).[11–13] AA and AD are rare but life-threatening events, with annual incidence rates of 3 to 13 per 100 000 general population for AA and 3 to 20 per 100 000 general population for AD[14,15]; the incidence rates are even higher in the older population.[16] Collagen-related adverse events might occur because of the activity of fluoroquinolones against metal ions in type I collagen synthesis and the activation of matrix metalloproteinases that lead to collagen degradation.

Observational studies and systematic reviews have mainly investigated the association of fluoroquinolones with AA and AD. However, because of the nature of observational studies, they would have not considered the effects of potential confounders, such as infection and baseline blood pressure, on their findings. Although an increasing number of studies have suggested a positive association of fluoroquinolones with AA and AD, the causal role of fluoroquinolones and AA and AD remains elusive. A nested case–control study demonstrated that the adjusted odds ratio (OR) of AA and AD for any indicated infection was 1.73 (95% CI, 1.66–1.81)[17]; moreover, this study did not observe an association of fluoroquinolones with an increased risk of AA and AD compared with an amoxicillin–clavulanate or ampicillin–sulbactam combination (OR, 1.01 [95% CI, 0.82–1.24]) in patients with indicated infections.

Although fluoroquinolones and cephalosporins are both indicated and prescribed frequently for patients with UTIs, concerns about the risk of AA and AD and adequate treatment of infection exist. Cephalosporins were not reported to increase the risk of AA and AD; however, whether the use of fluoroquinolones should be continued is a critical clinical question. Therefore, by using population-based data from Taiwan's National Health Insurance Research Database (NHIRD), we investigated the association between the risk of AA and AD and the use of fluoroquinolones compared with the use of first- or second-generation cephalosporins antibiotics for the treatment of UTIs.

METHODS

Data Access

Data were obtained from National Health Insurance database and are available from the authors with the permission of the National Health Insurance Administration of Taiwan. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Data Sources and Ethical Approval

Data were collected from Taiwan's NHIRD, which is maintained by the Health and Welfare Data Science Center for research purposes. National Health Insurance is the single-payer insurance system within Taiwan. The NHIRD contains the data of approximately 99% of Taiwan's population. No person may arbitrarily withdraw, except for those few who lose their insurance

eligibility, such as from death (the major reason), giving up Taiwan citizenship, expired Alien Resident Certificate, or missing. The database contains information on diagnoses, hospitalizations, medical orders, and prescriptions.[18] The Longitudinal Health Insurance Database 2000, a subset of the NHIRD that contains the 2000 to 2017 medical claims records of 2 million individuals randomly sampled from the year 2000 Registry for Beneficiaries of the NHIRD, was used for examining study variables. Because of the retrospective nature of this observational study and the use of an anonymous data set, the requirement of informed consent for participation was waived. This study was approved by the Human Research Ethics Committee of the Institutional Review Board of Chung Shan Medical University Hospital (CS2-20036).

Study Population and Exposure Definition

A total of 1 249 944 patients received a primary diagnosis of UTI on the basis of *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes 599.0, 595.x, and 590.x between 2002 and 2016. We initially defined the patients with UTI treated with fluoroquinolones as the study group, which was compared with 2 groups including patients with UTI treated with first- or second-generation cephalosporins, and patients treated with third-generation cephalosporins. The index date was the date of admission, which was approximately the date of the first administration of antibiotics, because the study included only patients who received a primary diagnosis of UTI. We excluded patients who withdrew from the National Health Insurance program before 2002 (n=24), patients aged younger than 18 years at the index date (n=23 704), patients who received both fluoroquinolones and cephalosporins (n=59 808), and patients who had AA or AD within 180 days before the index date (n=1261). A total of 191 564, 914 644, and 58 939 patients were treated with fluoroquinolones, first- or second-generation cephalosporins, and third-generation cephalosporins, respectively. To reduce confounding engendered by differences between the study groups, we matched the first- or second-generation cephalosporins, the third-generation cephalosporins, and the fluoroquinolones by sex, birth year, and the year of admission in the ratio of 1:1:1. Accordingly, we paired 43 907 patients in the fluoroquinolones group with 43 907 patients in the first- or second-generation cephalosporins group and 43 907 patients in the third-generation cephalosporins group after sex, birth year, and the index year matching (Figure 1). After the preliminary analysis, we excluded the patients treated with third-generation cephalosporins from primary analysis, because the third-generation cephalosporins was clinically used in patients with more severe disease and systemic symptoms, and that induces confounding by indication.

Baseline Covariates

The baseline period was defined as 1 year before the index date (not involving the data during hospitalization for UTI). Baseline demographic characteristics included sex, age, urbanization, insured category, marital status, educational level, length of hospital stay, comorbidities, and comedications. Age was calculated as the period (in years) between the birth date and the index date. Hence, the patients were classified into different age groups: 18 to 29, 30 to 44, 45 to 59, 60 to 74, and ≥75 years. Comorbidities (such as hypertension, coronary artery disease, chronic obstructive pulmonary disease, dyslipidemia, diabetes, asthma, organic sleep apnea, cardiac valve disease, chronic kidney disease, atrial fibrillation, seizure disorder, chronic ulcer of the skin, conduction disorders, peripheral arterial disease, and cancer) and comedications (including nonsteroidal anti-inflammatory drugs, aspirin, clopidogrel, statins, angiotensin-converting enzyme inhibitors, β-blockers, calcium channel blockers, anticoagulant agents, and antiarrhythmic agents) that might be correlated with antibiotics and the occurrence of AA and AD were identified through *ICD-9-CM* codes and Anatomical Therapeutic Chemical codes.

Follow-Up and Study End Points

We identified the first diagnosis of AA (*ICD-9-CM* codes 441.1, 441.2, 441.3, 441.4, 441.5, 441.6, 441.7, and 441.9) or AD (*ICD-9-CM* codes 441.0, 441.00, 441.01, 441.02, and 441.03) as the study event. The age, sex, and index year for matched patients were followed from the index date until the first occurrence of one of the following: AA and AD onset or death (linked with the Death Registry Database). Because we defined the follow-up period as 12 months, we collected patients newly diagnosed with UTI in 2016, leaving enough follow-up time of 12 months before the end of the study on December 31, 2017. The accuracy of the diagnoses of AA and AD in the NHIRD has been validated in previous studies, and the positive predictive value of *ICD-9-CM* codes was 97.06% for AD[19] and 92% for AA and AD.[11]

Statistical Analysis

Primary Analysis

We calculated the absolute standardized difference[20] to compare the statistical values of baseline covariates between the groups in this large-sample observational study. A threshold of 10% for the absolute standardized difference was used as a metric to indicate significant imbalance. Our study aims to investigate the risk

