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CLINICAL RESEARCH
Valvular Heart Disease

Oral fluoroquinolones and risk of aortic or mitral regurgitation: a nationwide nested case-control study

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Aims Reports have suggested an increased risk of aortic and mitral regurgitation associated with oral fluoroquinolones (FQs) resulting in a safety warning published by the European Medicines Agency (EMA). However, these findings have not yet been replicated.

Methods and results Using Danish administrative registers, we conducted a nested case-control study in a nationwide cohort of individuals between 2005 and 2018. Cases were defined as the first occurrence of aortic or mitral regurgitation. Exposure of interest was the use of oral FQs. Hazard ratios (HRs) with 95% confidence intervals (95% CI) were obtained by fitting time-dependent Cox regression models, with penicillin V as comparator, to assess the association between FQ use and incident valvular regurgitation. We identified 38 370 cases of valvular regurgitation with 1 115 100 matched controls. FQ exposure was not significantly associated with increased rates of aortic or mitral regurgitation (HR 1.02, 95% CI 0.95–1.09) compared with penicillin V users. Investigating the cumulative defined daily doses (cDDD) of FQs yielded similar results with no significant association between increasing FQ use and valvular regurgitation (e.g. HR 1.08, 95% CI 0.95–1.23 for cDDD >10 compared with cDDD 1–5). These results were consistent across several analyses including a cohort of patients with hypertension and using a case definition based on valvular surgical interventions.

Conclusions In a nationwide nested case-control study, FQs were not significantly associated with increased rates of valvular regurgitation. Our findings do not support a possible causal connection between FQ exposure and incident valvular regurgitation.

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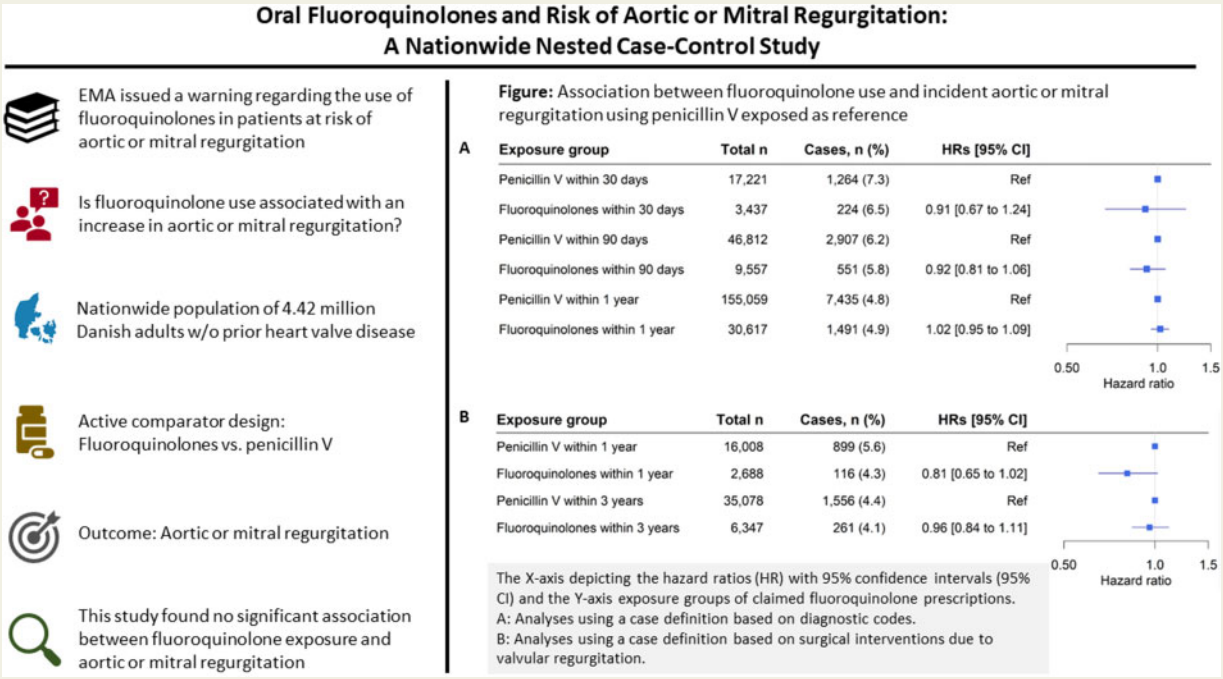
Graphical Abstract



Background, study design, methods, and main results of the present study investigating oral fluoroquionolones and risk of aortic or mitral regurgitation.

