Association between fluoroquinolones and hospitalization with aortic aneurysm or aortic dissection

Jeremy P Brown, MSc[1]; Kevin Wing, PhD[1]; Clémence Leyrat, PhD[1,2]; Stephen Evans, PhD[2]; Kathryn E. Mansfield, MBBS, PhD[1]; Angel YS Wong, PhD[1]; Liam Smeeth, MBChB, PhD[1]; Nicholas W Galwey, PhD[3]; Ian J Douglas, PhD[1]

1. Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK
2. Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, UK
3. R&D, GSK Medicines Research Centre, GSK, Stevenage, UK

Published manuscript: https://jamanetwork.com/journals/jamacardiology/article-abstract/2808412

Abstract

Importance

Fluoroquinolone use has been associated with increased hospitalization with aortic aneurysm or dissection (AA/AD) in non-interventional studies, but causality is unclear.

Objective

To determine the association between fluoroquinolone use and AA/AD using multiple study designs and multiple databases to increase the robustness of findings.

Design

Cohort and case-crossover studies were conducted separately in two databases of UK primary care records.

Setting

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

Participants

Adults with a systemic fluoroquinolone or cephalosporin prescription between 1st April 1997 to 31st December 2019 were included in cohort studies. Adults hospitalized with AA/AD within the eligibility period were included in case-crossover studies. Cases were matched 1:3 to non-cases on age, sex, index date, and clinical practice to adjust for calendar trends in prescribing.

Exposures

Systemic fluoroquinolone or comparator antibiotic.

Main Outcomes and Measures

Hazard ratios (HR) were estimated in the cohort studies for the association between prescription of fluoroquinolones and AA/AD hospitalization using stabilized inverse probability of treatment weighted Cox regression. Odds ratios (OR) were estimated in the case-crossover studies for the association between systemic fluoroquinolone use and AA/AD hospitalization using a conditional logistic regression model. Estimates were pooled across databases using fixed-effects meta-analysis.

Results

In the cohort studies we identified 3,134,231 adults in Aurum and 452,086 in GOLD prescribed fluoroquinolones or cephalosporins. In crude analyses fluoroquinolone relative to cephalosporin use was associated with increased AA/AD hospitalization (pooled HR 1.28, 95% CI 1.13-1.44, $p<0.001$), but after adjustment for potential confounders, this association disappeared (pooled adjusted HR 1.03, 95% CI 0.91-1.17, $p=0.649$). In the case-crossover studies we identified 84,841 individuals hospitalized with AA/AD in Aurum and 10,357 in GOLD. Relative to non-use, fluoroquinolones were associated with increased AA/AD hospitalization, but no association was found relative to other antibiotics (vs. cephalosporin pooled OR 1.05, 95% CI 0.87-1.27; vs. trimethoprim 0.89, 95% CI 0.75-1.06; vs. co-amoxiclav 0.98, 95% CI 0.82-1.18).

Conclusions and Relevance

Our results suggest that estimates of association of fluoroquinolones with AA/AD can be affected by confounding. When such confounding is accounted for no association is evident, providing reassurance on the safety of fluoroquinolones with respect to AA/AD.

Key points

Question

Does fluoroquinolone use increase the risk of hospitalization with aortic aneurysm or aortic dissection (AA/AD)?

Findings

After covariate adjustment and relative to comparator antibiotics there was no evidence of an association between fluoroquinolone use and AA/AD. This finding was consistent across two databases, Aurum and GOLD, and two study designs, cohort and case-crossover. An association was evident in unadjusted cohort study analyses and relative to non-use in the case-crossover studies, which may be explained by confounding.

Meaning

These findings suggest that fluoroquinolone use may not increase risk of AA/AD hospitalization and may instead be associated with AA/AD due to confounding.

Introduction

Safety concerns over fluoroquinolones have led the U.S. Food and Drug Administration to require a number of warnings be added to fluoroquinolone packaging.