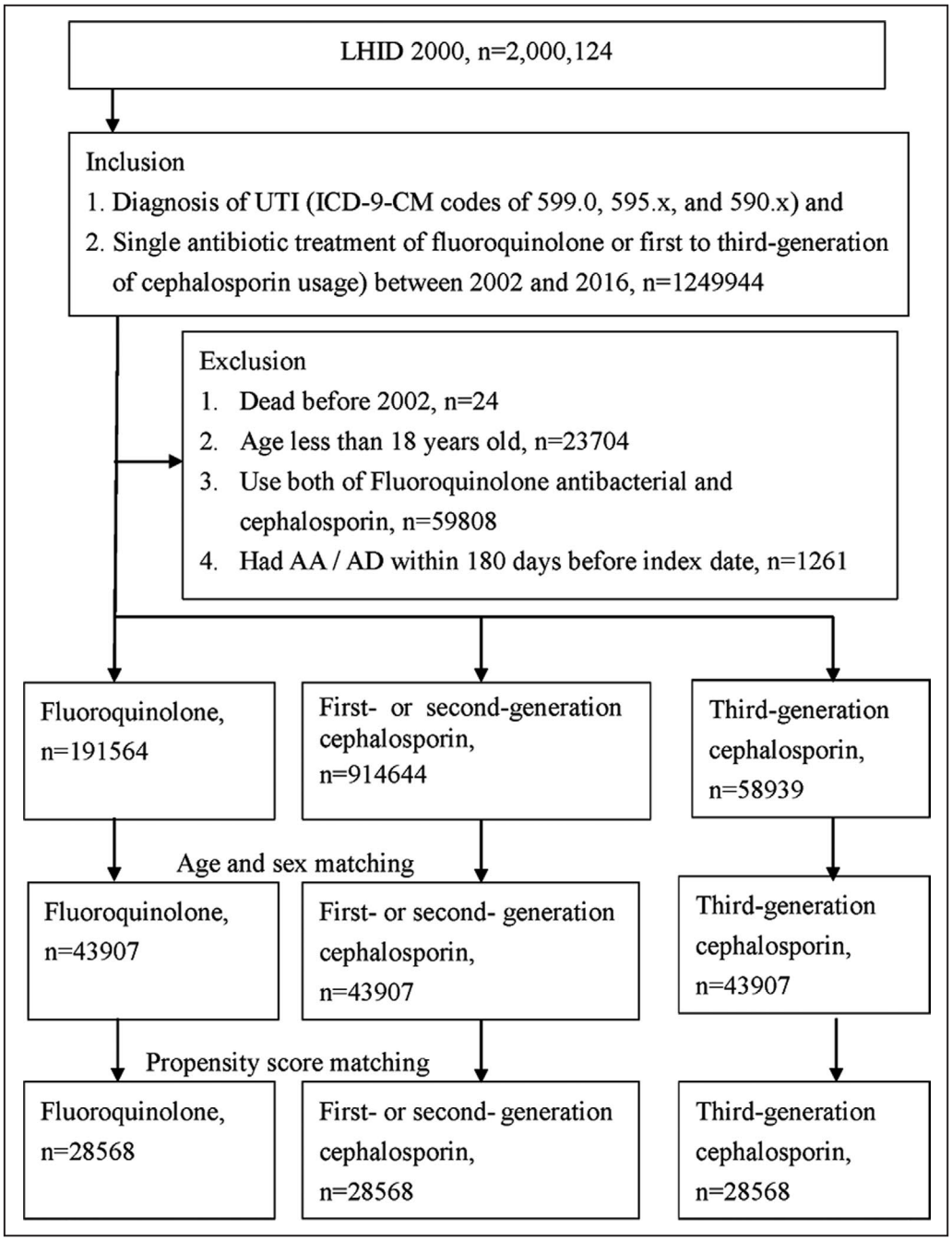

Figure 1. Flowchart of the cohort study group.
AA indicates aortic aneurysm; AD, aortic dissection; LHID, Longitudinal Health Insurance Database; *ICD-9-CM*, *International Classification of Diseases, Ninth Revision, Clinical Modification*; and UTI, urinary tract infection.

of AA/AD between fluoroquinolones, first- or second-generation cephalosporins, and third-generation cephalosporins. The crude incidence density and 95% CI for AA and AD was calculated by the Fisher exact test. The calculator can be found in OpenEpi. The incidence rates of AA and AD within 12 months after the index date were used to examine the short-term effect of UTIs and antibiotics on AA and AD, which is more reasonable and compatible with the clinical scenario. After testing the proportional hazard assumption, we used univariate and multivariable Cox proportional hazard models to estimate hazard ratios (HRs) along with 95% CIs for AA and AD. The 12-month cumulative probabilities of AA and AD were calculated using the Kaplan-Meier analysis and plotted as a step function. Furthermore, the log-rank test was used to determine differences

in Kaplan-Meier curves between the groups. The competing HR was estimated using the subdistribution Fine-Gray regression approach, wherein mortality was considered as the competing event. All statistical analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC). The significance level was set at 0.05, and a 2-tailed test was performed.

Propensity Score Matching, Subgroup, and Secondary Analysis

Propensity score matching (PSM) was performed after age, sex, and index year matching. We used PSM to minimize the potential confounding because of measured covariates such as demographics, baseline comorbidities, and comedication.[21] We chose patients with fluoroquinolones treatmenyt as the study group so that we could observe the risk of AA and AD compared with the patients with first- or second-generation cephalosporins treatment.

Propensity scores of fluoroquinolones treatment were calculated by using the following covariates: index year; baseline demographics (ie, sex, age, urbanization, insured category, marital status, and educational level), length of hospital stay, comorbidities, and comedications. We used the PSMATCH procedure in the SAS software and greedy nearest-neighbor matching within 0.01 caliper widths. Finally, we included 28 568 and 28 568 propensity score-matched patients in the fluoroquinolones and first- or second-generation cephalosporins groups, respectively. To observe the association of AA and AD between antibiotics in real-world practice, the third-generation cephalosporins were included in the additional analysis (Figure 1).

A subgroup analysis and test of interaction effects were performed to evaluate the effect of sex and age on different stratifications through multivariable Cox regression. Moreover, a landmark analysis was conducted to assess the potential time-varying effect of antibiotics on AA and AD during different periods, namely 0 to 12, 0 to 3, 3 to 6, and 6 to 12 months after the index date. Subgroup and landmark analyses could provide evidence of residual bias in our research.

RESULTS

Characteristics of Study Patients

We identified 1 249 944 patients who were diagnosed as having UTI and received antibiotic treatment from 2002 to 2016. After age, sex, and index year matching, we included 43 907, 43 907, and 43 907 patients who received fluoroquinolones, first- or second-generation cephalosporins, and third-generation cephalosporins, respectively (Figure 1). The characteristics of the patients with UTIs who received fluoroquinolones and the cephalosporins are listed in Table S1. The study sample had a higher proportion of women than did the control sample. The third-generation cephalosporins group had a higher proportion of patients who required hospitalization for >7 days when compared with the other 2 groups (35.80%). As to comorbidities, hypertension had the highest prevalence in both groups, followed by diabetes and lipid disorder. Demographic characteristics including age, sex, and socioeconomic status did not differ significantly between the fluoroquinolones group and the age- and sex-matched cephalosporins groups. The proportion of comorbidities was significantly higher in the third-generation cephalosporins group than in the other groups. Medication use did not differ significantly among the 3 groups.