Keywords Aortic regurgitation • Mitral regurgitation • Valvular heart disease • Fluoroquinolones • Antibiotics

Introduction

Fluoroquinolones (FQs) are a class of widely used antimicrobial agents with broad-spectrum activity against both gram-negative and gram-positive bacteria.[1,2] While being generally well-tolerated, the use of FQs is associated with adverse reactions related to several organ systems.[3] FQs are among the most commonly prescribed antibiotics worldwide, thus potential adverse effects are of significant public health importance.[4]

Studies have indicated that FQs cause degradation of collagen and extracellular matrix potentially increasing the risk of tendinopathy, aortic aneurysms, and aortic dissections.[5–8] Furthermore, it has been suggested that FQ-induced collagen degradation could potentially affect the valves of the heart leading to valvular regurgitation.[9] A recent study substantiated this claim with the finding of an increased risk of aortic and mitral valve regurgitation in patients treated with FQs.[10] Consequently, the European Medicines Agency (EMA) published a safety concern against the use of FQs, especially in patient populations considered at high risk of regurgitant valvular heart disease (e.g. patients with hypertension or connective tissue disorders).[11] However, the data underlying the EMA warning were based on one experimental study and one observational study and have yet to be reproduced.

Accordingly, using nationwide Danish administrative registers, we sought to investigate if the use of FQs was associated with increased rates of incident aortic or mitral regurgitation in a nationwide cohort of adults as well as in a high-risk population of patients with hypertension.

Methods

Setting

In Denmark, it is possible to follow all citizens using a unique identifying number assigned to all permanent residents. Using this unique identifier, different nationwide clinical databases and registers can be cross-linked allowing large-scale epidemiological research with nationwide coverage.[12]

The Danish National Patient Register holds information on all hospital contacts coded with one or more diagnostic codes according to the International Classification of Diseases 10th edition (ICD-10) as well as performed procedures and operations.[13] The Danish National Prescription Register contains data on all prescriptions filled at Danish pharmacies with detailed information on the dose of the drug, size of the package, number of packages dispensed as well as the drug in question coded according to the Anatomical Therapeutic Chemical Classification System.[14,15] Demographic variables including date of birth, date of migration, and date of death can be obtained from the Danish Civil Registration system.[16] The used registers have all been described in detail previously.[17]

Study population, design, and case definition

The main analyses of the study were conducted as nationwide nested case-control studies in the period between 2005 and 2018.[18] Individuals were excluded at baseline if they had prior registrations of regurgitant valvular disease (diagnoses or procedural codes as elaborated later), prosthetic heart valves, known connective tissue disorders (Marfan syndrome, rheumatic fever, rheumatoid arthritis, and Bechterew's disease), or previous infective endocarditis. Eligible individuals between 30 and 100 years of age were included between 2005 and 2018.

We pre-planned several complementary analyses to ensure the robustness of estimates considering the definition and timing of outcomes and selected subpopulations included in the EMA warning. Firstly, cases were defined as the first event of a diagnostic code of either aortic or mitral regurgitation during the study period in order to employ a sensitive case definition (i.e. to capture as many cases as possible). Secondly, in order to only capture patients with clinically significant valvular regurgitation, we performed an analysis restricting cases as being the first registered event of surgical interventions pertaining to aortic or mitral regurgitation. Lastly, we performed the first analysis, defining valvular regurgitation using diagnostic codes, in a cohort of patients diagnosed with arterial hypertension (i.e. patients considered at high risk of valvular regurgitation according to the EMA warning). As such, in this cohort, eligible patients were identified on the date of their first registered diagnosis of arterial hypertension and included in the cohort 3 years following hypertension diagnosis (baseline) as FQ exposure was defined up to a period of 3 years prior as explained later.

For all three analyses, controls were sampled from the described cohorts and matched to the cases in a 30:1 ratio on sex, age, and year of the index date. However, in the hypertension cohort, we matched on age groups. Individuals in the cohorts were continuously censored during follow-up if they were diagnosed with any of the competing events of infective endocarditis or connective tissue disorders. Further, in the analysis with a case definition of surgery, patients were censored if they were diagnosed with aortic stenosis to avoid capturing aortic valve replacement due to aortic stenosis as a case. Thus, the control group consisted of patients being alive, residing in Denmark, with native heart valves (without aortic stenosis in the secondary analysis), without a history of the outcome in question (diagnosis or surgery pertaining to valvular regurgitation, respectively), infective endocarditis, or connective tissue disorders at corresponding case date.

For full definitions and diagnostic codes, please see Supplementary material online, *Table S1*.

Exposure and variables of interest

The primary exposure of interest was prescriptions of oral FQs (ciprofloxacin or moxifloxacin) defined as any filled prescription within 1 year prior to the date of interest (date of aortic or mitral regurgitation for cases or corresponding date for controls). The included drugs were the formulations of FQs available for oral treatment in the study period in Denmark. Supplementary definitions of FQ exposure were defined as any filled prescription within 30 and 90 days prior to the date of interest to assess any short-term association between FQ use and valvular regurgitation. For the analysis of surgical interventions, we used time windows of 1 and 3 years prior to the case date for defining exposure. To help interpretation, we reported proportions of patients in the cohorts redeeming at least 1, 2, 3, or 4 FQ prescriptions within 5 years from inclusion.

