Associations Between Systemic Fluoroquinolone Use and Risk of Uveitis and Retinal Detachment

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Abstract

Importance

Fluoroquinolone use has been associated with increased risk of uveitis and retinal detachment in non-interventional studies, but findings have been conflicting and causality is unclear.

Objective

To estimate measures of association between systemic fluoroquinolone prescribing and two ocular outcomes, acute uveitis and retinal detachment, using multiple study designs and multiple databases to increase the robustness of results.

Design

Cohort study and self-controlled case series.

Setting

Clinical Practice Research Datalink Aurum and GOLD UK primary care records linked to hospital admissions data.

Participants

Adults prescribed a fluoroquinolone or a comparator antibiotic, cephalosporin, between April 1997 and December 2019 were included in a cohort study. Adults with uveitis or retinal detachment were included in a self-controlled case-series.

Exposures

Systemic fluoroquinolone or comparator antibiotic.

Main Outcomes and Measures

Hazard ratios (HR) were estimated in the cohort study for the association between fluoroquinolone prescription and both uveitis and retinal detachment, using stabilized inverse probability of treatment weighted Cox regression. Rate ratios (RR) were estimated in the self-controlled case series, using conditional Poisson regression. Estimates were pooled across databases using fixed-effects meta-analysis.

Results

In total 3,001,256 individuals in Aurum and 434,754 in GOLD were included in the cohort study. There was no evidence of an association between fluoroquinolone use, relative to cephalosporins, and uveitis at first treatment episode (pooled aHR 0.91; 95% CI 0.72-1.14) or all treatment episodes (pooled aHR 1.07, 95% CI 0.92-1.25); and similarly for retinal detachment at first (pooled aHR 1.37, 95% CI 0.80-2.36) or all treatment episodes (pooled aHR 1.18; 95% CI 0.84-1.65). In self-controlled case series, there was little evidence for an association between fluoroquinolone use and uveitis (pooled aRR relative to non-use [95% CI]: days 1-29 of exposure 1.13 [0.97-1.31], days 30-59 1.16 [1.00-1.34], days 60+ 0.98 [0.74-1.31]) or retinal detachment (days 1-29 1.15 [0.86-1.54], days 30-59 0.94 [0.69-1.30], days 60+ 1.03 [0.59-1.78]).

Conclusions and Relevance

These findings do not support a class-effect of systemic fluoroquinolones on uveitis or retinal detachment. While we cannot rule out an effect, our study findings indicate that any absolute increase in risk would be small and hence of limited clinical significance.

Key points

Question

Does fluoroquinolone use increase the risk of acute uveitis or retinal detachment?

Findings

After covariate adjustment, and relative to comparator antibiotics, there was little evidence of an association between systemic fluoroquinolone use and uveitis or retinal detachment. This finding was consistent across two databases, Aurum and GOLD, and two study designs, cohort and self-controlled case series.

Meaning

These findings give no indication that systemic fluoroquinolone use increases risk of retinal detachment or uveitis and indicate that any absolute increase in risk would be small.

Introduction

Fluoroquinolones are a class of widely prescribed broad-spectrum antibiotics used to treat a number of infections including urogenital, respiratory tract and skin infections.[1,2] Safety concerns have arisen given adverse events observed among fluoroquinolone users in case reports and non-interventional studies.[3-5] Both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have, as a result of available evidence, advised restrictions on usage and the addition of warnings to product labelling.[6-10]

It has been suggested that oral fluoroquinolones may cause both acute uveitis and retinal detachment. Case reports of uveitis with the use of oral fluoroquinolones, particularly moxifloxacin, prompted investigators to conduct non-interventional studies investigating the association.[11] These studies produced conflicting findings, with elevated risk observed in two case-control studies, but no increased risk in a cohort study.[12-14] There has been a long-recognized association between fluoroquinolones and tendon rupture, thought based on animal and laboratory studies to be mediated by the effect of fluoroquinolones on collagen.[5,15,16] Given that collagen is an important component of the retina, and on the basis of case reports, investigators conducted a nested case-control study, finding elevated risk with oral fluoroquinolone use relative to non-use.[15] Subsequent non-interventional studies produced divergent results and came to conflicting conclusions with regard to presence and causality of the association.[17] Given the limited number of effective antibiotics available, and the requirement for multiple antibiotics in the face of considerable antimicrobial resistance, it is important to understand the safety profile of fluoroquinolones.

The aim of this study was to estimate measures of association between prescribing of systemic fluoroquinolones and two ocular outcomes, acute uveitis and retinal detachment, using multiple study populations and study designs for more robust triangulation of the possible effects.[18]

Methods

Data Sources

Included individuals were selected from two databases of anonymized routinely collected UK primary care records: Clinical Practice Research Datalink (CPRD) Aurum and GOLD.[19,20] Together the two databases contain records of more than 10 million currently registered patients from over a thousand primary care practices using one of two software systems (EMIS in Aurum; Vision in GOLD).[21,22]

These primary care databases, Aurum and GOLD, were linked to secondary care hospital admissions in Hospital Episode Statistics Admitted Patient Care (HES APC) and to area-level deprivation data. HES APC contains the records of all hospital admissions funded by the National Health Service (NHS) in England. [23] Area-level deprivation data contain measures of socioeconomic deprivation based on postal code.[24] Healthcare is free at the point of use through the NHS for all individuals ordinarily resident in the UK, and most UK residents are registered with a primary care practice.[25]

Study design

Cohort and self-controlled case series (SCCS) studies were conducted separately in Aurum and GOLD to estimate measures of association between systemic fluoroquinolone use and both uveitis and retinal detachment.