We performed PSM by including 28 568 patients from the fluoroquinolones group and 28 568 matched controls from each of the first- or second-generation and third-generation cephalosporins groups (Figure 1). The third-generation cephalosporins groups was excluded in the primary analysis. The characteristics of these patients after PSM are presented in Table 1. After PSM, all of the absolute standardized differences in baseline characteristics, such as demographics (sex, age, urbanization, insured category, marital status, and educational level), comorbidities, and comedications, were <0.1 between fluoroquinolones and first- or second-generation groups.

Association of the Risk of AA and AD With Different Antibiotics

We observed that the incidence rates of AA and AD were not significantly different between the fluoroquinolones group and the first- or second-generation cephalosporins group (adjusted HR [aHR]: 0.86 [95% CI, 0.59–1.27]; competing HR, 0.85 [95% CI, 0.58–1.25]; Table 2). In addition, the mortality rate was slightly higher in the fluoroquinolones group than in the first- or second-generation cephalosporins group (aHR, 1.10 [95% CI, 1.04–1.16]). The Kaplan-Meier curve showed no significant difference in the incidence rates of AA or AD between the fluoroquinolones and the first- or second-generation cephalosporins group (log-rank test, P=0.2459) after PSM (Figure 2). However, the higher cumulative mortality risk of AA or AD was observed in patients treated with fluoroquinolones (log-rank test, P<0.0001).

The multivariable Cox regression model, including the propensity score matched population, revealed that other significant risk factors for AA and AD in patients with UTIs included male sex, old age (≥75 years), and peripheral arterial disease. Comedications such as aspirin, clopidogrel, calcium channel blockers, and anticoagulant agents were not associated with increased risk of AA and AD (Table 3).

Table 1. Baseline Characteristics of Study Subjects After Propensity Score Matched Groups

Variable	Fluoroquinolones	First- or second-generation cephalosporins	ASD
No. of cases	28 568	28 568	
Sex			0.0020
Men	8051 (28.18%)	8026 (28.09%)	
Women	20 517 (71.82%)	20 542 (71.91%)	
Age, y			0.0498
18–29	2629 (9.20%)	2829 (9.90%)	
30–44	4129 (14.45%)	4222 (14.78%)	
45–59	6115 (21.41%)	6022 (21.08%)	
60–74	7327 (25.65%)	7271 (25.45%)	
≥75	8368 (29.29%)	8224 (28.79%)	
Urbanization			0.1068
High urbanization	7967 (27.89%)	8459 (29.61%)	
Moderate urbanization	8356 (29.25%)	8184 (28.65%)	
Developing town	4566 (15.98%)	4476 (15.67%)	
General town	4421 (15.48%)	4338 (15.18%)	
Aged town	690 (2.42%)	671 (2.35%)	
Agriculture town	1492 (5.22%)	1387 (4.86%)	
Village	1076 (3.77%)	1053 (3.69%)	
Unit type of insured			0.0890
Government	2086 (7.30%)	2038 (7.13%)	
Privately held company	14 577 (51.03%)	14 892 (52.13%)	
Agricultural organizations	6504 (22.77%)	6170 (21.60%)	
Low income	272 (0.95%)	291 (1.02%)	
Nonlabor force	4699 (16.45%)	4788 (16.76%)	
Others	430 (1.51%)	389 (1.36%)	
Marital status			0.0251
Never married	6049 (21.17%)	6316 (22.11%)	
Had spouse	17 653 (61.79%)	17 312 (60.60%)	
Divorce	1165 (4.08%)	1133 (3.97%)	
Widow/widower	3701 (12.96%)	3807 (13.33%)	
Education level, y			0.0457
≤6	14 136 (49.48%)	14 110 (49.39%)	
7–12	10 925 (38.24%)	10 686 (37.41%)	
13–16	2176 (7.62%)	2323 (8.13%)	
>16	106 (0.37%)	110 (0.39%)	
Others	1225 (4.29%)	1339 (4.69%)	
All hospitalized stays, d			0.0344
0	21 727 (76.05%)	21 568 (75.50%)	
1–6	2628 (9.20%)	2873 (10.06%)	
≥7	4213 (14.75%)	4127 (14.45%)	
Comorbidities, within 1 y before index date			
Hypertension	6227 (21.80%)	5424 (18.99%)	0.0698
Coronary artery disease	1728 (6.05%)	1454 (5.09%)	0.0418
COPD	2646 (9.26%)	2210 (7.74%)	0.0548
Lipid disorder	3196 (11.19%)	2812 (9.84%)	0.0438
Diabetes	3350 (11.73%)	2992 (10.47%)	0.0399

(*Continued*)

Table 1. Continued

Variable	Fluoroquinolones	First- or second-generation cephalosporins	ASD
Asthma	1081 (3.78%)	964 (3.37%)	0.0221
Organic sleep apnea	57 (0.20%)	78 (0.27%)	0.0151
Cardiac valve disease	533 (1.87%)	441 (1.54%)	0.0249
Chronic kidney disease	1108 (3.88%)	1167 (4.08%)	0.0106
Atrial fibrillation	312 (1.09%)	234 (0.82%)	0.0281
Seizure disorder	219 (0.77%)	153 (0.54%)	0.0287
Chronic ulcer of skin	346 (1.21%)	259 (0.91%)	0.0298
Conduction disorders	39 (0.14%)	38 (0.13%)	0.0010
Peripheral arterial disease	443 (1.55%)	353 (1.24%)	0.0269
Cancer	1108 (3.88%)	1108 (3.88%)	0.0000
Medication use before index date			
NSAIDs	18 427 (64.50%)	17 745 (62.11%)	0.0496
Aspirin	4719 (16.52%)	4825 (16.89%)	0.0100
Clopidogrel	958 (3.35%)	949 (3.32%)	0.0018
Statins	3748 (13.12%)	3823 (13.38%)	0.0077
ACE inhibitors	2513 (8.80%)	2470 (8.65%)	0.0053
β-blockers	6211 (21.74%)	6067 (21.24%)	0.0123
Calcium channel blockers	8363 (29.27%)	8182 (28.64%)	0.0140
Anticoagulant agents	438 (1.53%)	467 (1.63%)	0.0081
Antiarrhythmic agents	694 (2.43%)	673 (2.36%)	0.0048

ACE indicates angiotensin-converting enzyme; ASD, absolute standardized difference; COPD, chronic obstructive pulmonary disease; and NSAIDs, nonsteroidal anti-inflammatory drugs.

Association of Risk of AA and AD With Different Antibiotics: Subgroup Analysis

We created a forest plot for the subgroup analysis in the propensity score matched groups (Figure 3). In the male subgroup, the use of first- or second-generation cephalosporins was significantly associated with lower mortality compared with the use of fluoroquinolones; however, a nonsignificant association was observed in the female subgroup. Mortality increased significantly in the age ≥75 years subgroup among different age stratifications. Risk of AA or AD did not significantly increase in both sexes in the first- or second-generation cephalosporins group, as well as in the age 60 to 74 years and ≥75 years subgroups. The case numbers of age 18 to 44 years subgroup were too small to evaluate the HR of AA and AD.