One major concern has been the safety of fluoroquinolones with respect to aortic aneurysm and aortic dissection (AA/AD). There is a long-recognized association between fluoroquinolones and tendon rupture linked to collagen degradation.[1] Given that aortic diseases similarly involve collagen degradation, a 2015 cohort study investigated the association, finding increased hospitalization with AA/AD following fluoroquinolone prescription.[2] Subsequent studies have produced conflicting findings and differing conclusions on the causality of the association.[3] It is estimated that abdominal aortic aneurysms are responsible for 1.3% of deaths in men aged 65-85 in high-income countries.[4] Given the burden of AA/AD, a causal association would be of concern to clinicians, patients, and regulators.

The aim of this study was to estimate the association between fluoroquinolones and AA/AD hospitalization using multiple study designs and study populations to increase the robustness of study findings.

Methods

Study design

We conducted cohort and case-crossover studies in Clinical Practice Research Datalink (CPRD) Aurum and GOLD. These two databases of anonymized UK primary care records were linked for this study to socioeconomic deprivation and hospital admissions data (Hospital Episode Statistics Admitted Patient Care).

The case-crossover study is a self-controlled design in which the occurrence of an exposure is compared, within individuals, in the period immediately prior to the outcome relative to an

earlier reference period.[5] Unlike a cohort study, the case-crossover study eliminates by design confounding by variables that are time-invariant over the study period (e.g. genetic conditions).

Study eligibility

We selected all adults aged 18 years or older eligible for linkage to hospital admission and socioeconomic deprivation data.

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

Cohort studies

In the cohort studies we estimated the association between prescription of fluoroquinolones, relative to cephalosporin, and hospitalization with AA/AD within 60 days of prescription (eFigure 1). Cephalosporins are a group of antibiotics with a similar prescribing profile in UK practice to fluoroquinolones, and are not known to have a causal effect on AA/AD.[6] Adults with a systemic prescription for either antibiotic within the eligibility window were selected. Adults with Marfan syndrome, a genetic condition associated with AA/AD, were excluded.

We included first treatment episode, and in secondary analyses included all episodes (see supplementary methods). Treatment episodes were censored at the earliest of hospitalization with AA/AD, death, prescription of the other antibiotic, and 60 days following prescription. Only treatment episodes starting prior to AA/AD hospitalization were included.

Case-crossover studies

Adults with a first AA/AD hospitalization within the eligibility window were selected. The odds of fluoroquinolone prescribing was compared in the 0-60 days, relative to 90-150 days, preceding the outcome. The association between fluoroquinolone prescribing and AA/AD was assessed relative to non-use and relative to comparator antibiotics: cephalosporin, co-amoxiclav, and trimethoprim.

To control for prescribing trends, cases were matched, on index date, year of birth, sex, and practice 1:3 to adults without AA/AD hospitalization (eFigure 2), an extension of the case-crossover known as the case-time-control design.[7].

Outcomes

The primary outcome was hospitalization with AA/AD as determined by an ICD-10 code recorded on hospital admission. A positive control outcome, tendon rupture, which has consistently been associated with fluoroquinolone use, was included in the cohort studies.[1]

Statistical analysis

Cohort studies

Potential confounders (see supplementary material for details) were adjusted for using stabilized inverse probability of treatment weights with a propensity score estimated by logistic regression. Missingness in ethnicity and BMI was handled using multiple imputation by chained equations with 10 imputed datasets.

To estimate the hazard ratio for AA/AD hospitalisation within 60 days of exposure, weighted Cox models were fitted with robust variance estimation.

Case-crossover studies

Conditional logistic regression models were fitted to estimate the odds ratio between fluoroquinolone prescribing and AA/AD hospitalisation. Odds ratios relative to comparator antibiotics were estimated using the simple ratio approach for active comparators in self-controlled studies.[8]

Both designs

Odds and hazard ratios were pooled across databases using fixed-effects meta-analysis. Secondary and sensitivity analyses are described in supplementary methods.

Data analyses were conducted in Stata 17 and R-4.12.

Results

Cohort studies

In Aurum we identified 1,077,584 adults prescribed fluoroquinolones and 2,056,537 prescribed cephalosporins. In GOLD we identified 160,636 adults prescribed fluroquinolones and 291,450 prescribed cephalosporins (eFigure 3).