To estimate a potential dose–response relationship, we calculated the cumulative defined daily doses (cDDD) of FQs based on all filled FQ prescriptions within 3 years prior to the date of interest, as we would expect any association between FQ and valvular degradation to become stronger with increased exposure to FQ. The DDD is the assumed daily dose of a drug as defined by the World Health Organization.[19] Thus, the cDDD of FQs was the sum of all consumed daily doses within 3 years prior to the date of interest. The DDD for ciprofloxacin is 1 g and the DDD for moxifloxacin is 0.4 g. The cDDD of FQ was divided into the following categories: cDDD 1–5, cDDD 6–10, and cDDD >10 based on the cDDD distributions.

To minimize the risk of protopathic bias, we used an active comparator design in which the non-exposed included in the analyses had to be exposed to a comparable class of antibiotic drugs.[20,21] Since valvular heart disease often presents with dyspnoea as the primary symptom, reverse causality could be feared as FQs could be prescribed for suspected pneumonia in patients with yet undiagnosed valvular regurgitation. Accordingly, the non-exposed individuals included in the main analysis had to be exposed to penicillin V, which is the first-line treatment for community-acquired pneumonia in Denmark.[22,23]

Comorbidities were defined as any primary or secondary diagnosis registered in a period of 5 years prior to the date of interest. We included the following comorbidities: ischaemic heart disease, congestive heart failure, atrial fibrillation, prior ischaemic stroke or transient cerebral ischaemia, chronic kidney disease, and chronic obstructive pulmonary disease (COPD) (Supplementary material online, *Table S1*).

Concomitant pharmacotherapy was defined as filled prescriptions for drugs of interest in a period of 180 days prior to the date of interest. Pharmacotherapy deemed relevant to the current study was treatment with beta-blockers, calcium-channel blockers, renin-angiotensin system inhibitors, anticoagulants, antiplatelet drugs, statins, loop diuretics, and non-loop diuretics.

Diabetes mellitus was defined as filled prescriptions for glucose-lowering drugs (Supplementary material online, *Table S1*).

Statistical methodology

The study population in question was described as cases and controls using descriptive statistics with continuous variables summarized by medians and interquartile ranges (IQR) and categorical variables by counts and percentages. Moreover, the cohorts (the overall population nest and the hypertension nest) were described and characterized at baseline.

The nested case-control design was applied to estimate the association between FQ exposure and the rates of incident valvular regurgitation using a time-dependent Cox proportional hazards regression model. Using conditional logistic regression software, the model was fitted to the nested case-control data providing hazard ratios (HRs) with 95% confidence intervals (95% CI).[24,25]

Furthermore, we performed an analysis investigating a potential dose–response relationship, using cDDD quantiles of FQs as the exposure of interest using the group with the shortest FQ exposure (1–5 cDDD) as a reference, thus comparing patients with prolonged FQ exposure with patients having a more limited exposure to FQs.

In order to characterize overall FQ use during the study period, redemptions of FQ prescriptions were analysed as a recurrent event using appropriate methods to handle the loss of follow-up (i.e. censoring) and the competing risk of death.[26]

All models were adjusted for pre-specified confounders (ischaemic heart disease, atrial fibrillation, heart failure, COPD, diabetes mellitus, and chronic kidney disease. Additionally, the hypertension cohort was adjusted for age).

To avoid collider bias, the potential confounders were only included in the adjusted model if occurring in the time period 5 years prior to the earliest date of possible exposure (1 year prior to case/control date for the main analysis and 90 days prior to case/control date in the 90-day exposure analysis, etc.).[27] Pertaining to the nested case-control design, the reported HRs should be interpreted as the estimates of a Cox model