DISCUSSION

The findings of this nationwide population-based cohort study revealed that the use of fluoroquinolones was not associated with an increased risk of AA and AD compared with the use of first- or second-generation cephalosporins (aHR, 0.86 [95% CI, 0.59–1.27]). Moreover, our subgroup analysis results demonstrated an association of male sex and age ≥75 years with an increased risk of AA and AD. In contrast to the findings of previous studies, our results revealed no increased risk of AA and AD in the fluoroquinolones group; this may be attributed to the different severity levels of UTIs in previous studies.

Previous observational studies have reported increased risks of AA and AD in patients with fluoroquinolones use and proposed plausible mechanisms underlying this increase. Lee et al performed a nationwide study in Taiwan by using 3 study designs to evaluate the association of the risk of AA and AD with oral fluoroquinolones use and nonuse. Their nested case–control design, case crossover design, and case–time control design all showed an increased risk of AA or AD (OR, 2.28 [95% CI, 1.67–3.13]; OR, 2.71 [95% CI, 1.14–6.46]; OR, 3.61 [95% CI, 3.56–3.63], respectively).[22] Pasternak et al also conducted a nationwide cohort study in Sweden and observed that treatment episodes of fluoroquinolones use were associated with an increased risk of AA and AD compared with matched comparator episodes of amoxicillin use (HR, 1.66 [95% CI, 1.12–2.46]).[12] Moreover, several systematic reviews and meta-analyses have reported a positive association between fluoroquinolones and the development of AA and AD.[13,23] Plausible mechanisms underlying this association include the chelation of fluoroquinolones against metal ions in type I collagen synthesis[24,25] and

Table 2. Risk of AA and AD and Mortality After Index Date With Different Antibiotics: PSM Population

Variable	Fluoroquinolone antibacterial	First- or second-generation cephalosporins
N	28 568	28 568
Risk of AA and AD		
0–12 mo		
Follow-up person-months	324 778	326 781
Event	52	56
Rate* (95% CI)	0.16 (0.12–0.21)	0.17 (0.13–0.22)
Crude HR (95% CI)	0.93 (0.64–1.35)	Reference
Adjusted HR† (95% CI)	0.86 (0.59–1.27)	Reference
Competing HR (95% CI)	0.85 (0.58–1.25)	Reference
0–3 mo		
Follow-up person-months	84 060	84 211
Event	20	22
Rate* (95% CI)	0.24 (0.15–0.37)	0.26 (0.16–0.40)
Crude HR (95% CI)	0.91 (0.50–1.67)	Reference
Adjusted HR† (95% CI)	0.88 (0.47–1.64)	Reference
Competing HR (95% CI)	0.87 (0.48–1.56)	Reference
3–6 mo		
Follow-up person-months	81 779	82 211
Event	17	17
Rate (95% CI)	0.21 (0.12–0.33)	0.21 (0.12–0.33)
Crude HR (95% CI)	1.00 (0.51–1.96)	Reference
Adjusted HR† (95% CI)	0.93 (0.47–1.85)	Reference
Competing HR (95% CI)	0.93 (0.47–1.89)	Reference
6–12 mo		
Follow-up person-months	158 939	160 359
Event	24	24
Rate* (95% CI)	0.15 (0.10–0.22)	0.15 (0.10–0.22)
Crude HR (95% CI)	1.01 (0.57–1.79)	Reference
Adjusted HR* (95% CI)	0.88 (0.50–1.56)	Reference
Competing HR (95% CI)	0.88 (0.49–1.56)	Reference
Risk of mortality		
0–12 mo		
Follow-up person-months	325 063	326 826
Event	2558	2248
Rate* (95% CI)	7.87 (7.57–8.18)	6.88 (6.60–7.17)
Crude HR (95% CI)	1.15 (1.09–1.22)	Reference
Adjusted HR* (95% CI)	1.10 (1.04–1.16)	Reference
0–3 mo		
Follow-up person-months	84 096	83 952
Event	1085	971
Rate* (95% CI)	12.90 (12.15–13.69)	11.57 (10.85–12.32)
Crude HR (95% CI)	1.12 (1.03–1.22)	Reference
Adjusted HR† (95% CI)	1.02 (0.93–1.12)	Reference
3–6 mo		
Follow-up person-months	81 842	82 282
Event	811	703
Rate* (95% CI)	9.91 (9.24–10.62)	8.54 (7.92–9.20)
Crude HR (95% CI)	1.16 (1.05–1.28)	Reference
Adjusted HR† (95% CI)	1.12 (1.01–1.23)	Reference
6–12 mo		
Follow up person-months	159 125	160 592
Event	1072	945
Rate* (95% CI)	6.74 (6.34–7.15)	5.88 (5.52–6.27)
Crude HR (95% CI)	1.15 (1.05–1.25)	Reference
Adjusted HR† (95% CI)	1.15 (1.05–1.25)	Reference

AA indicates aortic aneurysm; AD, aortic dissection; and HR, hazard ratio.
*Rate is the incidence density rate per 1000 person-months.
†The hazard ratio was adjusted by the covariates including sex, age, urbanization, unit type, marital status, education level, baseline hospitalized stays, baseline comorbidities, and baseline medication.

the activation of matrix metalloproteinases, resulting in decreased collagen synthesis and medial layer degeneration in blood vessels.[26,27] With the increasing emergence of positive evidence, both the US Food and Drug Administration and European Medicine Agency have announced safety warnings about the use of fluoroquinolones.

The aforementioned studies did not consider infection, which is a risk factor for AA and AD. An infected aneurysm, or mycotic aneurysm, is an arterial wall degeneration resulting from bacteremia or septic embolization.[28] Common microorganisms causing such an infection include *Staphylococcus aureus*,[29] *Salmonella*,[30] *Streptococcus pneumoniae*,[31] and other gram-negative organisms such as *Escherichia coli*,[32] *Klebsiella*,[33] and *Pseudomonas*.[34] Dong performed a nested case–control study to examine the association of the risk of AA and AD with infections and different antibiotics in indicated patients.[17] They observed that an increased risk of AA and AD was associated with infections (adjusted OR, 1.73 [95% CI, 1.66–1.81]) and septicemia (adjusted OR, 3.16 [95% CI, 2.63–3.78]) instead of fluoroquinolones use.