Cephalosporin and fluoroquinolone users were similar for most variables (Table 1), but a higher proportion of cephalosporin users were female (71% vs. 48% in Aurum, 71% vs 50% in GOLD). Absolute standardized mean differences were less than 0.1 for all covariates after weighting (eTable 2). Most prescriptions of fluoroquinolones were for ciprofloxacin (88.1% in Aurum and 87.7% in GOLD).

In unadjusted Cox regression (Figure 1) there was strong evidence of an association between fluroquinolone use and AA/AD hospitalization (pooled unadjusted hazard ratio [HR] 1.28, 95% CI 1.13-1.44). However, after adjustment for covariates there was no evidence of an association (pooled adjusted hazard ratio [aHR] 1.03, 95% CI 0.91-1.17). A post-hoc analysis adjusting for sex only resulted in a pooled aHR of 0.98 (95% CI 0.85-1.12 – eTable 7).

Strong evidence of an association with tendon rupture was observed (pooled aHR 1.98, 95% CI 1.56-2.50).

Case-crossover studies

Cases hospitalized with AA/AD (84,841 in Aurum and 10,357 in GOLD) were matched 3:1 to controls (eFigure 4, eTables 8 and 9).

Relative to non-use there was strong evidence for a positive association between fluoroquinolone prescribing and AA/AD hospitalization (pooled odds ratio [OR] 1.58, 95% CI 1.37-1.83) – Figure 1. However, risk was elevated for comparator antibiotics (eTable 10),

and compared to the comparator antibiotics there was no evidence for an association with fluoroquinolones (Figure 1).

Discussion

We found no evidence after covariate adjustment for increased AA/AD hospitalization with fluoroquinolone prescription relative to comparator antibiotics. Increased AA/AD hospitalization in unadjusted cohort analyses appeared to be primarily due to a sex imbalance between treatment groups.

In case-crossover studies increased AA/AD hospitalization was observed relative to non-use for multiple antibiotics, across different drug classes, including fluoroquinolones. Relative to comparator antibiotics no association with fluoroquinolones was evident.

A potential explanation is that infection itself may increase risk of AA/AD. In a nested case-control study, genitourinary and lower respiratory tract infections were associated with increased risk of AA/AD hospitalization after adjustment for antibiotic usage.[9] One potential mechanism is through infected aneurysms, which, although rare, frequently rupture.[10] Genitourinary and respiratory tract infections have previously been found to be associated with increased incidence of myocardial infarction and stroke, with potential mechanistic explanations including inflammatory and prothrombotic effects of infection.[11] Given the important role of inflammatory processes in aortic aneurysm development, [12] the inflammatory response to infection may also affect AA/AD. Further research on the mechanism of increased risk could usefully inform patient management and infectious disease control and prevention.

Previous studies have presented conflicting findings on the presence and causality of an association between fluoroquinolones and AA/AD.[3] Most studies identifying an association used non-use, amoxicillin, or azithromycin as comparators. Non-users are likely to differ

substantially from antibiotic users, in particular they will mostly not have an underlying infection. Confounding by indication, specifically at the time an antibiotic is prescribed, and particularly by infection type and severity, may explain previous associations. Further support for this view comes from null associations observed in earlier studies comparing fluoroquinolones to other antibiotics, namely co-amoxiclav, cephalosporins and co-trimoxazole.[9,13,14] Previous case-crossover studies made comparison to non-use, but by comparing to active comparators we have demonstrated the vulnerability of these studies to time-varying confounding by infection.[3]

Our study has important strengths. We observed consistent results across different study populations from different databases. Our use of comparator antibiotics, multiple study designs, and a positive control outcome increase the reliability of results. Cohort and self-controlled studies control for confounding by different mechanisms, and hence consistent results across designs increases the robustness of findings.

An assumption of the case-crossover design, consistent with the presumed effect of fluoroquinolones, is that the causal effect is short-term with minimal long-term effect.[5] In sensitivity analyses, findings were robust to different lengths of, and intervals between, assessment windows.