The SCCS is a self-controlled design where the frequency of the outcome is compared, within individuals, during exposed time, relative to non-exposed time.[26] Unlike a cohort study, where it is necessary to adjust for all potential confounders, the SCCS eliminates, by design, confounding that is time-invariant over the study period, though not time-varying confounding. We adjusted in analyses for potential time-varying confounding by age and calendar time.

Ethics approval was granted by the London School of Hygiene and Tropical Medicine research ethics committee (reference 22592). Reporting of the results follows RECORD-PE guidelines.[27]

Study eligibility

We selected, in both the SCCS and the cohort study, adults aged 18 years or older who were eligible for linkage to hospital admission and socioeconomic deprivation data. Individuals from overlapping practices present in both Aurum and GOLD were removed from the GOLD dataset. Overlaps occur due to practices switching software system (e.g., from EMIS to Vision).

The eligibility window started at the latest of: 1st April 1997, one year after practice data deemed by CPRD to be of research quality (date provided in GOLD only), one year after current registration of patient at practice, and 18th birthday. The eligibility window ended at the earliest of: 31st December 2019, death, patient transferred out of practice, and date of last practice data collection.

Exposure

Systemic fluoroquinolone prescription (ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin, or ofloxacin) was the exposure of interest. Comparator antibiotics were chosen that are prescribed for similar indications but have not been linked to uveitis or retinal detachment.[28] In the cohort study the comparator was prescription of a systemic cephalosporin. In the SCCS, the comparators were both non-use of systemic fluoroquinolones

and the following active comparators[29]: systemic cephalosporin, trimethoprim or co-amoxiclav. Prescriptions were identified in primary care records.

Outcomes

The primary outcomes were acute uveitis and retinal detachment, identified in primary care or hospital admissions. The hypothesized mechanism of detachment associated with fluoroquinolone use is thought to affect rhegmatogenous rather than tractional or serous retinal detachment, so we excluded codes for non-rhegmatogenous detachments from our definition of retinal detachment.[30,31] To increase specificity of the outcome definition for retinal detachment we required a clinical code followed by a subsequent surgical operation to treat retinal detachment (scleral buckle, pneumatic retinopexy or vitrectomy), recorded within 30 days. Tendon rupture was included in the cohort study as a positive control outcome. We anticipate an association with tendon rupture given the long-recognized association between fluoroquinolone use and tendon rupture.[5] In order to limit the studies to incident outcomes, only first record of each outcome per person was included. Restricting an SCCS to the first recorded outcome can introduce bias, but this bias should be minimal if the outcome is rare, as is the case here.[32]

Cohort study

In the cohort study we estimated the hazard ratio between systemic fluoroquinolone use, relative to systemic cephalosporin use, and uveitis and retinal detachment within 60 days of prescription (eFigure 1). A 60-day risk window was chosen given concern of an acute risk following prescription for both outcomes.[12,14] Adults with a prescription within the eligibility window for a systemic fluoroquinolone or cephalosporin were included.[26]

Individuals in the following categories were excluded: Marfan or Stickler syndrome, systemic conditions associated with retinal detachment; prior diabetic retinopathy, given the association between this condition and tractional retinal detachment; endophthalmitis or conditions predisposing to endophthalmitis (aphakia, ocular surgery, intravitreal injection, head or ocular injury) in the prior 90 days, given that oral fluoroquinolones may be used in the treatment of this condition, and the condition itself increases the risk of retinal detachment[33,34]; and ever prior tuberculosis or Lyme disease, as these bacterial infections are strongly associated with fluoroquinolone/cephalosporin prescribing and with both exudative retinal detachment and uveitis.

Multiple treatment episodes, defined by prescriptions occurring more than 60 days apart, were counted as separate episodes. Treatment episodes were censored at the earliest of death, prescription of alternative antibiotic (fluoroquinolone or cephalosporin), outcome occurrence, and 60 days following prescription. Only treatment episodes starting prior to any recorded uveitis, retinal detachment, or tendon rupture code were included, to limit the cohort to incident events.

Covariates

Potential confounders, specified in Box 1, were adjusted for in the cohort study.

