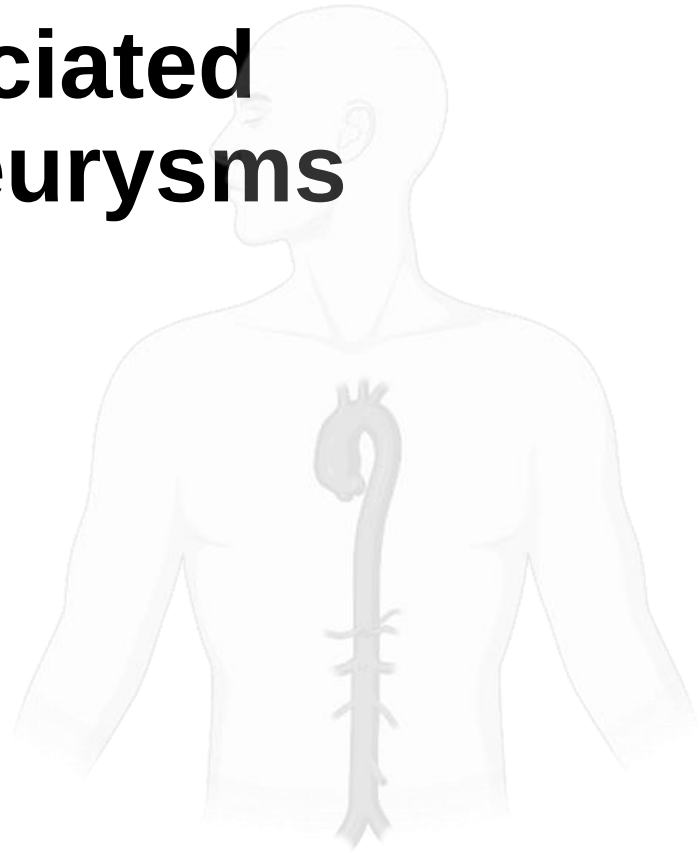
Is fluoroquinolone use really associated with the development of aortic aneurysms and aortic dissections?

OHDSI Save Our Sisyphus Challenge 2023



Initial collaborators

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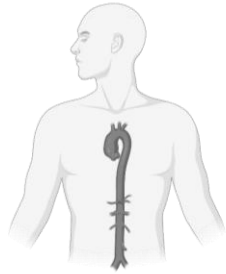
Background:



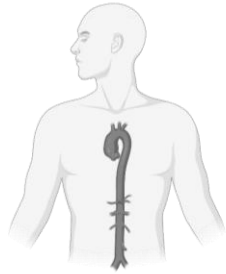
- Fluoroquinolones are broad spectrum antibiotics

- Indications:
  - **Urinary tract infections**, gastrointestinal infections, **bronchial infections**, skin and skin structure infections, bone and joint infections, prostatitis, eye infections, septicaemia, otitis media

- Consumption of fluoroquinolones is rising internationally [1]

[1] Van Boeckel TP, Gandra S, Ashok A, Caudron Q, Grenfell BT, Levin SA, Laxminarayan R. Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. Lancet Infect Dis. 2014 Aug;14(8):742-750. doi: 10.1016/S1473-3099(14)70780-7. Epub 2014 Jul 9.

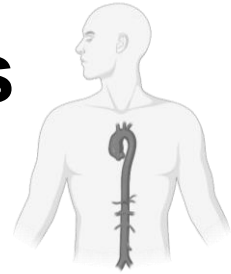
Background: fluoroquinolones



- Generally well-tolerated

- Post-marketing studies identified:
  - ↑ neurological and cardiovascular adverse events
  - ↑ **rare risk of aortic aneurysms or dissections**
    - Pharmacological mechanism not well understood
    - International regulators responded with black box warnings and limitations to prescribing

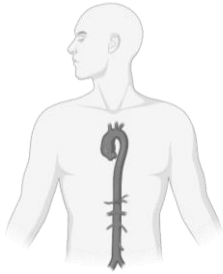
Fluoroquinolones and aortic aneurysms/dissections



- Quality of evidence underpinning the association is moderate:
  - *Meta-analysis of 5 observational studies:*
    - FQ users had ↑ risk of aortic diseases compared to those who used other antibiotics (adjusted odds ratio 2.10; 95% CI 1.65-2.68) [2]
    - 2.8M patients, inconsistencies in study designs
      - Active comparators, follow-up, patient age, time of quinolone consumption, stratify by quinolone versus class effect
  - Several other studies published since meta-analyses have conflicting results [3] and may be affected by confounding by indication and surveillance bias [4]

[2] Dai XC, Yang XX, Ma L, Tang GM, Pan YY, Hu HL. Relationship between fluoroquinolones and the risk of aortic diseases: a meta-analysis of observational studies. BMC Cardiovasc Disord. 2020;20(1):49
[3] JAMA Surg. 2021;156(3):264-272.
[4] JAMA Intern Med. 2020;180(12):1596-1605

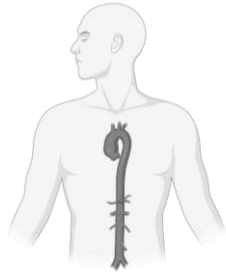
Primary research questions



Does exposure to FQ actually increase the risk of experiencing aortic aneurysm or dissection within 1 year after exposure start?