One limitation is the potential for misclassification of exposure because adherence is not captured. However, adherence to prescribed antibiotics is high in the UK.[15] Ruptured aneurysms and dissections leading to death before hospitalization will not be identified. Given these are not anticipated to be differentially related to antibiotic, and specificity of outcome definition is high, bias is expected to be minimal. A further limitation is that most fluoroquinolone prescriptions (~88%) were for ciprofloxacin and the majority of

fluoroquinolone prescriptions in the UK are for urinary tract infection, potentially limiting generalizability of findings to other fluoroquinolones and other indications.

Given the need for multiple antibiotics to combat antibiotic resistance, an informed understanding of the safety of the limited number of effective existing antibiotics is critical. Prescribers should base treatment decisions on the risk and benefit of different treatment options. We consistently found no evidence for an association with AA/AD hospitalization relative to comparator antibiotics, using multiple study designs and databases, providing reassurance to prescribers on risk of AA/AD.

Acknowledgments

This study is based in part on data from the Clinical Practice Research Datalink obtained under licence 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. The study was approved by the Independent Scientific Advisory Committee (protocol number: 20_106RA).

References

1. Stephenson AL, Wu W, Cortes D, Rochon PAJDs. Tendon injury and fluoroquinolone use: a systematic review. 2013;36(9):709-721.
2. Daneman N, Lu H, Redelmeier DA. Fluoroquinolones and collagen associated severe adverse events: a longitudinal cohort study. *BMJ Open.* 2015;5(11):e010077.
3. Ribeiro NV, Melo RG, Guerra NC, et al. Fluoroquinolones are associated with increased risk of aortic aneurysm or dissection: systematic review and meta-analysis. Paper presented at: Seminars in Thoracic and Cardiovascular Surgery2021.
4. Sakalihasan N, Limet R, Defawe OD. Abdominal aortic aneurysm. *Lancet.* 2005;365(9470):1577-1589.
5. Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. *Am J Epidemiol.* 1991;133(2):144-153.
6. Dolk FCK, Pouwels KB, Smith DR, Robotham JV, Smieszek TJJoAC. Antibiotics in primary care in England: which antibiotics are prescribed and for which conditions? 2018;73(suppl_2):ii2-ii10.
7. Suissa S. The case-time-control design. *Epidemiology.* 1995:248-253.
8. Hallas J, Whitaker H, Delaney JA, Cadarette SM, Pratt N, Maclure M. The Use of active Comparators in self-controlled Designs. *American Journal of Epidemiology.* 2021;190(10):2181-2187.
9. Dong YH, Chang CH, Wang JL, Wu LC, Lin JW, Toh S. Association of Infections and Use of Fluoroquinolones With the Risk of Aortic Aneurysm or Aortic Dissection. *JAMA Intern Med.* 2020;180(12):1587-1595.
10. Kim Y-w. Infected aneurysm: current management. *Annals of Vascular Diseases.* 2010;3(1):7-15.

11. Davidson JA, Warren-Gash C. Cardiovascular complications of acute respiratory infections: current research and future directions. *Expert review of anti-infective therapy.* 2019;17(12):939-942.

12. Lu H, Rateri DL, Bruemmer D, Cassis LA, Daugherty A. Novel mechanisms of abdominal aortic aneurysms. *Current atherosclerosis reports.* 2012;14(5):402-412.