Box 1. Covariates adjusted for in cohort study

- **Demographic and lifestyle variables:** age, sex, socioeconomic deprivation, body mass index (BMI), smoking status, alcohol consumption, ethnicity
- **Indicators of frailty and comorbidity in 6 months prior to baseline:** number of hospital admissions, number of general (i.e., primary care) practitioner (GP) appointments
- **Ever prior comorbidities:** coronary heart disease, hypertension, diabetes, uncontrolled diabetes, cerebrovascular disease, dementia, HIV, chronic liver disease, chronic kidney disease, peripheral vascular disease, myocardial infarction, carotid artery disease, multiple sclerosis
- **Additional risk factors for retinal detachment or uveitis:** ever prior glaucoma, cataract, HSV1 infection, posterior vitreous detachment,
- **Additional risk factors for tendon rupture:** corticosteroid use in 6 months prior, ever prior rheumatoid arthritis

Socioeconomic deprivation was defined based on practice postal code using deciles of the Carstairs Index, a measure of deprivation based upon male unemployment, overcrowding, car ownership, and socioeconomic class.[35,36] BMI was defined based on recorded height and weight measurements.[37]

In the SCCS the potential time-varying confounders calendar time (in 5-year categories) and age (in 1-year categories) were adjusted for in analysis.

Code lists are available online at LSHTM Data Compass **<link to be provided at publication>.**

Self-controlled case series

Separate SCCS were conducted for uveitis and retinal detachment in Aurum and GOLD, to estimate the rate ratio for each outcome with systemic fluoroquinolone use. Adults with a first occurrence of the outcome within the eligibility window were selected. The observation period between start and end of eligibility was categorized by exposure status.

Prescriptions occurring more than 60 days apart were categorized as separate treatment episodes. We subcategorized the treatment episode into the following risk windows: 30 days pre-exposure, day 0, days 1-29, day 30-59, and days 60+ (Figure 1), with exposure starting at the day after first prescription and lasting for 60 days following final prescription within a treatment episode. Day 0 is separated from other exposure windows because we anticipate more frequent recording of clinical events on this day as a result of the primary care appointment. We separated a 30-day pre-exposure period from baseline time, to prevent bias from any short-term effect of the outcome on likelihood of prescribing, which may result, for example, due to reduced prescribing during a hospitalization.[38]

Statistical analysis

Data management was performed using Stata 17, and statistical analyses were conducted using R version 4.12.

Cohort study

In the cohort study, propensity score weighting, using stabilized inverse probability of treatment weights, was used to adjust for covariates.[39] Propensity scores were estimated using a logistic regression model. The continuous covariates, age and BMI, were modelled using a restricted cubic spline.

Hazard ratios for retinal detachment and uveitis within 60 days of exposure were estimated using weighted Cox regression models with robust variance estimation. Schoenfeld's residuals were used to assess hazard proportionality. A weighted Kaplan-Meier estimator was used to estimate adjusted risk differences.[40,41] Estimates were pooled across databases using fixed-effects meta-analysis.

Missing BMI and ethnicity values were imputed using multiple imputation with chained equations with 10 imputed datasets, assuming a missingness at random mechanism.[37,42] Propensity scores and treatment effect were estimated in each imputed dataset, and combined using Rubin's rules.[43] Individuals without recorded alcohol consumption were defined as not heavy drinkers and those with no recorded smoking status as not current smokers. [44]

Self-controlled case series

In the SCCS, conditional Poisson regression models, conditional on the individual and adjusted for age and calendar time, were fitted to estimate rate ratios between fluroquinolone use and each outcome. Rate ratios relative to comparator antibiotics were estimated using the simple ratio approach for active comparators, each comparison being made within a particular risk window (e.g., days 1-29 fluoroquinolones vs. days 1-29 cephalosporins).[29] Estimated rate ratios were pooled across databases using fixed-effect meta-analysis.

Sensitivity analyses

In a sensitivity analysis, in both the cohort and the SCCS, the definition of uveitis was limited to exclude posterior or intermediate uveitis codes, given that case reports raised concern specifically in relation to anterior uveitis.[12] Additionally, the definition of retinal detachment was relaxed to include any relevant clinical code, regardless of the presence of a subsequent procedure.

Further sensitivity analyses were conducted in the cohort study, as follows: 1) we excluded individuals with subsequent cataract surgery within 30 days of prescription, to prevent the potential inclusion of patients with pre-existing cataracts, prescribed fluoroquinolones as prophylaxis prior to cataract surgery; 2) we restricted to individuals with an indication for urinary tract infection within two weeks prior, to mitigate confounding by indication; 3) we restricted to first prescription only (i.e. to new users); 4) we excluded individuals with prior diabetes, to reduce the likelihood of inclusion of tractional retinal detachment; 5) we conducted a complete-case analysis, to investigate sensitivity of results to missingness assumptions; 6) we estimated propensity scores within six-year strata of calendar year, in case covariate-related prescribing trends were present.

Results

Cohort

In the Aurum database we selected 3,001,256 adults prescribed systemic fluoroquinolones or cephalosporins (eFigure 2). Of these, at first treatment episode 1,027,341 (34.2%) were prescribed fluoroquinolones and 1,973,915 cephalosporins. Across all treatment episodes there were 2,131,292 (33.3%) treatment episodes of fluoroquinolones and 4,266,152 of cephalosporins.

In GOLD we selected 434,754 individuals prescribed systemic fluoroquinolones or cephalosporins. At first treatment episode, 153,854 (35.4%) were prescribed fluoroquinolones and 280,900 cephalosporins. In total there were 309,349 (34.9%) treatment episodes of fluoroquinolones and 577,082 of cephalosporins.