Our study focused on only one infection source rather than all types of infections or even coexisting infections, because different infection locations and sources represent different disease patterns and antibiotic requirements. Moreover, both fluoroquinolones and first- or second-generation cephalosporins used for the treatment of UTIs possess similar

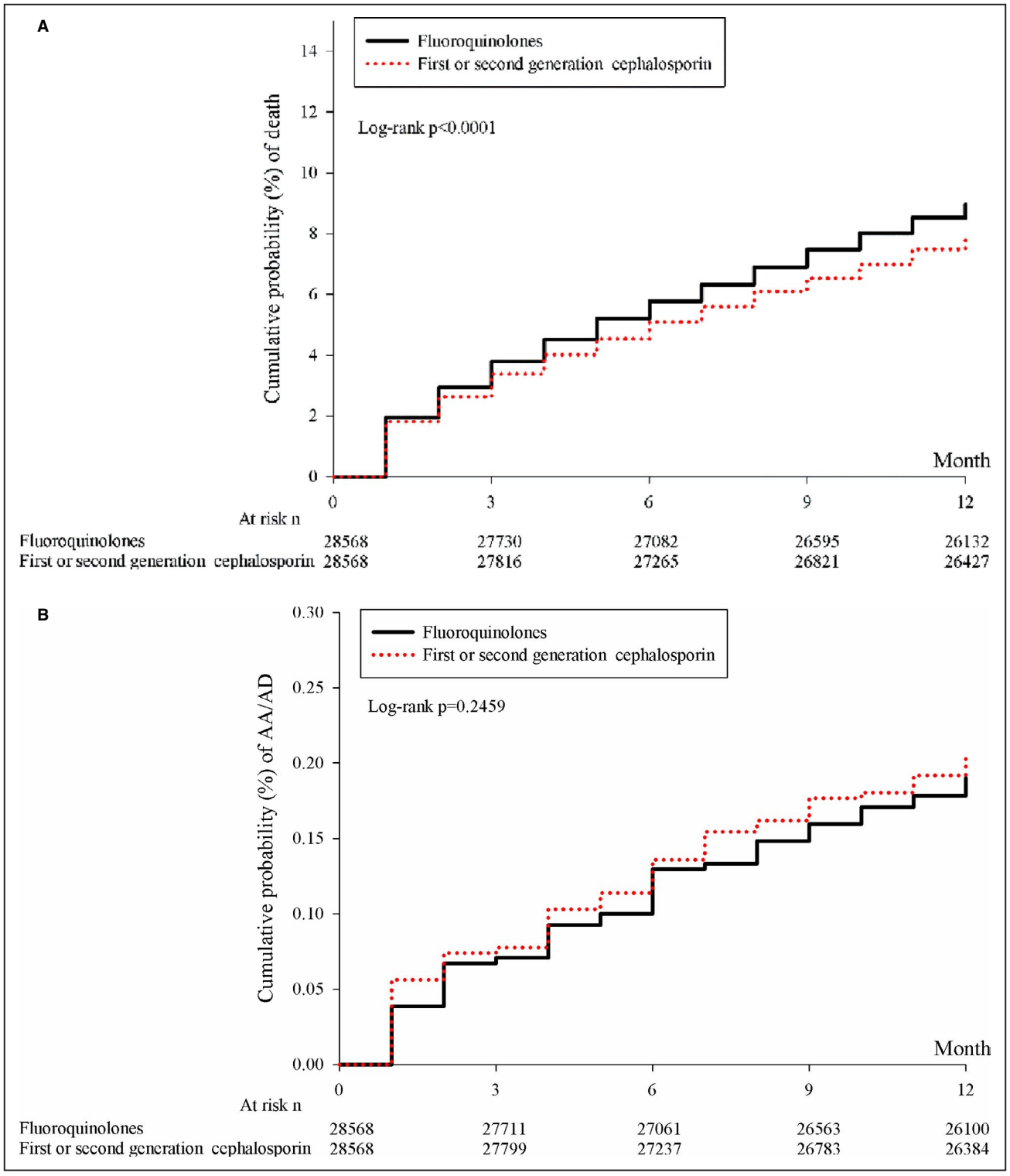

Figure 2. Kaplan-Meier curves of the cumulative proportions of (A) mortality among PSM fluoroquinolones and first- or second-generation cephalosporins groups and (B) incidence rate of AA/AD among PSM fluoroquinolones and first- or second-generation cephalosporins groups.
AA indicates aortic aneurysm; AD, aortic dissection; and PSM, propensity score matching.

characteristics in terms of their frequent use and similar spectrum of common microorganisms. On the basis of the results of our study and a previous study,[17] fluoroquinolones should not be precluded from prescriptions in clinical practice for indicated patients considering the concern of AA and AD.

Table 3. Multiple Cox Regression for Hazard Ratio of Aortic Aneurysm/Aortic Dissection Within 1 Year After Index

	aHR (95% CI)	*P* value
Group		
Fluoroquinolones	0.86 (0.59–1.27)	0.4598
First- or second-generation cephalosporins	Reference	
Sex		
Men	3.29 (2.12–5.10)	<0.0001
Women	Reference	
Age, y		
18–29	1.73 (0.07–41.15)	0.735
30–44	Reference	
45–59	0.41 (0.03–6.90)	0.5387
60–74	6.17 (0.76–50.18)	0.089
≥75	19.81 (2.46–159.45)	0.005
Urbanization		
High urbanization	Ref	
Moderate urbanization	1.29 (0.69–2.42)	0.4198
Developing town	1.19 (0.57–2.50)	0.6408
General town	1.71 (0.83–3.53)	0.1490
Aged town	1.72 (0.51–5.77)	0.3836
Agriculture town	0.40 (0.09–1.91)	0.2514
Village	2.60 (0.97–6.98)	0.0574
Unit type of insured		
Government	1.43 (0.74–2.76)	0.2900
Privately held company	Ref	
Agricultural organizations	0.74 (0.41–1.34)	0.3266
Low income	Cannot estimate	…
Nonlabor force	0.79 (0.45–1.39)	0.4138
Others	0.63 (0.08–4.81)	0.6591
Marital status		
Never married	Ref	
Had spouse	1.68 (0.50–5.67)	0.3999
Divorce	7.04 (1.88–26.32)	0.0038
Widow/widower	1.57 (0.44–5.69)	0.4900
Education level, y		
≤6	Ref	
7–12	1.06 (0.65–1.72)	0.83
13–16	1.02 (0.44–2.33)	0.966
>16	Cannot estimated	…
Others	2.20 (0.19–25.54)	0.5302
All hospitalized stays, d		
0	Ref	
1–6	2.20 (1.35–3.58)	0.0015
>=7	1.25 (0.78–2.00)	0.3627
Comorbidities (within 1 y before index date)		
Hypertension	1.27 (0.81–2.00)	0.306
Coronary artery disease	0.85 (0.47–1.55)	0.5921
COPD	1.61 (0.95–2.74)	0.0777
Lipid disorder	0.66 (0.32–1.35)	0.2516
Diabetes	0.97 (0.55–1.69)	0.9059
Asthma	1.09 (0.50–2.38)	0.8274
Organic sleep apnea	Cannot estimate	…
Cardiac valve disease	1.90 (0.85–4.25)	0.1161
Chronic kidney disease	1.32 (0.70–2.50)	0.3964
Atrial fibrillation	1.91 (0.81–4.53)	0.1404
Seizure disorder	Cannot estimate	…
Chronic ulcer of skin	0.47 (0.06–3.38)	0.4498
Conduction disorders	Cannot estimate	…
Peripheral arterial disease	3.79 (1.94–7.39)	<0.0001
Cancer	0.52 (0.19–1.42)	0.1997
Medication use before index date		
NSAIDs	1.29 (0.84–1.96)	0.2424
Aspirin	1.26 (0.83–1.91)	0.2765
Clopidogrel	1.59 (0.85–2.96)	0.1462
Statins	1.07 (0.62–1.84)	0.8129
ACE inhibitors	0.73 (0.42–1.29)	0.2804
β-Blockers	1.20 (0.79–1.83)	0.3918
Calcium channel blockers	1.42 (0.94–2.14)	0.0976
Anticoagulant agents	1.90 (0.88–4.10)	0.1026
Antiarrhythmic agents	0.91 (0.40–2.05)	0.8145

ACE indicates angiotensin-converting enzyme; aHR, adjusted hazard ratio; COPD, chronic obstructive pulmonary disease; and NSAIDs, nonsteroidal anti-inflammatory drugs.