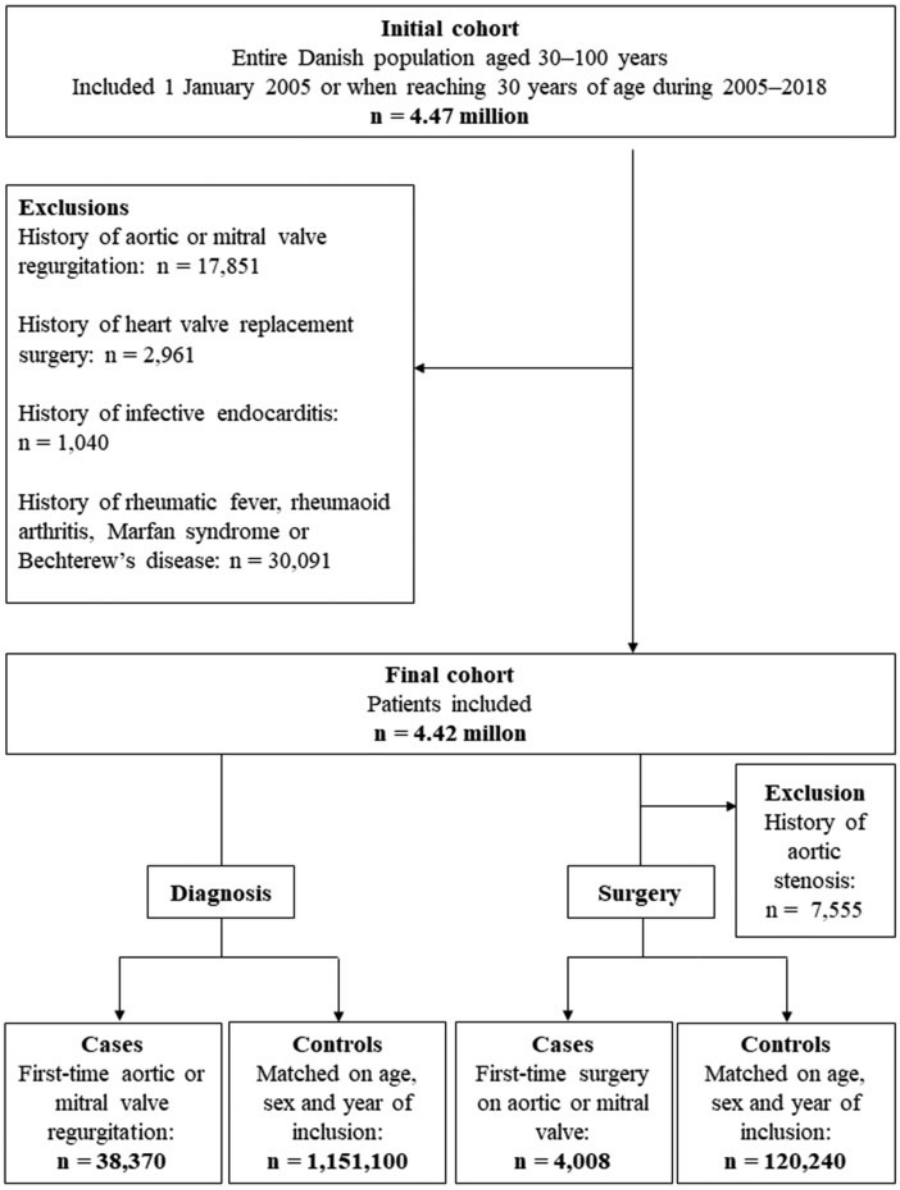


Figure 1 Flow chart of the study population depicting study inclusion, baseline exclusion, as well as sampling of cases and controls.

fitted with time-varying covariates using the entire sampling population as a cohort with both patient characteristics for adjustments as well as FQ exposure updated continuously.[24,25] The level of statistical significance was set at 5%. Analyses were conducted in R (version 3.6.1).[28]

Supplementary analyses

Instead of using penicillin V as the active comparator drug, supplementary analyses were performed using macrolides and amoxicillin separately as reference. These drugs were chosen as they were deemed comparable due to somewhat similar clinical indications in a Danish context. However, as previously stated, penicillin V is the first-line treatment for suspected pneumonia in patients without severe COPD. As such, amoxicillin use in Denmark is somewhat limited and this group of patients is likely more selected.[22,23] To investigate differences in age groups, the main cohort and the hypertension cohort were stratified in tertiles according to age. To account for differences in overall health status between FQ and penicillin V exposed patients, we conducted analyses taking the number of previous hospitalizations and history of cancer into account.

Ethics

Register-based studies with de-identified data and no active participation by study subjects do not require approval by an ethics committee in Denmark. The use of register-based data has been approved by the Danish Data Protection Agency and the current project is registered at the responsible institute (Approval No. P-2019-348).

Table 1 Study population characteristics using a case definition based on diagnostic codes

	Cases (n = 38 370)	Controls (n = 1 151 100)[a]
Age (years), median [IQR]	70 [61, 78]	70 [61, 78]
Male sex, *n* (%)	18 924 (49)	567 720 (49)
Comorbidity, *n* (%)		
Myocardial infarction	2174 (6)	19 986 (2)
Ischaemic heart disease	6803 (18)	72 932 (6)
Heart failure	3941 (10)	26 743 (2)
Atrial fibrillation	6606 (17)	58 276 (5)
Ischaemic stroke/TIA	1912 (5)	29 848 (3)
Diabetes	2848 (7)	88 486 (8)
COPD	2223 (6)	40 075 (4)
Chronic kidney disease	1508 (4)	18 631 (2)
Concomitant pharmacotherapy, *n* (%)		
Beta-blockers	12 392 (32)	172 379 (15)
Calcium-channel blockers	8740 (23)	177 180 (15)
RAS inhibitors	15 015 (39)	299 466 (26)
Loop diuretics	7966 (21)	88 841 (8)
Non-loop diuretics	11 712 (31)	251 723 (22)
Statins	12 295 (32)	255 151 (22)
Acetylsalicylic acid	11 301 (30)	20,5,79 (17)
ADP inhibitor	6285 (16)	59 087 (5)
Oral anticoagulant	2363 (6)	34 805 (3)

ADP, adenosine-diphosphate; COPD, chronic obstructive pulmonary disease; RAS, renin-angiotensin system; TIA, transient ischaemic attack.
[a]Controls were matched on sex, age, and year of the index date.