Individual characteristics at first treatment episode are presented in Table 1 (see eTable 2 for characteristics over all treatment episodes). Systemic fluoroquinolone and cephalosporin users were similar with regard to most studied characteristics except sex. There was a lower proportion of female fluoroquinolone users than of cephalosporin users (47.7% vs. 71.1% in Aurum – similar numbers presented for GOLD in Table 1). Absolute standardised mean differences were below 0.1 for all covariates after weighting (eTables 3-4). Most fluoroquinolone prescriptions were for ciprofloxacin (87.4% in Aurum and 87.1% in GOLD at first treatment episode – eTables 5-6), while the majority of cephalosporin prescriptions were for cefalexin (72.5% in Aurum and 71.0% in GOLD at first treatment episode).

There was no evidence of an association at first treatment episode (Figure 2) between systemic fluoroquinolone use, relative to systemic cephalosporin use, and uveitis (pooled adjusted hazard ratio [aHR] 0.91, 95% CI 0.72-1.14) or retinal detachment (pooled aHR 1.37, 95% CI 0.80-2.36). Similarly, there was no evidence of an association across all treatment episodes (Figure 2) for uveitis (pooled aHR 1.07, 95% CI 0.92-1.25) or retinal detachment (pooled aHR 1.18, 95% CI 0.84-1.65).

As anticipated, there was strong evidence of an association of systemic fluoroquinolone use, relative to systemic cephalosporin use, with tendon rupture in both Aurum and GOLD at first treatment episode (pooled aHR 2.04, 95% CI 1.60-2.60) and all treatment episodes (pooled aHR 1.92, 95% CI 1.66-2.23) (Figure 2).

The pooled adjusted absolute difference in 60-day risk between users of systemic fluoroquinolone and cephalosporin per 100,000 first-treatment episodes was -1.09 (95% CI -3.36 to 1.17) cases of uveitis and 0.54 (95% CI -0.42 to 1.51) retinal detachments (Table 2). Across all treatment episodes, the pooled adjusted 60-day risk difference per 100,000 treatment episodes was 0.76 (95% CI -0.88 to 2.39) uveitis cases and 0.37 (95% CI, -0.37 to 1.10) retinal detachments (Table 2).

Self-controlled case series

Among 23,530,905 individuals in Aurum and 3,072,555 in GOLD we identified and included the following numbers of cases: uveitis - 72,251 in Aurum and 8,301 in GOLD; retinal detachment - 23,395 in Aurum and 2,761 in GOLD. Median follow-up for uveitis cases was 16.4 years in Aurum and 12.5 years in GOLD, and for retinal detachment cases was 18.6 years in Aurum and 13.5 years in GOLD.

There was little evidence for an association between systemic fluoroquinolone use, relative to non-use, and uveitis (pooled adjusted rate ratio [aRR] for days 1-29 of exposure 1.13, 95% CI 0.97-1.31; days 30-59 aRR 1.16, 95% CI 1.00-1.34; days 60+ aRR 0.98, 95% CI 0.74-1.31),

and no evidence for a harmful association with uveitis relative to either systemic cephalosporins or co-amoxiclav (Figure 3). There was weak evidence of an association at days 30-59 relative to systemic trimethoprim use (aRR 1.20; 95% CI 1.01-1.43), but this association was not consistent across exposure windows.

There was no evidence for an association between systemic fluoroquinolone use and retinal detachment relative to non-use (pooled aRR for days 1-29 1.15, 95% CI 0.86-1.54; days 30-59 aRR 0.94, 95% CI 0.69-1.30; days 60+ aRR 1.03, 95% CI 0.59-1.78), and no evidence for an association relative to either systemic cephalosporins, co-amoxiclav, or trimethoprim (Figure 3).

Sensitivity analyses

Sensitivity analyses had minimal impact on study results (eFigure 3 & 4 & eTables 7 to 17).

Discussion

There was little evidence, after adjusting for covariates, for increased risk of uveitis or retinal detachment with systemic fluoroquinolone use. These findings were consistent across two different study designs, cohort study and SCCS, conducted in two databases, CPRD Aurum and GOLD.

While we cannot rule out a small increase in risk of uveitis or retinal detachment with systemic fluoroquinolones, it is apparent from the estimated risk differences that any increase in absolute risk would be minimal (<1 in 10,000 treatment episodes) and of questionable clinical significance.

Two previous nested case-control studies found increased risk of uveitis with fluoroquinolone use, relative to non-use.[12-14] However, a subsequent US cohort study comparing fluoroquinolone to beta-lactam use did not find evidence for an association after adjustment for covariates.[14] Individuals prescribed antibiotics are likely to differ considerably from non-users, not least due to the presence of an infection. These differences might explain the increased risk observed in these earlier case-control studies. Further evidence to support this argument is that in the US cohort study, fluoroquinolone use was associated with increased incidence of systemic diseases that are known to be associated with uveitis (e.g., sarcoidosis).