Infection control can instead reduce the risk of AA and AD.

Our study demonstrated that advanced age was another risk factor for AA and AD, and the risk significantly increased in patients aged ≥75 years (HR, 19.81 [95% CI, 2.46–159.45] for age ≥75 years). These results are consistent with those of a UK population-based study that reported that the risk of AA increased with age.[35] Furthermore, Gawinecka et al conducted a review study on the pathogenesis of and risk factors for AD, and indicated that an age of >65 years is a risk factor for AD; the increased risk can be attributed to the presence of other comorbidities such as hypertension, diabetes, and atherosclerosis.[36]

Third-generation cephalosporins were initially included in our study population but excluded eventually. According to the European Association of Urology guidelines on urological infection, the indications for third-generation cephalosporins include bacterial prostatitis, acute infective epididymitis, and complicated UTIs, such as patients with a UTI and systemic symptoms. On the other hand, for fluoroquinolones, the indications included uncomplicated pyelonephritis, bacterial prostatitis, and complicated UTIs as well, only if the prevalence of fluoroquinolones resistance is thought to be <10% and the

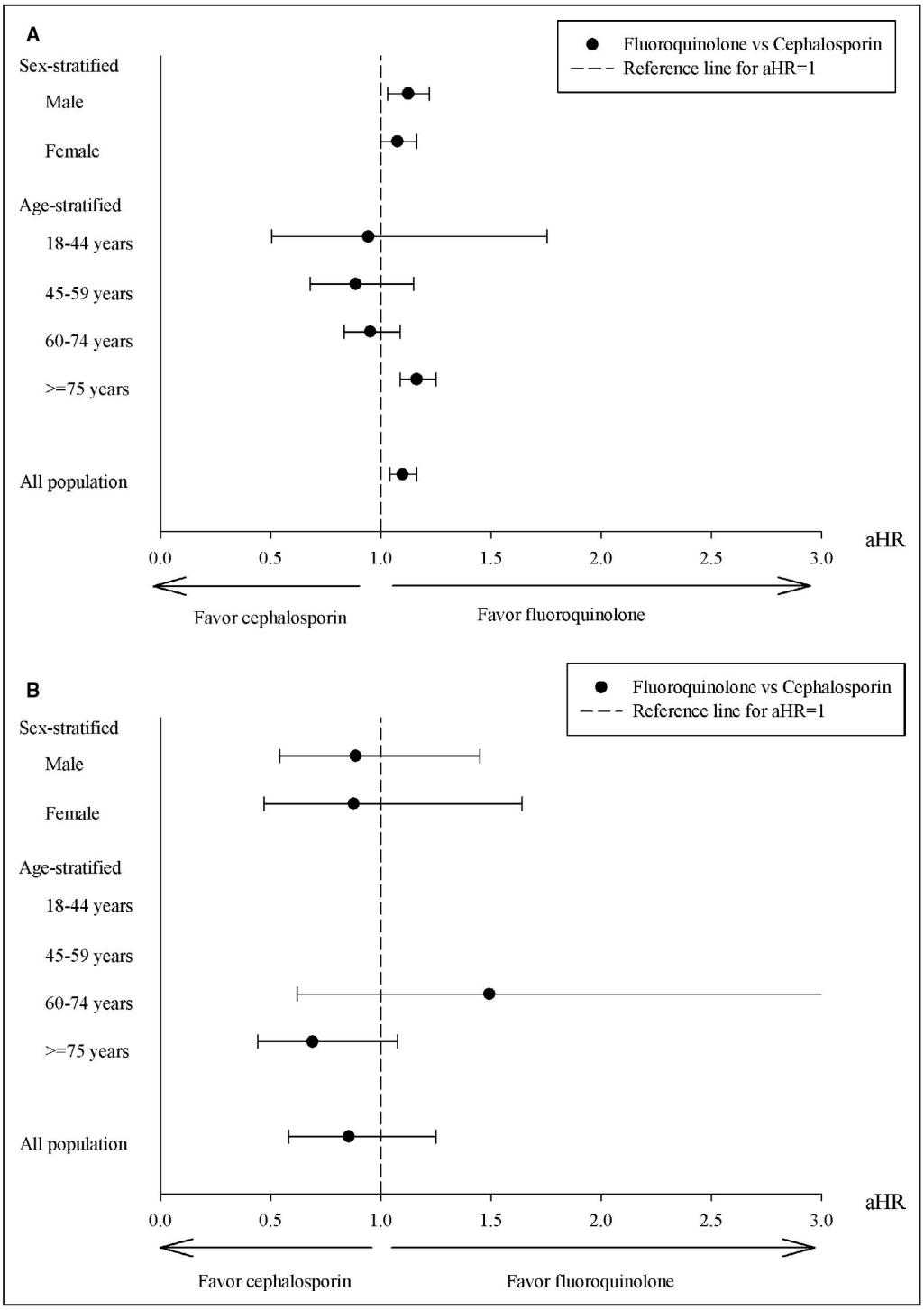

Figure 3. Forrest plot for subgroup analysis (A) adjusted hazard ratio of mortality and (B) adjusted hazard ratio of AA/AD after PSM.
AA indicates aortic aneurysm; AD, aortic dissection; and PSM, propensity score matching.

patient has contraindications for third-generation cephalosporins. Furthermore, the entire treatment of fluoroquinolones should be given orally, and the patients do not require hospitalization. Patients who receive third-generation cephalosporins tend to have a more severe illness than those treated with fluoroquinolones after comparing the indications and clinical usage. Hence, we adjusted the focus of our study to the AA and AD risk with fluoroquinolones compared with first- or second-generation cephalosporins, rather than third-generation cephalosporins, to reduce the potential confounding of different disease severity.[37–39]

This observational study has several limitations that should be addressed. First, the NHIRD does not provide information on lifestyle or personal behavioral factors including smoking, alcohol consumption, and body mass index, which might have affected the risk of AA and AD. However, we adjusted for these factors by including related comorbidities and performing PSM. Second, data on the UTI severity, aneurysm diagnosis modality, and AA and AD location and size are not included in the NHIRD. Septicemia and intra-abdominal infection had the highest increased risk than other infections based on previous study.[17,40] Third, we included only patients with UTIs who received the monotherapy of fluoroquinolones or cephalosporins, leading to a relatively limited number of events in the subgroup analysis. However, by excluding the concomitant use of different antibiotics, we reduced the potential confounding of exposure to multiple antibiotics. Fourth, the NHIRD represents the population of Taiwan, and our results may not be generalizable to other ethnic populations. Finally, because of the nature of an observational study, additional rigorous clinical randomized trials with a sufficiently large sample size, adequate patient selection, and controlled intervention are required.

