

Risk of aortic aneurysm or dissection following exposure to fluoroquinolone antibiotics

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Background

Fluoroquinolone (FQ) antibiotics are a broad-spectrum class of antibiotics. Whilst FQ antibiotics are generally well tolerated, neurological and cardiovascular adverse events have been identified in post-market surveillance studies. A meta-analysis of four observational studies found that FQ antibiotics were associated with an increased risk of aortic diseases compared to other antibiotics (adjusted odds ratio 2.10; 95% CI 1.65-2.68). However, the quality of this study was rated as moderate and the results from later studies were conflicted. Due to the discordance in results of previous studies depending on country, data source and study design, and considering the widespread international use of FQs and severity of outcome, a large-scale international distributed network analysis was executed to characterise and estimate the risk of AA/AD with FQ exposure. Hence we aimed to determine whether exposure to FQ are associated with aortic aneurysm or dissections within 30 days, 60 days, 90 days or 365 days of initiating treatment

Methods

This study is being conducted through international collaboration through OHDSI network in Save Our Sisyphus (SOS) challenge. Participating sites and data partners obtained approval or exemption from respective institutional review boards to participate in the study. The study utilised data from January 2010 to December 2019.

We used a new-user comparative cohort design including all patients diagnosed with urinary tract infection (UTI) and initiating either treatment with systemic FQ or an active comparator of either trimethoprim (+/- sulfamethoxazole) (TMP-SMX) or cephalosporin (CEF). The index date (cohort start date) was defined as the day of initiating the antibiotic. Patients were included in the cohort if they did not have a UTI on or within 7 days prior to antibiotic exposure and were not hospitalised (inpatient or emergency room) on or within 7 days prior to antibiotic exposure. Patients were included if they were ≥ 35 years of age and new users of FQ or comparator antibiotic (TMP-SMX or CEF) for UTI. Fixed risk windows were defined as cohort start day plus one day through to cohort start day plus 30, 60, 90 or 365 days. The primary endpoint was a composite outcome of aortic aneurysm or dissection (AA/AD). Large-scale

propensity score (PS) model was derived using measured covariates at baseline. PS models were generated using regularised regression and employed 1:1 matching. To account for residual systemic bias negative control outcomes were identified as recommended by CommonEvidenceModel and manually reviewed by a team of clinical experts and empirical calibration was used. After application of PS matching evaluation of clinical equipoise was performed by calculation of preference scores. The study protocol and executable code is publicly available at <https://github.com/ohdsi-studies/FluoroquinoloneAorticAneurysm>.

Results

The analysis of this study is ongoing and the results will be presented at the Global symposium.

Preliminary results are available here: As of June 19, 2023, 10 databases have produced results. Among them, 4 databases failed in part of the study diagnostics process and could not yield results in FQ versus TMP-SMX comparisons, and 3 databases could not yield results in FQ versus CEF comparisons.

It is evident that treatment patterns vary considerably in different jurisdictions and there is some heterogeneity in results across different data sources. We are waiting for the results of additional databases and will conduct a meta-analysis as soon as the results are collected.

Conclusion

This is the largest study conducted on this subject. It will help to clarify the risk of AA/AD following FQ use. This study will provide regulators with clearer understanding and may help to clarify sub-populations who are at increased risk.

Reference

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