One nested case-control study identified a strong association for current fluoroquinolone use relative to non-use and retinal detachment (adjusted rate ratio 4.50, 95% CI 3.56-5.70).[30] However, this study was conducted in a selected population of adults attending ophthalmology clinics, introducing the possibility of selection bias if fluoroquinolone prescribing is associated with ophthalmology clinic attendance.[45] Furthermore, this population had higher prevalence of risk factors for retinal detachments such as prior cataract surgery and myopia, which may, given greater prevalence, more strongly confound associations when partially measured or uncontrolled. Subsequent studies, including our own, found either no evidence for an association or evidence for an association of smaller magnitude (relative risk < 2).[31,46-56] Individuals with conditions leading to elevated risk of retinal detachment, such as cataracts or diabetes, may be more likely to receive oral fluoroquinolones (e.g., for prophylaxis for cataract surgery or to treat diabetes-associated urinary tract infections). There was evidence to support this argument in our cohort study, where there was a crude association between systemic fluoroquinolones and retinal detachment, but no evidence for an association after adjusting for covariates.

Our study had numerous strengths including the large study population and the use of two databases, two study designs, and multiple sensitivity analyses to increase the robustness of findings. Self-controlled studies inherently control for time-invariant covariates (e.g., myopia) by estimating within-person effects. The cohort study design complemented the self-controlled study by enabling the estimation of absolute risk of the outcome.

There were some study limitations. There is likely to be a degree of outcome misclassification, e.g. some individuals identified as having a retinal detachment may have non-rhegmatogenous detachments. However, the inclusion of non-rhegmatogenous detachments was reduced by specifying surgical treatment, which is not typically used in the treatment of serous detachment, in the outcome definition, and by excluding people with diabetic retinopathy, as these individuals are prone to tractional detachment. Furthermore, sensitivity analyses, varying outcome definitions, and excluding individuals with diabetes, had minimal impact on estimates. Restrictions made on the cohort study population to limit outcome misclassification and reduce confounding may reduce the generalizability of study findings, though these restrictions affect a small fraction of fluoroquinolone and

cephalosporin users (<5%). Careful interpretation of associations is necessary in view of the multiple comparisons made. Possible residual confounding means that associations observed in non-interventional studies, such as this study, may not be causal.

The majority of prescriptions for systemic fluoroquinolone antibiotics were for ciprofloxacin, with few prescriptions for moxifloxacin, the fluoroquinolone antibiotic for which the strongest safety signals concerning uveitis from case reports and non-interventional studies have been observed.[11,13,14] While our study cannot rule out an effect of moxifloxacin, it does provide some reassurance against a class-wide effect. Safety signals observed for moxifloxacin may also relate to confounding. Moxifloxacin is prescribed differently to other fluoroquinolones, including more frequently for ocular indications.[57] Non-interventional studies examining moxifloxacin safety need to account carefully for this potential confounding, given the potential for residual bias.

Conclusions

In conclusion, whilst prescribing of antibiotics should always aim to account for potential risks as well as benefits, taken together, our findings indicate that restrictions on usage of systemic fluoroquinolones on the basis of uveitis or retinal detachment may be unwarranted.

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Role of funder/sponsor statement

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Conflict of interest disclosures

JPB reported grants from GSK funding his PhD studentship during the conduct of the study and personal fees from the World Health Organization Europe for COVID-19 surveillance consulting and from CorEvitas for unrelated consulting outside the submitted work. KEM reported personal fees from Amgen outside the submitted work. AYSW supervises a PhD student funded by GSK. NWG is an employee and shareholder of GSK. IJD reported grants from GSK during the conduct of the study and stock shares from GSK outside the submitted work. No other disclosures were reported.

Access to data and data analysis

JPB and IJD had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Data Sharing

Clinical Practice Research Datalink is available to researchers for approved projects. The study was approved by the CPRD Independent Scientific Advisory Committee (protocol number: 20_106RA).

This study is based in part on data from the Clinical Practice Research Datalink obtained under license from the UK Medicines and Healthcare products Regulatory Agency. The data is provided by patients and collected by the NHS as part of their care and support. The interpretation and conclusions contained in this study are those of the author/s alone. Hospital Episode Statistics**:** Copyright © (2022), re-used with the permission of The Health & Social Care Information Centre. All rights reserved.

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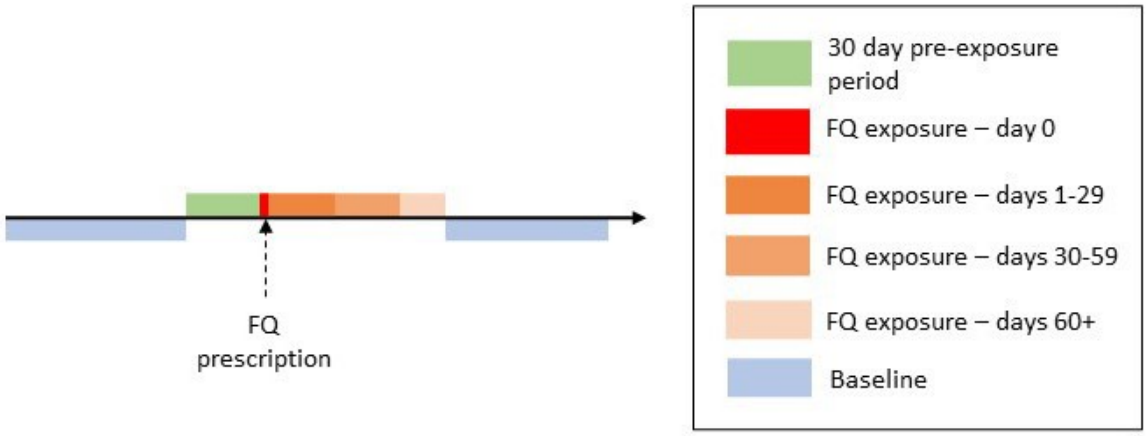