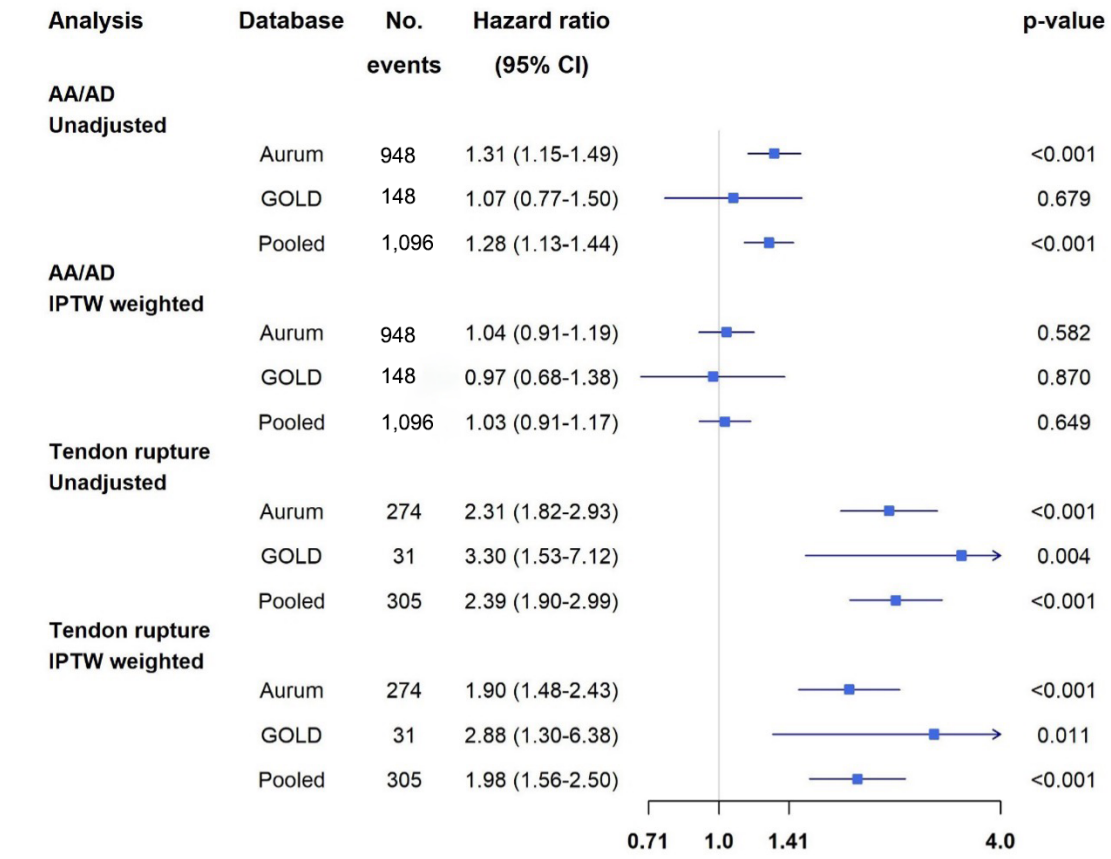
13. Gopalakrishnan C, Bykov K, Fischer MA, Connolly JG, Gagne JJ, Fralick M. Association of Fluoroquinolones With the Risk of Aortic Aneurysm or Aortic Dissection. *JAMA Intern Med.* 2020;180(12):1596-1605.

14. Chen YY, Yang SF, Yeh HW, et al. Association Between Aortic Aneurysm and Aortic Dissection With Fluoroquinolones Use in Patients With Urinary Tract Infections: A Population-Based Cohort Study. *J Am Heart Assoc.* 2022;11(6):e023267.

15. McNulty CA, Boyle P, Nichols T, Clappison P, Davey P. The public's attitudes to and compliance with antibiotics. *The Journal of antimicrobial chemotherapy.* 2007;60 Suppl 1(suppl_1):i63-68.

Figures

A)


Analysis
Database
No. events
Hazard ratio (95% CI)
p-value
AA/AD Unadjusted
Aurum 948 1.31 (1.15-1.49) <0.001
GOLD 148 1.07 (0.77-1.50) 0.679
Pooled 1,096 1.28 (1.13-1.44) <0.001
AA/AD IPTW weighted
Aurum 948 1.04 (0.91-1.19) 0.582
GOLD 148 0.97 (0.68-1.38) 0.870
Pooled 1,096 1.03 (0.91-1.17) 0.649
Tendon rupture Unadjusted
Aurum 274 2.31 (1.82-2.93) <0.001
GOLD 31 3.30 (1.53-7.12) 0.004
Pooled 305 2.39 (1.90-2.99) <0.001
Tendon rupture IPTW weighted
Aurum 274 1.90 (1.48-2.43) <0.001
GOLD 31 2.88 (1.30-6.38) 0.011
Pooled 305 1.98 (1.56-2.50) <0.001
0.71
1.0
1.41
4.0

B)