CONCLUSIONS

This is the first population-based cohort study of a single-infection condition to demonstrate that the use of fluoroquinolones was not associated with an increased risk of AA and AD in patients with UTI compared with the use of first- or second-generation cephalosporins. For patients with indicated UTIs, the priority is to treat and control infection with adequate antibiotics rather than postpone or even exclude treatment with fluoroquinolones considering the risk of AA and AD.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Table S1

REFERENCES

1. Schmiemann G, Kniehl E, Gebhardt K, Matejczyk MM, Hummers-Pradier E. The diagnosis of urinary tract infection: a systematic review. *Deutsc Arztebl Int*. 2010;107:361–367. doi: 10.3238/arztebl.2010.0361
2. Chu CM, Lowder JL. Diagnosis and treatment of urinary tract infections across age groups. *Am J Obstet Gynecol*. 2018;219:40–51. doi: 10.1016/j.ajog.2017.12.231
3. ACOG practice bulletin No. 91: treatment of urinary tract infections in nonpregnant women. *Obstet Gynecol*. 2008;111:785–794. doi: 10.1097/AOG.0b013e318169f6ef
4. Leligdowicz A, Dodek PM, Norena M, Wong H, Kumar A, Kumar A. Association between source of infection and hospital mortality in patients who have septic shock. *Am J Respir Crit Care Med*. 2014;189:1204–1213. doi: 10.1164/rccm.201310-1875OC
5. Bonkat GRB, Bruyère F, Cai T, Geerlings SE, Köves B, Schubert S, Wagenlehner F, Guidelines Associates: Mezei TAP, Pradere B, Veeratterapillay R. EAU guidelines on urological infections 2020. *Eur Assoc Urol*. 2020; 13–22.
6. Owens RC Jr, Ambrose PG. Antimicrobial safety: focus on fluoroquinolones. *Clin Infect Dis*. 2005;41:S144–S157. doi: 10.1086/428055
7. Van Bambeke F, Tulkens PM. Safety profile of the respiratory fluoroquinolone moxifloxacin: comparison with other fluoroquinolones and other antibacterial classes. *Drug Saf*. 2009;32:359–378. doi: 10.2165/00002018-200932050-00001
8. Gorelik E, Masarwa R, Perlman A, Rotshild V, Abbasi M, Muszkat M, Matok I. Fluoroquinolones and cardiovascular risk: a systematic review. meta-analysis and network meta-analysis. *Drug Saf*. 2019;42:529–538. doi: 10.1007/s40264-018-0751-2
9. van der Linden PD, Sturkenboom MC, Herings RM, Leufkens HG, Stricker BH. Fluoroquinolones and risk of Achilles tendon disorders: case-control study. *BMJ*. 2002;324:1306–1307. doi: 10.1136/bmj.324.7349.1306
10. Sutter R, Rüegg S, Tschudin-Sutter S. Seizures as adverse events of antibiotic drugs: a systematic review. *Neurology*. 2015;85:1332–1341. doi: 10.1212/wnl.0000000000002023
11. Lee CC, Lee MT, Chen YS, Lee SH, Chen YS, Chen SC, Chang SC. Risk of aortic dissection and aortic aneurysm in patients taking oral fluoroquinolone. *JAMA Intern Med*. 2015;175:1839–1847. doi: 10.1001/jamainternmed.2015.5389
12. Pasternak B, Inghammar M, Svanström H. Fluoroquinolone use and risk of aortic aneurysm and dissection: nationwide cohort study. *BMJ*. 2018;360: doi: 10.1136/bmj.k678
13. Yu X, Jiang D-S, Wang J, Wang R, Chen T, Wang K, Cao S, Wei X. Fluoroquinolone use and the risk of collagen-associated adverse events: a systematic review and meta-analysis. *Drug Saf*. 2019;42:1025–1033. doi: 10.1007/s40264-019-00828-z
14. Pacini D, Di Marco L, Fortuna D, Belotti LMB, Gabbieri D, Zussa C, Pigini F, Contini A, Barattoni MC, De Palma R, et al. Acute aortic dissection: epidemiology and outcomes. *Int J Cardiol*. 2013;167:2806–2812. doi: 10.1016/j.ijcard.2012.07.008