Figure 1: Definition of risk windows in SCCS

Definitions: FQ, fluoroquinolone

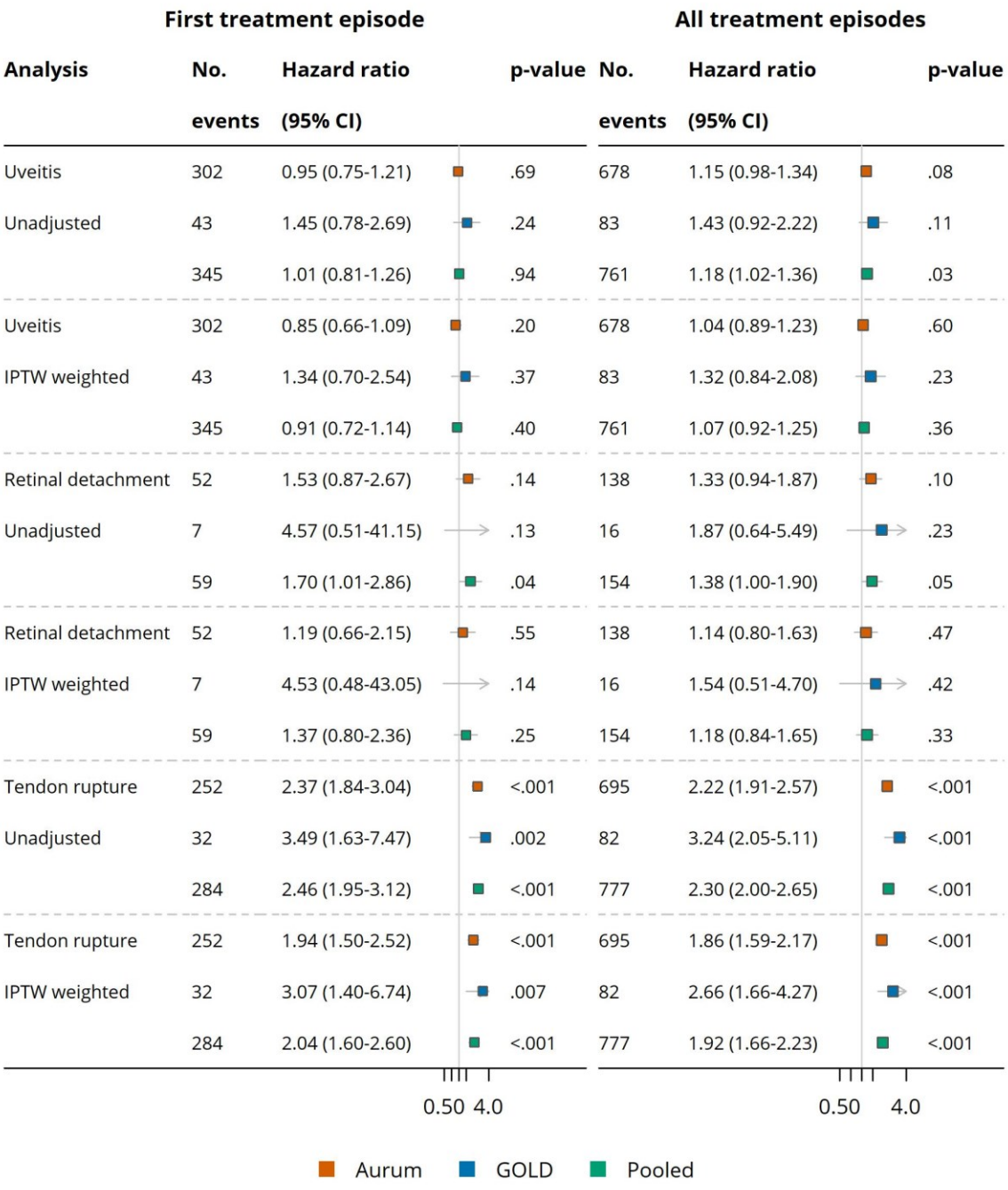

Figure 2: Cohort study - Hazard ratios comparing risk of uveitis, retinal detachment and tendon rupture following fluoroquinolone prescription, relative to cephalosporin prescription

Definitions: CI, confidence interval. Note: arrows represent a confidence interval extending beyond the axis range.