Results

Main cohort

A total of 4 416 252 individuals were eligible for inclusion in the cohort (*Figure 1*). The median age was 46 years (IQR 32–61) and there was a small majority of males (51%). Prevalent comorbidities were ischaemic heart disease (3%), diabetes (3%), and atrial fibrillation (1%) (Supplementary material online, *Table S2*). Within 5 years of inclusion, 6.2% of patients had redeemed at least one prescription of FQ and just below 1% had redeemed at least three (Supplementary material online, *Figure S1*).

Using diagnostic codes, we identified a total of 38 370 cases of aortic or mitral valve regurgitation and 1 115 100 control subjects matched on age group, sex, and calendar year. Of these cases, 18 906 (49.3%) were based on a diagnosis pertaining to the aortic valve, 17 503 (45.6%) to the mitral valve, and 1961 (5.1%) had regurgitant disease of both valves.

The median age of the matched cases and controls was 70 years (IQR 61–78) with a slight overweight of females (51%). Cardiovascular comorbidities were much more prevalent among cases than controls regarding ischaemic heart disease (18% vs. 6%), atrial fibrillation (17% vs. 5%), and heart failure (10% vs. 2%) (*Table 1*).

Regarding surgery, we identified 4008 cases of surgical interventions due to aortic or mitral valve regurgitation with 120 240 matched controls. The median age was 66 years (IQR 57–73) with more males (68%). The cases generally had much more cardiovascular comorbidity than their matched controls (*Table 2*).

Rates of diagnoses of valvular regurgitation

Treatment with FQs within 1 year prior to the date of interest conferred no increase in the rates of aortic or mitral valve regurgitation compared with patients exposed to penicillin V (HR 1.02, 95% CI 0.95–1.09) (*Figure 2A*).

When examining more recent exposure to FQs (30 and 90 days), we found similar results with no indications of increased rates of valvular regurgitation (30 days: HR 0.91, 95% CI 0.67–1.24 and 90 days: HR 0.92, 95% CI 0.81–1.06).

Rates of surgery due to valvular regurgitation

Restricting our case definition to only included cases of regurgitation undergoing surgery did not change our conclusions. As such, FQs did not lead to increased rates of surgeries due to aortic or mitral valve regurgitation compared with penicillin V (*Figure 2B*).

Dose-response association of fluoroquinolone exposure

We observed no dose–response relationship between the cumulative exposure to FQs and the rates of valvular regurgitation. As such, having a cDDD of 6–10, and a cDDD >10 conferred comparable rates of valvular regurgitation to patients with a cDDD of 1–5 [HR 1.06 (95% CI 0.95–1.19) and HR 1.08 (95% CI 0.95–1.23)] (*Figure 3A*). Using a case definition based on surgical interventions due to valvular regurgitation showed similar results (*Figure 3B*).

Table 2 Study population characteristics using a case definition based on surgical interventions

	Cases (n = 4008)	Controls (n = 120 240)[a]
Age (years), median [IQR]	66 [57, 73]	66 [57, 73]
Male sex, *n* (%)	2736 (68)	82 080 (68)
Comorbidity, *n* (%)		
Myocardial infarction	401 (10)	1911 (2)
Ischaemic heart disease	1432 (36)	6951 (6)
Heart failure	971 (24)	2247 (2)
Atrial fibrillation	1377 (34)	5009 (4)
Ischaemic stroke/TIA	147 (4)	2466 (2)
Diabetes	278 (7)	9152 (8)
COPD	290 (7)	3466 (3)
Chronic kidney disease	201 (5)	1843 (2)
Concomitant pharmacotherapy, *n* (%)		
Beta-blockers	1648 (41)	16 024 (13)
Calcium-channel blockers	754 (19)	16 421 (14)
RAS inhibitors	1861 (46)	29 723 (25)
Loop diuretics	1555 (39)	6464 (5)
Non-loop diuretics	1154 (29)	22 541 (19)
Statins	1449 (36)	26 056 (22)
Acetylsalicylic acid	1181 (30)	17 965 (15)
ADP inhibitor	268 (7)	3290 (3)
Oral anticoagulant	1105 (28)	5259 (4)

ADP, adenosine-diphosphate; COPD, chronic obstructive pulmonary disease; RAS, renin-angiotensin system; TIA, tansient ischaemic attack.
[a]Controls were matched on sex, age, and year of the index date.