For a patient with UTI or pneumonia, what is the probability that they will go on to have an aortic aneurysm or dissection following initiation of a fluoroquinolone

The questions and framework



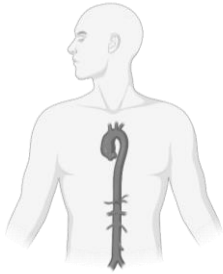
Characterizing, estimating and predicting the risk of aortic aneurysm and aortic dissection associated with fluoroquinolone exposure

Characterization: incidence and time-to-event of aortic events following quinolone exposure

- Amongst patients who are new users of fluoroquinolones, *how many* patients experience aortic aneurysms or dissections within 1 year of initiating treatment?

- Amongst patients who are new users of fluoroquinolones, what is the *time-to-event* distribution between exposure and aortic aneurysm or dissection?

The questions and framework



Characterizing, estimating and predicting the risk of aortic aneurysm and aortic dissection associated with fluoroquinolone exposure

Estimation: comparative safety of quinolones vs other antibiotics; comparative safety between fluoroquinolones

- Does exposure to FQs ↑ risk of experiencing aortic aneurysm or dissection within 30d, 60d, 90d and 365d of initiating treatment?

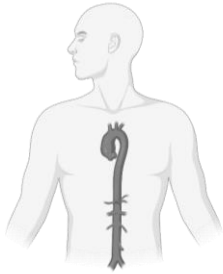
- Does exposure to FQs have a different risk of experiencing aortic aneurysm and dissection within 30d, 60d, 90d and 365d of initiating treatment, relative to other antibiotics

The questions and framework: study design + cohorts

	Cohort 1		Cohort 2	
	Community acquired pneumonia		Urinary tract infection	
	FQs	Active comparators	FQs	Active comparators
Outpatient setting	Ciprofloxacin Levofloxacin Moxifloxacin Gemifloxacin	Amoxicillin Amoxicillin/clavulanic acid Azithromycin Clarithromycin Doxycycline Cefpodoxime Cefuroxime	Ciprofloxacin Levofloxacin Norfloxacin	TMP/SMX Cefpodoxime Cefixime Cefdinir Cefditoren
Hospital setting	Ciprofloxacin Levofloxacin Moxifloxacin Gemifloxacin	Ceftriaxone Cefotaxime Ampicillin/sulbactam Amoxicillin/clavulanic acid	Ciprofloxacin Levofloxacin Norfloxacin	TMP/SMX Ceftriaxone Cefotaxime Ampicillin/sulbactam Amoxicillin/clavulanic acid

FQs or active comparators can be added where relevant for each data source and jurisdiction

The questions and framework

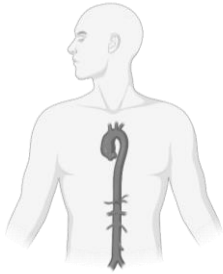


Characterizing, estimating and predicting the risk of aortic aneurysm and aortic dissection associated with fluoroquinolone exposure

Design a risk prediction model:

- Question: for a given patient who is a new user of fluoroquinolones, what is the probability that they will have an aortic aneurysm or dissection in 1 year?

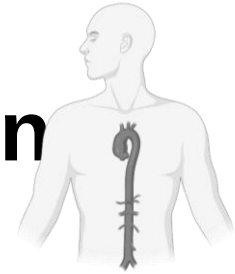
Contribution of this project: additional studies



- Additional outcomes of interest include:
  - Serious arrhythmia (ventricular tachycardia or flutter, cardiac arrest or sudden death)
  - Mitral and aortic valve regurgitation
  - Achilles tendonitis and tendon rupture
  - Retinal detachment
  - Dysglycemia (hyperglycemia or hypoglycemia)
  - Seizure
  - Peripheral neuropathy

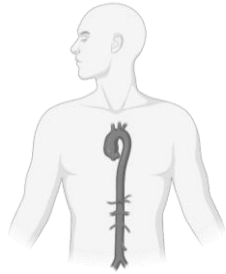
- Utilisation of the common data model would allow for better characterisation of risk of these outcomes with use of FQ antibiotics

Contribution of this project: importance of question



- Conflicting results and conclusions from previous studies
- Findings in meta-analyses and systematic reviews are limited by study designs
- Due to rarity of outcomes, RCTs are unlikely to uncover significant findings
  - Utilisation of Common Data Model via OHDSI distributed network analysis will allow for:
    - Improved exploration of this association
    - ↑ statistical power (more databases, greater generalisability of findings)
    - Characterisation of time-to-event
    - Analysis of effect estimates in different age strata
    - Risk prediction
    - Enhance evidence on which regulators base warnings and recommendations

How you can contribute



- Participate in study design and protocol development
- Execution of analyses in your jurisdiction and sharing of results
- Co-author publications from distributed network analysis