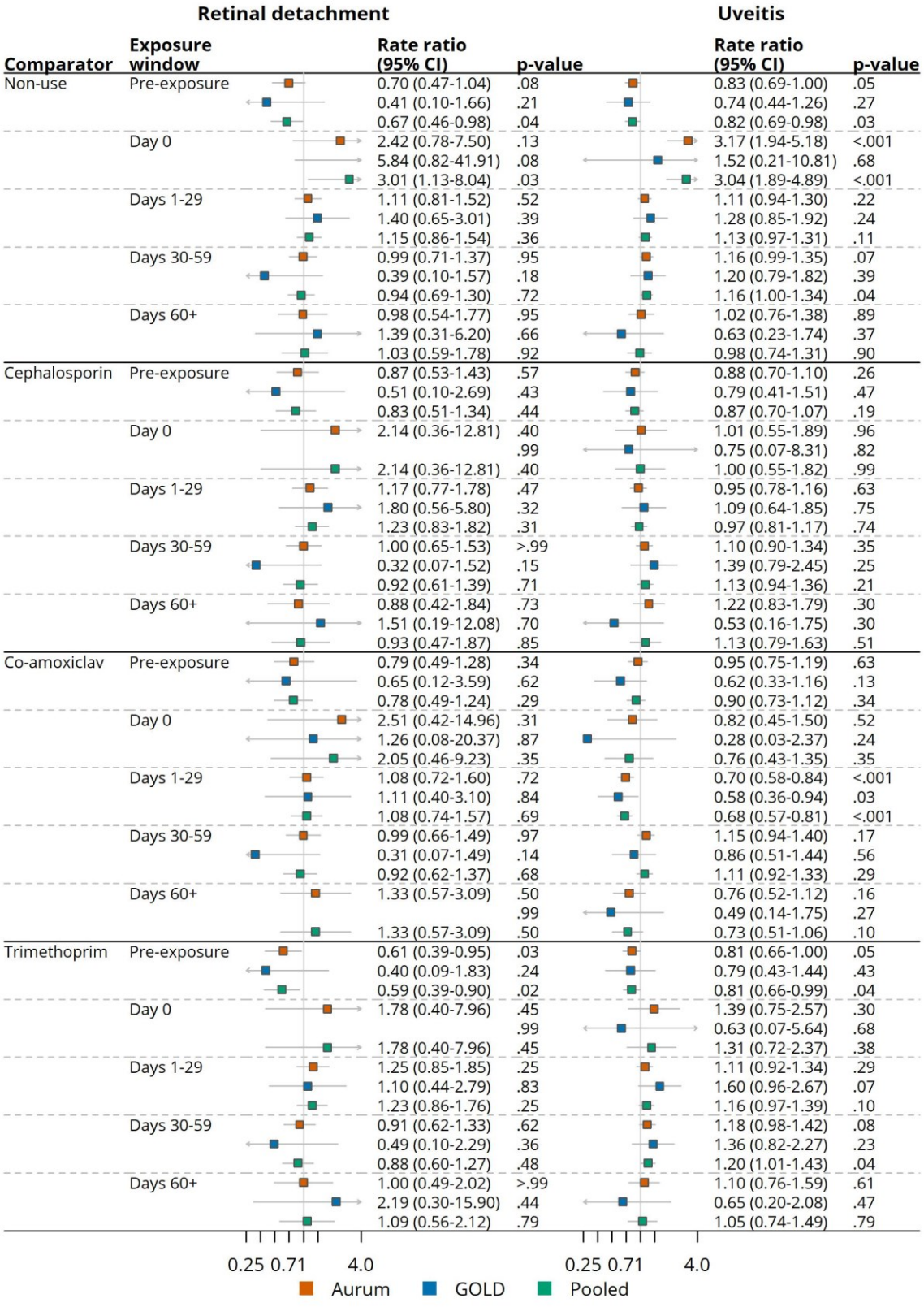

Figure 3: Self-controlled case series - Rate ratios for uveitis and retinal detachment comparing fluoroquinolone use to non-use or to use of comparator antibiotics

Definitions: CI, confidence interval. Note: arrows represent a confidence interval extending beyond the axis range.

Table 1: Cohort study - Baseline characteristics of fluoroquinolone and cephalosporin users at first treatment episode