Hypertension cohort

We included a supplementary cohort comprising 448 274 patients diagnosed with arterial hypertension. Eligible patients had a median age of 69 years (IQR 59–78), a slight majority of females (54%), and a general high prevalence of cardiovascular comorbidities compared with the main analysis cohort (Supplementary material online, *Table S3*). Further, FQ use was much more common in the hypertension cohort (Supplementary material online, *Figure S1*).

Similarly, in patients with hypertension, treatment with FQs was not associated with an increase in the rates of aortic or mitral valve regurgitation compared with patients exposed to penicillin V (HR 1.06, 95% CI 0.92–1.21). Moreover, we found no associations between FQ exposure and valvular regurgitation when investigating more recent exposure windows (30 and 90 days) as well as a potential dose–response relationship (*Figure 4*).

Supplementary analyses

Performing the primary analyses of the study using different active comparator drugs (macrolides and amoxicillin) did not alter our conclusions. As such, treatment with FQs did not confer increased rates of aortic or mitral regurgitation compared with patients treated with macrolides or amoxicillin (Supplementary material online, *Figure S2*). Differences in rates of aortic or mitral regurgitation were found according to age groups in the main cohort using diagnoses codes as case definition. No differences in age groups were found when using surgical intervention as a case definition in the hypertension cohort, and no dose–response relationship was found (Supplementary material online, *Tables S4–S6*). Adjusting for previous hospitalizations and history of cancer yielded results comparable to the main analysis as well (Supplementary material online, *Table S7*).

Discussion

In this nationwide nested case-control study, there were several important findings: (i) in our data, FQ use was not associated with significantly increased rates of aortic or mitral regurgitation in contrast with what has been reported elsewhere; (ii) no dose–response relationship between the cDDD of FQs and the rates of aortic or mitral regurgitation was found; and (iii) these results were consistent when restricting the definition of valvular regurgitation to patients undergoing surgical interventions as well as in a cohort of patients with hypertension deemed at high risk of valvular regurgitation (***Graphical abstract***).

Fluoroquinolones are a class of relatively commonly prescribed antibiotics due to their broad spectrum of antimicrobial activity.[1,4,22] Fluoroquinolones have been shown to up-regulate matrix metalloproteinases resulting in degradation of collagen fibrils, especially in type I collagen, which is also the presumed mechanism behind the increased risk of tendinitis and tendon rupture associated with FQs.[8,29,30] As type I and type III collagen comprise 80–90% of the collagen in the aorta, concerns regarding aortic aneurysms and aortic dissections associated with FQ treatment have been raised in epidemiological studies.[5–7,31] Similarly, collagen fibres consisting of predominantly type I collagen are a primary constituent of the native valves of the heart and is the putative mechanistic link between FQ