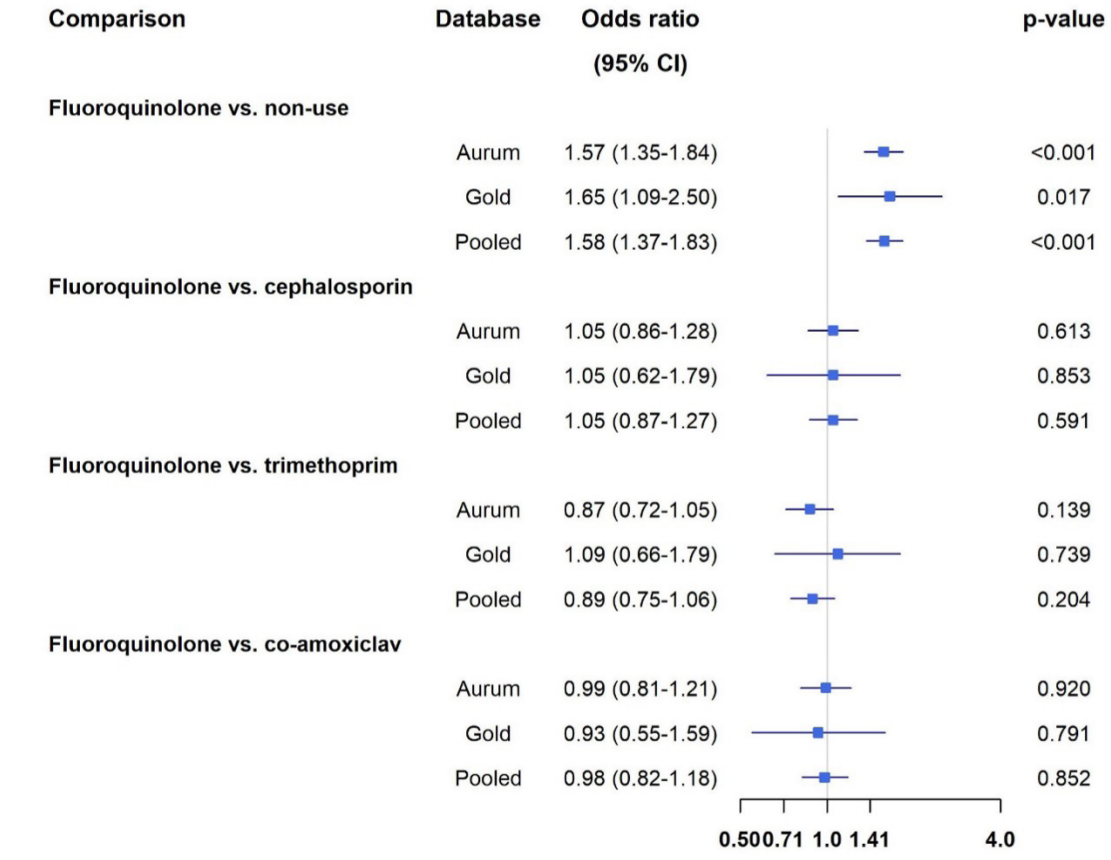

Comparison
Database
Odds ratio (95% CI)
p-value
Fluoroquinolone vs. non-use
Aurum 1.57 (1.35-1.84) <0.001
Gold 1.65 (1.09-2.50) 0.017
Pooled 1.58 (1.37-1.83) <0.001
Fluoroquinolone vs. cephalosporin
Aurum 1.05 (0.86-1.28) 0.613
Gold 1.05 (0.62-1.79) 0.853
Pooled 1.05 (0.87-1.27) 0.591
Fluoroquinolone vs. trimethoprim
Aurum 0.87 (0.72-1.05) 0.139
Gold 1.09 (0.66-1.79) 0.739
Pooled 0.89 (0.75-1.06) 0.204
Fluoroquinolone vs. co-amoxiclav
Aurum 0.99 (0.81-1.21) 0.920
Gold 0.93 (0.55-1.59) 0.791
Pooled 0.98 (0.82-1.18) 0.852
0.50
0.71
1.0
1.41
4.0

Figure 1: Associations A) between fluoroquinolone relative to cephalosporin prescribing and AA/AD hospitalisation or tendon rupture in cohort studies and B) between fluoroquinolone prescribing and AA/AD hospitalisation relative to comparator antibiotics in case-crossover studies