Characteristic	Aurum		GOLD	
	Cephalosporin, N = 1,973,915	**Fluoroquinolone, N = 1,027,341**	**Cephalosporin, N = 280,900**	**Fluoroquinolone, N = 153,854**
Age, median (IQR)	50 (34, 69)	52 (37, 68)	53 (35, 70)	54 (39, 69)
Female	1,403,191 (71.1)	490,370 (47.7)	199,911 (71.2)	76,348 (49.6)
Below 10th percentile Carstairs Index	95,571 (4.8)	56,777 (5.5)	10,753 (3.8)	7,179 (4.7)
Above 90th percentile Carstairs Index	244,649 (12.4)	97,456 (9.5)	32,935 (11.7)	17,160 (11.1)
BMI, median (IQR)	27.5 (24.2, 31.8)	27.5 (24.3, 31.4)	25.7 (22.7, 29.4)	26.0 (23.1, 29.7)
Missing	360,885	190,228	30,094	16,532
Current smoker	647,063 (32.8)	324,144 (31.6)	89,351 (31.8)	45,596 (29.6)
Heavy drinker	45,668 (2.3)	34,817 (3.4)	5,671 (2.0)	4,480 (2.9)
Prior 6 months				
Number of GP appointments, median (IQR)*	1.0 (0.0, 4.0)	2.0 (0.0, 5.0)	4.0 (2.0, 8.0)	5.0 (2.0, 9.0)
Hospitalized	348,572 (17.7)	196,013 (19.1)	50,663 (18.0)	30,147 (19.6)
Corticosteroid use	138,116 (7.0)	85,869 (8.4)	24,543 (8.7)	16,613 (10.8)
Ever prior				
Coronary heart disease	161,295 (8.2)	84,819 (8.3)	25,510 (9.1)	13,847 (9.0)
Hypertension	402,367 (20.4)	219,421 (21.4)	60,823 (21.7)	34,822 (22.6)
Diabetes	120,111 (6.1)	65,860 (6.4)	32,563 (11.6)	18,006 (11.7)
Uncontrolled diabetes	61,976 (3.1)	35,710 (3.5)	9,404 (3.3)	5,856 (3.8)
Cerebrovascular disease	100,972 (5.1)	48,986 (4.8)	15,139 (5.4)	7,428 (4.8)
Dementia	39,360 (2.0)	13,779 (1.3)	5,559 (2.0)	1,829 (1.2)
HIV	1,402 (0.1)	1,633 (0.2)	121 (0.0)	114 (0.1)
Chronic liver disease	6,082 (0.3)	5,118 (0.5)	775 (0.3)	685 (0.4)
Chronic kidney disease	225,982 (11.4)	113,033 (11.0)	38,120 (13.6)	20,331 (13.2)
Peripheral vascular disease	36,959 (1.9)	22,247 (2.2)	6,390 (2.3)	3,862 (2.5)
Myocardial infarction	56,426 (2.9)	31,012 (3.0)	8,921 (3.2)	5,127 (3.3)
Carotid artery disease	4,631 (0.2)	2,726 (0.3)	787 (0.3)	481 (0.3)
Multiple sclerosis	8,679 (0.4)	4,772 (0.5)	1,452 (0.5)	785 (0.5)
Cataract	127,840 (6.5)	64,078 (6.2)	19,854 (7.1)	10,415 (6.8)
Glaucoma	36,292 (1.8)	19,275 (1.9)	6,041 (2.2)	3,219 (2.1)

Characteristic	Aurum		GOLD	
	Cephalosporin, N = 1,973,915	**Fluoroquinolone, N = 1,027,341**	**Cephalosporin, N = 280,900**	**Fluoroquinolone, N = 153,854**
Posterior vitreous detachment	11,273 (0.6)	7,697 (0.7)	1,692 (0.6)	1,165 (0.8)
HSV1 infection	27,712 (1.4)	13,550 (1.3)	6,942 (2.5)	3,398 (2.2)
Rheumatoid arthritis	26,804 (1.4)	11,762 (1.1)	6,059 (2.2)	2,856 (1.9)

Definitions: BMI, body mass index; GP, general practitioner; HSV1, herpes simplex virus 1; HIV, human immunodeficiency virus; IQR, interquartile range.

* Ability to characterize primary care appointment by type (i.e., primary care physician appointment vs. other appointment) is limited in Aurum.

Main value in each table cell is number of patients, and value in brackets is percentage of individuals, except for age, BMI, and no. of GP appointments where median and interquartile range are presented. Ethnicity and calendar year are presented in eTable 1.

Table 2: Cohort study - Risk differences of uveitis and retinal detachment for use of fluoroquinolones relative to cephalosporins

Treatment episode	Outcome	Analysis	Aurum			GOLD			Pooled		
			RD per 100,000	95% CI	p-value	RD per 100,000	95% CI	p-value	RD per 100,000	95% CI	p-value
First	Uveitis	Unadjusted	-0.50	-2.90, 1.90	.68	3.82	-2.76, 10.40	.26	0.01	-2.25, 2.26	>.99
		Adjusted	-1.60	-4.01, 0.80	.19	3.02	-3.79, 9.84	.39	-1.09	-3.36, 1.17	.35
	Retinal detachment	Unadjusted	0.78	-0.29, 1.86	.15	2.56	-0.49, 5.60	.10	0.98	-0.03, 1.99	.06
		Adjusted	0.32	-0.71, 1.35	.55	2.08	-0.59, 4.76	.13	0.54	-0.42, 1.51	.27
All	Uveitis	Unadjusted	1.52	-0.24, 3.27	.09	3.57	-0.95, 8.08	.12	1.78	0.15, 3.42	.03
		Adjusted	0.47	-1.29, 2.22	.60	2.71	-1.84, 7.27	.24	0.76	-0.88, 2.39	.37
	Retinal detachment	Unadjusted	0.65	-0.16, 1.46	.12	1.20	-0.85, 3.25	.25	0.72	-0.03, 1.47	.06
		Adjusted	0.29	-0.51, 1.10	.47	0.73	-1.09, 2.56	.43	0.37	-0.37, 1.10	.33

Definitions: RD, risk difference; CI, confidence interval.