15. Wang S-W, Huang Y-B, Huang J-W, Chiu C-C, Lai W-T, Chen C-Y. Epidemiology, clinical features, and prescribing patterns of aortic aneurysm in Asian population from 2005 to 2011. *Medicine*. 2015;94:e1716. doi: 10.1097/MD.0000000000001716
16. Howard Dominic PJ, Banerjee A, Fairhead JF, Handa A, Silver LE, Rothwell PM. Population-based study of incidence of acute abdominal aortic aneurysms with projected impact of screening strategy. *J Am Heart Assoc*. 2015;4. doi: 10.1161/JAHA.115.001926
17. Dong Y-H, Chang C-H, Wang J-L, Wu L-C, Lin J-W, Toh S. Association of infections and use of fluoroquinolones with the risk of aortic aneurysm or aortic dissection. *JAMA Intern Med*. 2020;180:1587–1595. doi: 10.1001/jamainternmed.2020.4192
18. Hsieh CY, Su CC, Shao SC, Sung SF, Lin SJ, Kao Yang YH, Lai EC. Taiwan's national health insurance research database: past and future. *Clin Epidemiol*. 2019;11:349–358. doi: 10.2147/clep.s196293
19. Hsu M-E, Chou A-H, Cheng Y-T, Lee H-A, Liu K-S, Chen D-Y, Wu VC-C, Chu P-H, Chen T-H, Chen S-W. Outcomes of acute aortic dissection surgery in octogenarians. *J Am Heart Assoc*. 2020;9:e017147. doi: 10.1161/JAHA.120.017147
20. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med*. 2009;28:3083–3107. doi: 10.1002/sim.3697
21. Austin PC. An Introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivar Behav Res*. 2011;46:399–424. doi: 10.1080/00273171.2011.568786
22. Lee C-C, Lee M-tG, Hsieh R, Porta L, Lee W-C, Lee S-H, Chang S-S. Oral fluoroquinolone and the risk of aortic dissection. *J Am Coll Cardiol*. 2018;72:1369–1378. doi: 10.1016/j.jacc.2018.06.067
23. Dai X-C, Yang X-X, Ma L, Tang G-M, Pan Y-Y, Hu H-L. Relationship between fluoroquinolones and the risk of aortic diseases: a meta-analysis of observational studies. *BMC Cardiovasc Disord*. 2020;20:49. doi: 10.1186/s12872-020-01354-y
24. 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. doi: 10.1128/AAC.44.2.261-266.2000
25. Khaliq Y, Zhanel GG. Fluoroquinolone-associated tendinopathy: a critical review of the literature. *Clin Infect Dis*. 2003;36:1404–1410. doi: 10.1086/375078
26. Chen L, Wang X, Carter SA, Shen YH, Bartsch HR, Thompson RW, Coselli JS, Wilcken DL, Wang XL, LeMaire SA. 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;131:1045–1052. doi: 10.1016/j.jtcvs.2006.01.003
27. 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;46:3034–3040. doi: 10.1002/art.10617
28. Sekar N. Primary aortic infections and infected aneurysms. *Ann Vasc Dis*. 2010;3:24–27. doi: 10.3400/avd.ctiia09000
29. Brown SL, Busuttil RW, Baker JD, Machleder HI, Moore WS, Barker WF. Bacteriologic and surgical determinants of survival in patients with mycotic aneurysms. *J Vasc Surg*. 1984;1:541–547. doi: 10.1016/0741-5214(84)90040-5
30. Moneta GL, Taylor LM Jr, Yeager RA, Edwards JM, Nicoloff AD, McConnell DB, Porter JM. Surgical treatment of infected aortic aneurysm. *Am J Surg*. 1998;175:396–399. doi: 10.1016/s0002-9610(98)00056-7
31. Brouwer RE, van Bockel JH, van Dissel JT. Streptococcus pneumoniae, an emerging pathogen in mycotic aneurysms? *Neth J Med*. 1998;52:16–21. doi: 10.1016/s0300-2977(97)00067-3
32. McCann JF, Fareed A, Reddy S, Cheesbrough J, Woodford N, Lau S. Multi-resistant *Escherichia coli* and mycotic aneurysm: two case reports. *J Med Case Rep*. 2009;3:6453. doi: 10.1186/1752-1947-3-6453
33. Hsu RB, Lin FY. Psoas abscess in patients with an infected aortic aneurysm. *J Vasc Surg*. 2007;46:230–235. doi: 10.1016/j.jvs.2007.04.017
34. Dick J, Tiwari A, Menon J, Hamilton G. Abdominal aortic aneurysm secondary to infection with Pseudomonas aeruginosa: a rare cause of mycotic aneurysm. *Ann Vasc Surg*. 2010;24:692.e691–694. doi: 10.1016/j.avsg.2010.02.003
35. Howard DPJ, Banerjee A, Fairhead JF, Handa A, Silver LE, Rothwell PM, Oxford VS. Age-specific incidence, risk factors and outcome of acute abdominal aortic aneurysms in a defined population. *Br J Surg*. 2015;102:907–915. doi: 10.1002/bjs.9838
36. Gawinecka J, Schönrath F, von Eckardstein A. Acute aortic dissection: pathogenesis, risk factors and diagnosis. *Swiss Med Wkly*. 2017;147: doi: 10.4414/smw.2017.14489
37. Hooton TM. Clinical practice. Uncomplicated urinary tract infection. *N Engl J Med*. 2012;366:1028–1037. doi: 10.1056/NEJMcp1104429
38. van der Starre WE, van Nieuwkoop C, Paltansing S, van't Wout JW, Groeneveld GH, Becker MJ, Koster T, Wattel-Louis GH, Delfos NM, Ablij HC, et al. Risk factors for fluoroquinolone-resistant *Escherichia coli* in adults with community-onset febrile urinary tract infection. *J Antimicrob Chemother*. 2011;66:650–656. doi: 10.1093/jac/dkq465
39. Ren H, Li X, Ni Z-H, Niu J-Y, Cao B, Xu J, Cheng H, Tu X-W, Ren A-M, Hu Y, et al. Treatment of complicated urinary tract infection and acute pyelonephritis by short-course intravenous levofloxacin (750 mg/day) or conventional intravenous/oral levofloxacin (500 mg/day): prospective, open-label, randomized, controlled, multicenter, non-inferiority clinical trial. *Int Urol Nephrol*. 2017;49:499–507. doi: 10.1007/s11255-017-1507-0
40. Lin CH, Hsu RB. Primary infected aortic aneurysm: clinical presentation, pathogen, and outcome. *Acta Cardiologica Sinica*. 2014;30:514–521. doi: 10.6515/acs20140630a

SUPPLEMENTAL MATERIAL

Table S1. Characteristics of age-sex matched Subjects during UTI hospitalization.

Variables	Fluoroquinolones	First- or second-generation cephalosporins	Third-generation cephalosporins
Number of cases	43907	43907	43907
All hospitalized stays, days			
1-6 days	39199 (89.28%)	39451 (89.85%)	25576 (58.25%)
>=7 days	4708 (10.72%)	4456 (10.15%)	18331 (41.75%)
Co-morbidities			
Hypertension	1950 (4.44%)	1890 (4.30%)	4668 (10.63%)
Coronary artery disease	423 (0.96%)	376 (0.86%)	949 (2.16%)
COPD	502 (1.14%)	249 (0.57%)	481 (1.10%)
Lipid disorder	215 (0.49%)	222 (0.51%)	153 (0.35%)
DM	1083 (2.47%)	799 (1.82%)	1869 (4.26%)
Asthma	126 (0.29%)	60 (0.14%)	123 (0.28%)
Organic sleep apnea	3 (0.01%)	4 (0.01%)	13 (0.03%)
Cardiac valve disease	114 (0.26%)	147 (0.33%)	302 (0.69%)
Chronic kidney disease	900 (2.05%)	715 (1.63%)	2628 (5.99%)
Atrial fibrillation	208 (0.47%)	163 (0.37%)	505 (1.15%)
Seizure disorder	105 (0.24%)	77 (0.18%)	360 (0.82%)
Chronic ulcer of skin	302 (0.69%)	190 (0.43%)	852 (1.94%)
Conduction disorders	15 (0.03%)	15 (0.03%)	32 (0.07%)
Peripheral arterial disease	37 (0.08%)	23 (0.05%)	91 (0.21%)
Cancer	1073 (2.44%)	862 (1.96%)	2906 (6.62%)
Medication use			
NSAIDs	10564 (24.06%)	11095 (25.27%)	13169 (29.99%)
Aspirin	2782 (6.34%)	2912 (6.63%)	7219 (16.44%)
Clopidogrel	487 (1.11%)	437 (1.00%)	1310 (2.98%)
Statins	530 (1.21%)	701 (1.60%)	1380 (3.14%)
ACE inhibitors	778 (1.77%)	791 (1.80%)	2124 (4.84%)
Beta-blockers	1370 (3.12%)	1524 (3.47%)	4189 (9.54%)
Calcium-channel blockers	3070 (6.99%)	3198 (7.28%)	8501 (19.36%)
Anticoagulant agents	339 (0.77%)	384 (0.87%)	1536 (3.50%)
Antiarrhythmic agents	562 (1.28%)	477 (1.09%)	2112 (4.81%)

COPD: Chronic obstructive pulmonary disease

DM: Diabetes mellitus

NSAIDs: Non-steroidal anti-inflammatory drugs

ACE: Angiotensin converting enzyme