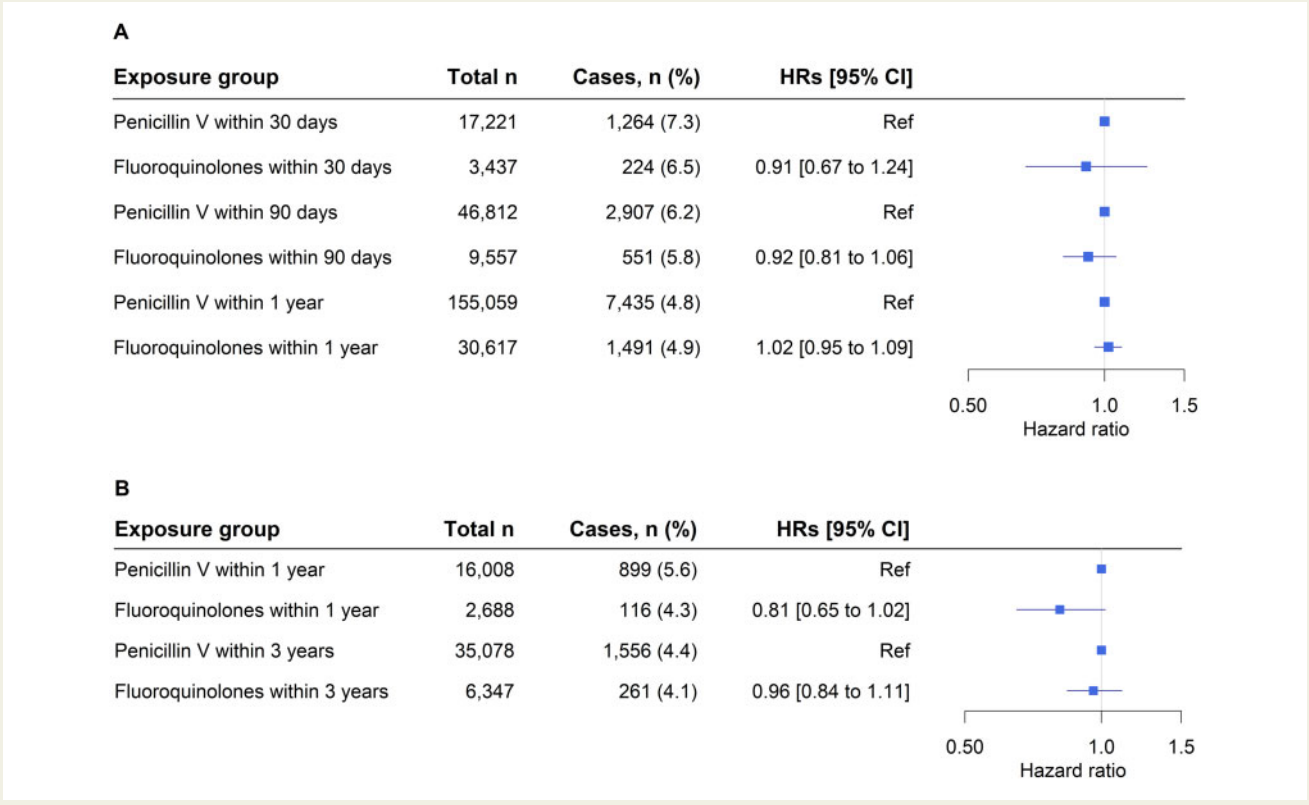


Figure 2 Forest plot depicting the association between fluoroquinolone use and incident aortic or mitral regurgitation using penicillin V exposed as reference. The *x*-axis depicting the hazard ratios with 95% confidence intervals and the *y*-axis exposure groups of claimed fluoroquinolone prescriptions. (*A*) Analyses using a case definition based on diagnostic codes. (*B*) Analyses using a case definition based on surgical interventions due to valvular regurgitation.

exposure and valve regurgitation.[32] In this context, a study hypothesized that the collagen degrading effects of FQs could affect the cerebral arteries but found no association between FQ exposure and increased risks of intracranial aneurysm or dissection.[33]

A recent study based on a sample from a large health insurance claims database from the USA reported increased risks of aortic and mitral regurgitation in patients with a history of FQ use.[10] The authors reported rate ratios of valvular regurgitation ranging from 2.4 to 1.8, depending on the comparator drug. These data, along with basic research indicating that FQ exposure causes impaired collagen-1 expression in human aortic myofibroblasts, have led the EMA to publish a direct communication to healthcare professionals warning that FQs may cause damage to the heart valves leading to valvular regurgitation—especially in certain high-risk groups of patients.[9,11]

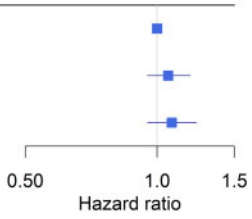
However, the definition of the study population as well as general data quality and reliability of important study variables were somewhat unclear in the referenced study.[10] Further, it is unclear if the authors considered the indication of the active comparators as symptoms displayed by the diseases could lead to surveillance bias. Lastly, differences in prescription patterns of antibiotics and the censoring of patients at diagnosis of endocarditis done in our study may account for the differences in the results.

Interestingly, in our study comprising both a nationwide cohort of adults as well as a population of patients categorized as potentially high-risk patients (i.e. patients with documented hypertension), we were not able to reproduce this finding. We consistently found no association between FQ use and increased rates of incident aortic or mitral regurgitation. To further strengthen this conclusion, we did not find any dose–response relationship between increased cumulative exposure to FQs and aortic or mitral regurgitation. We believe this is a strong argument against any clinically meaningful relationship between FQs and valvular damage as we would expect that an increased risk of valvular regurgitation would be accentuated with prolonged FQ exposure.

Several case reports have suggested that, when present, the clinical presentation of the collagen degrading properties of FQs could be potentially acute with aortic valve prolapse or tendon rupture occurring within days of treatment initiation.[34,35] However, changing the definition of our exposure to a maximum of 30 days elapsed since the latest filled FQ prescription and, as such, only capturing patients with very recent FQ exposure did not alter our conclusions. Moreover, from a clinical and mechanistic standpoint, such a noticeable relationship between FQ use and short-term risk of severe valvular regurgitation seems rather unlikely.