Definitions: AA/AD, aortic aneurysm or dissection; CI, confidence interval; IPTW, inverse probability of treatment weight

Tables

Table 1: Cohort studies - Baseline characteristics of fluoroquinolone and cephalosporin users at first prescription

	Aurum		GOLD	
Characteristic	Cephalosporin, N = 2,056,537	Fluoroquinolone, N = 1,077,584	Cephalosporin, N = 291,450	Fluoroquinolone, N = 160,636
Age[1]	51 (34, 70)	53 (37, 68)	53 (36, 71)	55 (39, 70)
Female	1,456,580 (71%)	512,677 (48%)	206,929 (71%)	79,573 (50%)
Below 10th percentile Carstairs Index	99,265 (4.8%)	59,340 (5.5%)	11,139 (3.8%)	7,394 (4.6%)
BMI[1]	28 (24, 32)	28 (24, 32)	25.7 (22.7, 29.5)	26.1 (23.1, 29.7)
Missing	375,309	199,397	30,884	16,900
Current smoker	669,169 (33%)	337,182 (31%)	91,894 (32%)	47,160 (29%)
Heavy drinker	47,340 (2.3%)	36,336 (3.4%)	5,847 (2.0%)	4,678 (2.9%)
Number of GP appointments in prior 6m[1,2]	1.0 (0.0, 5.0)	2.0 (0.0, 5.0)	4.0 (2.0, 8.0)	5.0 (2.0, 9.0)
Hospitalized in prior 6m	374,199 (18%)	213,609 (20%)	53,937 (19%)	32,535 (20%)
Statin in prior 6 months	240,967 (12%)	154,578 (14%)	35,651 (12%)	23,992 (15%)
Corticosteroid in prior 6 months	117,259 (5.7%)	77,514 (7.2%)	21,517 (7.4%)	15,271 (9.5%)
Coronary heart disease	177,028 (8.6%)	94,405 (8.8%)	27,402 (9.4%)	15,110 (9.4%)
Hypertension	440,438 (21%)	243,475 (23%)	65,242 (22%)	37,887 (24%)
Diabetes	152,140 (7.4%)	89,380 (8.3%)	26,726 (9.2%)	16,134 (10%)
Uncontrolled diabetes	93,696 (4.6%)	57,910 (5.4%)	12,651 (4.3%)	8,383 (5.2%)
Cerebrovascular disease	110,396 (5.4%)	54,326 (5.0%)	16,286 (5.6%)	8,106 (5.0%)
Dementia	42,638 (2.1%)	15,197 (1.4%)	5,871 (2.0%)	1,961 (1.2%)
HIV	1,541 (<0.1%)	1,783 (0.2%)	128 (<0.1%)	120 (<0.1%)
Chronic liver disease	6,703 (0.3%)	5,708 (0.5%)	837 (0.3%)	742 (0.5%)
Chronic kidney disease	250,855 (12%)	127,059 (12%)	41,223 (14%)	22,318 (14%)

	Aurum		GOLD	
Characteristic	Cephalosporin, N = 2,056,537	Fluoroquinolone, N = 1,077,584	Cephalosporin, N = 291,450	Fluoroquinolone, N = 160,636
Peripheral vascular disease	38,486 (1.9%)	23,113 (2.1%)	6,520 (2.2%)	4,064 (2.5%)
Myocardial infarction	61,886 (3.0%)	34,520 (3.2%)	9,583 (3.3%)	5,565 (3.5%)
Carotid artery disease	5,151 (0.3%)	3,071 (0.3%)	854 (0.3%)	531 (0.3%)
Aortic aneurysm	4,140 (0.2%)	2,547 (0.2%)	609 (0.2%)	379 (0.2%)
Multiple sclerosis	9,039 (0.4%)	4,981 (0.5%)	1,502 (0.5%)	822 (0.5%)
Rheumatoid arthritis	28,902 (1.4%)	12,818 (1.2%)	6,444 (2.2%)	3,083 (1.9%)

Note: the distribution of ethnicity and calendar year are provided in eTable 1

1. Median (interquartile range)
2. Ability to characterize primary care appointment type by type (i.e., primary care physician appointment versus other appointment) is limited in Aurum