A

Dose-response within 3 years	Total n	Cases, n (%)	HRs [95% CI]
1-5 cDDD, fluoroquinolones	25,302	1,060 (4.2)	Ref
6-10 cDDD, fluoroquinolones	27,636	1,308 (4.7)	1.06 [0.95 to 1.19]
>10 cDDD, fluoroquinolones	16,504	802 (4.9)	1.08 [0.95 to 1.23]



B

Dose-response within 3 years	Total n	Cases, n (%)	HRs [95% CI]
1-5 cDDD, fluoroquinolones	2,229	103 (4.6)	Ref
6-10 cDDD, fluoroquinolones	2,659	99 (3.7)	0.81 [0.53 to 1.22]
>10 cDDD, fluoroquinolones	1,459	59 (4.0)	0.77 [0.47 to 1.24]

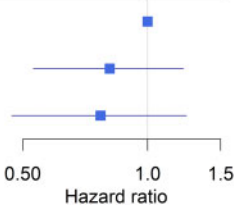


Figure 3 Forest plot depicting the association between the cumulative defined daily doses (cDDD) of fluoroquinolones and the rates of incident aortic or mitral regurgitation. The *x*-axis depicting the hazard ratios with 95% confidence intervals and the *y*-axis exposure groups of claimed fluoroquinolone prescriptions. (*A*) Analyses using a case definition based on diagnostic codes. (*B*) Analyses using a case definition based on surgical interventions due to valvular regurgitation.

Exposure group	Total n	Cases, n (%)	HRs [95% CI]
Penicillin V within 30 days	3,299	195 (5.9)	Ref
Fluoroquinolones within 30 days	953	46 (4.8)	0.82 [0.45 to 1.49]
Penicillin V within 90 days	8,948	430 (4.8)	Ref
Fluoroquinolones within 90 days	2,472	114 (4.6)	1.10 [0.81 to 1.48]
Penicillin V within 1 year	28,755	1,128 (3.9)	Ref
Fluoroquinolones within 1 year	7,937	314 (4.0)	1.06 [0.92 to 1.21]
Dose-response within 3 years			
1-5 cDDD, fluoroquinolones	5,629	191 (3.4)	Ref
6-10 cDDD, fluoroquinolones	7,423	300 (4.0)	1.12 [0.90 to 1.39]
>10 cDDD, fluoroquinolones	5,002	187 (3.7)	0.98 [0.77 to 1.24]

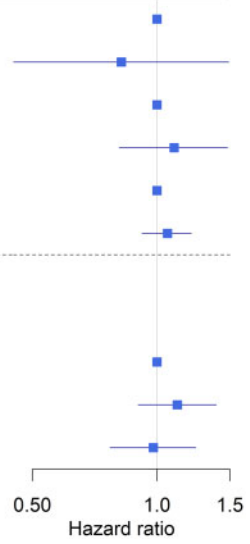


Figure 4 Forest plot depicting the association between fluoroquinolone use and incident aortic or mitral regurgitation, using penicillin V exposed as a reference, in a cohort of patients with diagnosed arterial hypertension. The *x*-axis depicting the hazard ratios with 95% confidence intervals and the *y*-axis exposure groups of claimed fluoroquinolone prescriptions.

The weak effect of age on rates of aortic or mitral regurgitation was only found in the main analysis and no differences were observed between FQ and penicillin V across age groups in the hypertension cohort, surgical interventions, and no dose–response relationship was found. Possible differences in patient characteristics according to age group may explain this association rather than an effect of FQ itself.

Conclusively, despite recent reports in the literature of increased risks of valvular regurgitation associated with FQs, using a contemporary nationwide cohort of patients, we were not able to reproduce this finding.

Our data are noteworthy, given that FQs should be used with caution for this specific reason according to the EMA, especially in high-risk groups such as patients with hypertension.[11] These conflicting data underline the need for further research before any conclusions regarding the harm or safety of FQs pertaining to valvular regurgitation can be drawn.

Strengths and limitations

The main limitations of our study are related to the observational nature of our study design and since our data are not randomized, causality cannot be directly inferred as residual confounding may influence the study. However, this is a difficult research question to answer in a randomized controlled trial stressing the need for observational data. Using large healthcare registers, the potential for misclassification bias must also be acknowledged as some of the diagnostic and procedural codes used in the definition of covariates have not been validated. However, the majority of codes used for defining important study variables have undergone scrutiny for data quality with high positive predictive values including the codes for aortic and mitral regurgitation as well as valvular surgery.[36–38] The data used in the Danish National Prescription Register for defining antibiotic exposure have, to the best of our knowledge, not been validated. However, the register is generally believed to be of high quality and validation studies examining the quality of registered prescriptions for oral anticoagulants and strong analgesics reported a high degree of completeness of registration.[15] Finally, using complete nationwide databases in a setting with universal and equal access to healthcare services, drastically decreases selection bias.

Conclusions

In this nationwide register-based nested case-control study, we did not find evidence to support that treatment with FQs was associated with significantly increased rates of aortic or mitral regurgitation. This lack of a significant association was consistent across a subgroup of high-risk patients with hypertension as well as when investigating a potential dose–response effect. These data are conflicting with previous reports on the subject as well as a recent safety concern published by the EMA. Our findings do not support a possible causal connection between FQ exposure and incident valvular regurgitation. Therefore, further research is needed before conclusions can be drawn regarding the safety of FQs pertaining to valvular regurgitation.

Supplementary material

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Data availability

Danish data protection laws prohibits sharing of the data used for this study.

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